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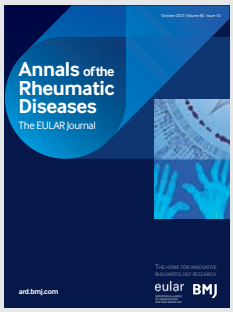

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SARS-CoV-2 and the rheumatology patient: the last 12 months and a boost in the future

Kevin L Winthrop [1], Richard J Whitley,[2] Daniel Aletaha [3]

EDITORIAL

It is a rare opportunity to enter the backside (hopefully) of a pandemic. Not since the Spanish influenza has the world experienced such a level of contagion. While we averted a worldwide crisis 20 years ago with the first SARS virus infection, SARS-CoV-2 with its unique ability to transmit easily among asymptomatic persons has altered our 21st-century appreciation and respect for viral diseases. From a scientific standpoint, we believe the scientific collaboration and innovation of the last 12 months have been unprecedented. The pandemic united rheumatologists and infectious disease physicians in an effort to develop both therapeutics and vaccines. While some of our patients appear to be partially protected with the currently available vaccines, we must continue our efforts at understanding optimal ways to manage Disease Modifying Anti-Rheumatic Drug (DMARD) therapy and vaccination in light of COVID-19. Providing a booster dose of vaccine to those with suboptimal vaccine responses, particularly those at greatest risk due to immune compromise, must urgently be pursued and evaluated.

In this themed issue of the *Annals of the Rheumatic Diseases*, focused on COVID-19 and SARS-CoV-2 vaccination in rheumatology, a number of papers have been assembled, which advance our understanding in this area and should allow for optimising the approach to this pandemic in the near future.[1–20] To date, our understanding of COVID-19 risk in rheumatology comes primarily from observational registry-based cohorts. A clear signal has emerged in that patients receiving B-cell depletion therapy or high-dose glucocorticoids at baseline are at higher risk of more severe COVID-19 outcomes if infected.[14] In addition, and most recently, the global alliance data suggest an increased risk for Janus kinase (JAK) inhibitors as well, although less statistically sophisticated analysis from inflammatory bowel disease registries does not suggest an increased risk for tofacitinib.[21] Similarly, the findings of these studies are affected by channelling bias/confounding by indication (eg, those with higher disease activity are more likely to be using these agents), and it is clear that many rheumatology patients who perceive themselves at higher risk are more likely to practise avoidance behaviour to minimise the risk of infection.[22] Despite the difficulty in controlling for these factors within these studies, there is strong biologic plausibility as to why these drug classes could diminish antiviral host defences. The development of a neutralising antibody response is clearly important in recovery from an initial infection and protection from subsequent infection.[23–25] Furthermore, interferon signalling is an essential host response to a number of viral infections, including SARS-CoV-2.[26]

THERAPEUTICS

The rheumatological therapeutic armamentarium took centre stage from the beginning of the pandemic, with an effort to repurpose existing drugs for both antiviral and anti-inflammatory purposes. Despite the 'Trumped-up' early results of hydroxychloroquine studies, randomised controlled trials (RCTs) provided no evidence of efficacy. Despite initial observational studies suggesting efficacy,[27] the eventual triumph of interleukin 6 inhibition after multiple negative RCTs was notable,[28] whereby a small magnitude of effect could only be 'significant' with an RCT of unusually large proportions. The Recovery trial enrolled >4000 hospitalised hypoxic patients with COVID-19 randomised to tocilizumab or standard of care and observed a decrease in mortality from 33% to 29% (corresponding to a number needed to treat of 25)[29]; this was consistent across other similar RCTs when subjected to meta-analysis (OR for survival, 0.83 (0.74–0.92)),[30] but taken as individual 'pivotal' clinical trials, these studies were deemed 'negative', lacking the statistical power to detect a relatively small magnitude of effect. The evolution of study end points and inclusion criteria across these studies is beyond the scope of this editorial, but suffice it to say, trials eventually settled on the prevention of severe disease (ie, a combined outcome of mechanical ventilation and death) as a primary outcome measure. To date, monoclonal antibodies provide our best antiviral approach (more below), and more recently, from a drug class of initial concern (JAK inhibition) in potentially diminishing host antiviral response, baricitinib has been shown to shorten time to clinical recovery when used with remdesivir and to reduce mortality when used in combination with dexamethasone.[31 32] In addition, tofacitinib was more recently shown to do much the same.[33] Thank you Rheumatologists for leading the way!

VACCINATION

While we lack well-defined 'immune correlates of protection', experimental studies in non-human primates suggest the importance of both cell-mediated and humoral vaccine responses. Use of monoclonal antibodies in infected naïve macaques was protective in dose-dependent fashion following infectious challenge. Antibodies limited both the risk of infection and the extent/length of disease among those infected. Regarding T-cell immunity, when comparing previously infected macaques, those that were experimentally depleted of CD8 + T lymphocytes (n=5) were easily reinfected on challenge compared with macaques with intact cell-mediated immunity (n=5) that did not develop infection.[34] These data lay the foundation for our observations in human RCTs of monoclonal antibody therapy against SARS-CoV-2—data from pivotal phase III vaccination studies, as well as observational studies of breakthrough infections among those previously vaccinated; taken together, these data inform strategies as to how to best to manage the rheumatology patient in this pandemic era.

We now have human data that recapitulate those from the experimental macaque studies. Prophylactic use of anti-SARS-CoV-2 monoclonal antibodies among uninfected humans shows the ability to prevent infection.[35] Furthermore, among those infected who have

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not yet mounted an antibody response, neutralising antibodies have proven able to prevent progression of infection from mild to severe disease.[35 36] The development of these antibodies started with high-dose products, but eventually proved that lower doses were equivalent in antiviral capacity. These data suggest that some threshold level is necessary to provide protection; however, this threshold remains undefined and might differ depending on whether cell-mediated immune responses are present. The data from phase III vaccine studies attest to a correlation of high vaccine efficacy with both robust humoral and T-cell responses.[37] Importantly, diminished efficacy against some variants correlates with in vitro reductions in vaccine-induced neutralising capacity against these variants.[38 39] Finally, while little published data exist on 'breakthrough' infections to date, early reports suggest immunocompromised patients are disproportionately affected. Up to 40% of a large cohort (n=152) of breakthrough infections in recipients of the Pfizer messenger RNA (mRNA) vaccine in Israel were immunocompromised, and B-cell depletion therapy was an important identified risk factor.[40]

To date, studies from rheumatic diseases, transplant, glomerular diseases and multiple sclerosis have consistently identified a large percentage of vaccinated individuals who have no measurable humoral responses after vaccination.[41] B-cell depletion therapy, mycophenolate, tacrolimus and high-dose corticosteroids have all been associated with a lack of seroconversion.[6 42 43] Interestingly, some data suggest that patients using rituximab still develop cell-mediated immunity despite a lack of humoral response.[44] Methotrexate has been shown to strongly diminish the development of cytotoxic CD8 + responses, documented to be important in SARS-CoV-2 protection at least among macaques.[8 34] There are data suggesting JAK inhibitors and tumour necrosis factor blockers also diminish responses, but to much lesser degrees.[42]

BOOST OR NOT TO BOOST

As we write, the American College of Immunisation Practices is meeting to consider this very issue. The demonstrable efficacy of exogenous monoclonal antibodies clearly speaks to the importance of protective neutralising antibody responses so that, in our mind, patients with an undetectable antibody response after vaccination will not likely have the same protection as those with positive titres. While the level of sufficient or 'protective' titre is unknown, it is hard to believe that an absence of titre does not equate to diminished protection, even if vaccine-induced cell-mediated immune responses are developed. Accordingly, for those individuals receiving B-cell depletion and other therapies strongly associated with a lack of seroconversion, it seems reasonable to evaluate postvaccination titres, recognising such serological assessments are not necessary for otherwise healthy individuals. It is also important to recognise that there is wide variability in the reliability of existing licensed assessments. If antibodies are absent, however, then a booster dose of vaccine will increase the likelihood of their development and ultimately might increase protection.[45] For all other DMARD recipients, while levels of postvaccination titres might be somewhat diminished, it is unclear whether this is problematic and whether a booster of vaccine would be required or even helpful. In fact, the first study in immunosuppressed non-responders to mRNA vaccination has been completed, in which a randomised comparison of inducible humoral and cellular immune answers to a third booster vaccination with mRNA vaccine versus single switch boost using a vector vaccine was done, and results are awaited eagerly (clinical trial registration number: 2021-002348-57). In the meantime, our patients who are likely to develop inadequate vaccine responses should live like it was 2020, with masking and avoidance in mind, and sceptics need to be reminded the greatest risk of inadequate immune response occurs with a failure to get vaccinated! We should continue to pursue studies to evaluate the effect of holding certain DMARDs to determine whether this assists with the building or maintenance of vaccine-induced immune responses associated with both primary and booster immunisations alike. Finally, we should reassure our patients that the vaccines in use are safe, not associated with underlying disease flare to date and much more enjoyable to receive than COVID-19 itself.[7 11 14 15 46]

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Call for emergency action to limit global temperature increases, restore biodiversity and protect health

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Wealthy nations must do much more, much faster.

The United Nations General Assembly in September 2021 will bring countries together at a critical time for marshalling collective action to tackle the global environmental crisis. They will meet again at the biodiversity summit in Kunming, China, and the climate conference (Conference of the Parties (COP)26) in Glasgow, UK. Ahead of these pivotal meetings, we—the editors of health journals worldwide—call for urgent action to keep average global temperature increases below 1.5°C, halt the destruction of nature and protect health.

Health is already being harmed by global temperature increases and the destruction of the natural world, a state of affairs health professionals have been bringing attention to for decades.[1] The science is unequivocal; a global increase of 1.5°C above the preindustrial average and the continued loss of biodiversity risk catastrophic harm to health that will be impossible to reverse.[2 3] Despite the world's necessary preoccupation with COVID-19, we cannot wait for the pandemic to pass to rapidly reduce emissions.

Reflecting the severity of the moment, this editorial appears in health journals across the world. We are united in recognising that only fundamental and equitable changes to societies will reverse our current trajectory.

The risks to health of increases above 1.5°C are now well established.[2] Indeed, no temperature rise is 'safe'. In the past 20 years, heat-related mortality among people aged over 65 has increased by more than 50%.[4] Higher temperatures have brought increased dehydration and renal function loss, dermatological malignancies, tropical infections, adverse mental health outcomes, pregnancy complications, allergies, and cardiovascular and pulmonary morbidity and mortality.[5 6] Harms disproportionately affect the most vulnerable, including children, older populations, ethnic minorities, poorer communities and those with underlying health problems.[2 4]

Global heating is also contributing to the decline in global yield potential for major crops, falling by 1.8%–5.6% since 1981; this, together with the effects of extreme weather and soil depletion, is hampering efforts to reduce undernutrition.[4] Thriving ecosystems are essential to human health, and the widespread destruction of nature, including habitats and species, is eroding water and food security and increasing the chance of pandemics.[3 7 8]

The consequences of the environmental crisis fall disproportionately on those countries and communities that have contributed least to the problem and are least able to mitigate the harms. Yet no country, no matter how wealthy, can shield itself from these impacts. Allowing the consequences to fall disproportionately on the most vulnerable will breed more conflict, food insecurity, forced displacement and zoonotic disease, with severe implications for all countries and communities. As with the COVID-19 pandemic, we are globally as strong as our weakest member.

Rises above 1.5°C increase the chance of reaching tipping points in natural systems that could lock the world into an acutely unstable state. This would critically impair our ability to mitigate harms and to prevent catastrophic, runaway environmental change.[9 10]

GLOBAL TARGETS ARE NOT ENOUGH

Encouragingly, many governments, financial institutions and businesses are setting targets to reach net-zero emissions, including targets for 2030. The cost of renewable energy is dropping rapidly. Many countries are aiming to protect at least 30% of the world's land and oceans by 2030.[11]

These promises are not enough. Targets are easy to set and hard to achieve. They are yet to be matched with credible short-term and longer-term plans to accelerate cleaner technologies and transform societies. Emissions reduction plans do not adequately incorporate health considerations.[12] Concern is growing that temperature rises above 1.5°C are beginning to be seen as inevitable, or even acceptable, to powerful members of the global community.[13] Relatedly, current strategies for reducing emissions to net zero by the middle of the century implausibly assume that the world will acquire great capabilities to remove greenhouse gases from the atmosphere.[14 15]

This insufficient action means that temperature increases are likely to be well in excess of 2°C,[16] a catastrophic outcome for health and environmental stability. Critically, the destruction of nature does not have parity of esteem with the climate element of the crisis, and every single global target to restore biodiversity loss by 2020 was missed.[17] This is an overall environmental crisis.[18]

Health professionals are united with environmental scientists, businesses and many others in rejecting that this outcome is inevitable. More can and must be done now—in Glasgow and Kunming—and in the immediate years that follow. We join health professionals worldwide who have already supported calls for rapid action.[1 19]

Equity must be at the centre of the global response. Contributing a fair share

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[2]Journal of Health, Population and Nutrition, Baltimore, Maryland, USA
[3]Danish Medical Journal, Copenhagen, Denmark
[4]PLOS Medicine, Cambridge, UK
[5]The BMJ, London, UK
[6]British Dental Journal, London, UK
[7]The Lancet, London, UK
[8]UK Health Alliance on Climate Change, London, UK
[9]Revista de Saúde Pública, São Paulo, Brazil
[10]International Journal of Nursing Studies, London, UK
[11]CMAJ, Ottawa, Ontario, Canada
[12]Pharmaceutical Journal, London, UK
[13]Dutch Journal of Medicine, Nijmegen, The Netherlands
[14]NEJM, Boston, Massachusetts, USA
[15]National Medical Journal of India, New Delhi, India
[16]Medical Journal of Australia, Newcastle, New South Wales, Australia
[17]International Nursing Review, Geneva, Switzerland
[18]Pan American Journal of Public Health, Washington, DC, USA

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to the global effort means that reduction commitments must account for the cumulative, historical contribution each country has made to emissions, as well as its current emissions and capacity to respond. Wealthier countries will have to cut emissions more quickly, making reductions by 2030 beyond those currently proposed[20 21] and reaching net-zero emissions before 2050. Similar targets and emergency action are needed for biodiversity loss and the wider destruction of the natural world.

To achieve these targets, governments must make fundamental changes to how our societies and economies are organised and how we live. The current strategy of encouraging markets to swap dirty for cleaner technologies is not enough. Governments must intervene to support the redesign of transport systems, cities, production and distribution of food, markets for financial investments, health systems, and much more. Global coordination is needed to ensure that the rush for cleaner technologies does not come at the cost of more environmental destruction and human exploitation.

Many governments met the threat of the COVID-19 pandemic with unprecedented funding. The environmental crisis demands a similar emergency response. Huge investment will be needed, beyond what is being considered or delivered anywhere in the world. But such investments will produce huge positive health and economic outcomes. These include high-quality jobs, reduced air pollution, increased physical activity, and improved housing and diet. Better air quality alone would realise health benefits that easily offset the global costs of emissions reductions.[22]

These measures will also improve the social and economic determinants of health, the poor state of which may have made populations more vulnerable to the COVID-19 pandemic.[23] But the changes cannot be achieved through a return to damaging austerity policies or the continuation of the large inequalities of wealth and power within and between countries.

COOPERATION HINGES ON WEALTHY NATIONS DOING MORE

In particular, countries that have disproportionately created the environmental crisis must do more to support low-income and middle-income countries to build cleaner, healthier and more resilient societies. High-income countries must meet and go beyond their outstanding commitment to provide $100 billion a year, making up for any shortfall in 2020 and increasing contributions to and beyond 2025. Funding must be equally split between mitigation and adaptation, including improving the resilience of health systems.

Financing should be through grants rather than loans, building local capabilities and truly empowering communities, and should come alongside forgiving large debts, which constrain the agency of so many low-income countries. Additional funding must be marshalled to compensate for inevitable loss and damage caused by the consequences of the environmental crisis.

As health professionals, we must do all we can to aid the transition to a sustainable, fairer, resilient and healthier world. Alongside acting to reduce the harm from the environmental crisis, we should proactively contribute to global prevention of further damage and action on the root causes of the crisis. We must hold global leaders to account and continue to educate others about the health risks of the crisis. We must join in the work to achieve environmentally sustainable health systems before 2040, recognising that this will mean changing clinical practice. Health institutions have already divested more than $42 billion of assets from fossil fuels; others should join them.[4]

The greatest threat to global public health is the continued failure of world leaders to keep the global temperature rise below 1.5°C and to restore nature. Urgent, society-wide changes must be made and will lead to a fairer and healthier world. We, as editors of health journals, call for governments and other leaders to act, marking 2021 as the year that the world finally changes course.

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Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases

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ABSTRACT

Patients with rheumatic diseases are at increased risk of infectious complications; vaccinations are a critical component of their care. Disease-modifying antirheumatic drugs may reduce the immunogenicity of common vaccines. We will review here available data regarding the effect of these medications on influenza, pneumococcal, herpes zoster, SARS-CoV-2, hepatitis B, human papilloma virus and yellow fever vaccines. Rituximab has the most substantial impact on vaccine immunogenicity, which is most profound when vaccinations are given at shorter intervals after rituximab dosing. Methotrexate has less substantial effect but appears to adversely impact most vaccine immunogenicity. Abatacept likely decrease vaccine immunogenicity, although these studies are limited by the lack of adequate control groups. Janus kinase and tumour necrosis factor inhibitors decrease absolute antibody titres for many vaccines, but do not seem to significantly impact the proportions of patients achieving seroprotection. Other biologics (interleukin-6R (IL-6R), IL-12/IL-23 and IL-17 inhibitors) have little observed impact on vaccine immunogenicity. Data regarding the effect of these medications on the SARS-CoV-2 vaccine immunogenicity are just now emerging, and early glimpses appear similar to our experience with other vaccines. In this review, we summarise the most recent data regarding vaccine response and efficacy in this setting, particularly in light of current vaccination recommendations for immunocompromised patients.

INTRODUCTION

Patients with inflammatory rheumatic diseases are at increased risk of vaccine-preventable infectious diseases.[1–6] Vaccinations reduce the risks of infectious complications in patients with rheumatic disease,[7 8] yet are under utilised.[9 10] While vaccinations are critically important, the drugs used to treat inflammatory diseases may impair responses to vaccines. This review addresses available data regarding the effect of disease-modifying anti-rheumatic drugs (DMARDs) on vaccine immunogenicity (table 1) and summarises vaccination recommendations made for this population (table 2).

Vaccine immunogenicity is typically measured as a surrogate for clinical vaccine efficacy. Interpreting and harmonising results from studies of vaccine immunogenicity are complicated by several factors. First, the arsenal of DMARD therapy is rapidly expanding with new drug classes and more drugs within each class, and these may have subtle yet important differences (eg, differences in Janus kinase (JAK)-inhibitor targets and JAK selectivity.) Second, recommended vaccines continue to change; pneumococcal and influenza vaccines frequently change, and we now have multiple critically important SARS-CoV-2 vaccines. Lastly, outcome measures (timing of response measurement, how response is measured, definitions of response[11]) and study design (control groups, concomitant methotrexate (MTX) or low-dose glucocorticoid therapy) are inconsistent across studies, making it difficult to parse out the true impact of the drug on vaccine immunogenicity or efficacy.

We will summarise here the available data evaluating the effect of DMARDs on vaccine immunogenicity, as well as to summarise current recommendations for how and when to vaccinate patients with rheumatic disease on DMARD therapy. While all vaccines are potentially important, we will focus on influenza, pneumococcus, herpes zoster, hepatitis B virus (HBV), tetanus, human papilloma virus (HPV) and yellow fever (YF) vaccines, as well as the newly emerging data for the SARS-CoV-2 vaccines (table 1). We will additionally review safety data regarding live vaccines (herpes zoster and YF) and newer highly immunogenic recombinant herpes zoster and SARS-CoV-2 vaccines.

INFLUENZA VACCINATION

Background

Intramuscular influenza vaccines are available as trivalent vaccines containing two strains of influenza A and one strain of influenza B, and quadrivalent vaccines, which contain an additional B strain.[12 13] Two quadrivalent vaccines are currently recommended for adults age ≥65—a high-dose quadrivalent vaccine (Fluzone High-Dose) and an adjuvanted quadrivalent vaccine (Fluad Quadrivalent).[12 13] The live attenuated intranasal influenza vaccine is contraindicated in patients taking biologics or other immunomodulatory therapies (eg, JAK inhibitors). Influenza vaccine efficacy is estimated using a surrogate of haemagglutinin inhibition titres. A titre of 1:40 is considered 'seroprotected' (as defined as 50% vaccine efficacy).

Effect of DMARD therapy of vaccine efficacy

Rituximab[14–21] and MTX[14 22 23] reduce influenza vaccine immunogenicity. Abatacept likely impairs immunogenicity though data are limited.[24–26] Post-vaccination antibody titres are lower in patients on tumour necrosis factor (TNF)[14 20 27–29] and JAK inhibitors,[30] although the proportion of patients achieving seroprotection is similar to patients with

Table 1 Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity

	Influenza	Pneumococcal	Herpes zoster	Hepatitis B	Human papilloma virus	Tetanus	SARS-CoV-2 (mRNA)
Methotrexate	↓[14 22 24]	↓[50 51]	OK (ZVL)[52]		OK[117 132 133]	↓[121]	↓[82 84 85]
TNF inhibitors	OK[14 16 20 27 28]	OK[14 56]	OK (ZVL)[64]	↓[103–105]	OK[117 132]	OK[121 124]*	OK[84 85 88]
Rituximab	↓↓[14–17 19–21 24 134]	↓↓[14 18 45–47]				↓[18 121]	↓↓[81–84]
Abatacept	↓[24 26]	↓[45 46]				OK (SQ)[122] ↓(IV)[123]	↓[84]
JAK inhibitor	OK[30]	↓[30]				OK (tofacitinib)[120] ↓(baricitinib)[53]	↓[82 84]
IL-6R inhibitor	OK[31]	OK[31]				OK[125]	OK[84]
IL-12/IL-23 inhibitor	OK[32]	OK[54]		↓[105]		OK[54]	OK[82]
IL-17 inhibitor	OK[33–35]	OK[55]				OK[55]	OK[84]

OK indicates no significant/meaningful effect on vaccine immunogenicity (may include reduction in absolute postvaccination titres if rates of protective titres are unchanged.) ↓ reduces vaccine immunogenicity. ↓↓ significantly reduces vaccine immunogenicity. For OK, ↓ and ↓↓ if no control group is available, data are compared with expected vaccine responses in the general population. Empty cells indicate lack of data.
IL, interleukin; JAK, Janus kinase; RZV, recombinant zoster vaccine; SQ, subcutaneous; TNF, tumour necrosis factor; ZVL, zoster vaccine live.

rheumatic disease not treated with these medications. Interleukin (IL)-6, IL-12/IL-23 and IL-17 inhibitors do not appear to impact the influenza vaccine[31–35] (table 1).

Influenza vaccination responses may be improved for rituximab[16 21] and MTX[22 23] treated patients by optimally timing the drug and vaccine. Timing the influenza vaccine 6–10 months after rituximab yielded modestly better results than 4–8 weeks after rituximab (5/12 vs 1/11 patients achieved seroprotection, p=0.108).[21] In a randomised controlled trial, 316 patients with rheumatoid arthritis (RA) were randomised to take continuous MTX or to hold MTX for 2 weeks after influenza vaccine. Those who held MTX had higher rates of satisfactory vaccine response (75.5% vs 54.5%, p<0.001); however, lower doses of MTX ≤7.5 mg/week did not show a significant improvement with MTX dose interruption.[23] Post-hoc analyses found that MTX reduced vaccine response only in patients with high B cell activating factor (BAFF) levels, raising questions about whether these results are generalisable to all patients or only a subset with elevated BAFF (which is not routinely evaluated).[36]

Abatacept likely impairs influenza vaccine immunogenicity, though data are limited.[24–26] Two studies of the pandemic 2009 influenza A/H1N1 vaccine found that patients on abatacept had a substantially lower rate of seroconversion; in one study this rate was as low as 9% compared with 69% of controls (p=0.001).[24 26] However, an uncontrolled study of the trivalent 2011–2012 seasonal influenza vaccine found that 81.2% of patients on subcutaneous abatacept were able to mount protective antibody titres,[25] which is only modestly reduced compared with general population rates (89%–97% for each influenza strain).[37]

Low-dose glucocorticoid use has not been shown to impact influenza vaccine response when added to other DMARD therapy. In a study of infliximab and influenza vaccine response, concomitant low-dose glucocorticoids (mean doses 5–10 mg/day) were not found to impact influenza vaccine response.[38] Similarly, low-dose prednisone (mean 8 mg/day) in RA did not adversely affect influenza vaccine response in a multivariant regression analysis when evaluated alongside other DMARD therapy.[27]

Recommendations

Routine yearly influenza vaccines are recommended for all people aged 6 months or older.[12 39] The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) both recommend yearly intramuscular influenza vaccinations for all patients with RA.[40 41]

High-dose influenza vaccines may be more effective in patients with rheumatic disease,[42–44] although at this time the high-dose vaccine is recommended only for adults aged ≥65.[12] A randomised study of 279 patients with RA found that those receiving the high-dose influenza vaccine were more likely to seroconvert (OR: 2.99, 95% CI: 1.46 to 6.11); this effect was similar in patients on synthetic and biologic DMARDs.[42]

Rituximab-treated patients should ideally receive the influenza vaccine before initiating rituximab, or as long after the last dose of rituximab and 2–4 weeks before the next dose,[41] as compatible with the influenza season. However, when this timing is not compatible with the influenza season, patients on rituximab may still be able to mount a T-cell response to the vaccination (although it is not known whether T-cell responses correlate with influenza protection).[17] Patients on MTX can improve influenza vaccination responses by holding MTX for 2 weeks after vaccination, particularly for those on ≥15 mg/week; holding MTX did not appear to increase disease activity measures, although this group had a small increase in the rate of flares (5.1% vs 10.6%, p=0.07).[22 23]

PNEUMOCOCCAL VACCINATION

Background

Two pneumococcal vaccines are commonly used, pneumococcal conjugate vaccine 13-valent (PCV13) and pneumococcal polysaccharide vaccine 23-valent (PPSV23). PCV13 is conjugated to a diphtheria protein and is more immunogenic than the polysaccharide vaccine. Both PCV13 and PPSV23 vaccine immunogenicity is typically measured by postvaccination antibody titres against serotypes found in each vaccine, although the titre level chosen as 'protective' can be variable and is arbitrary, as no level of 'seroprotection' against most pneumococcal disease has been established.[11]

Effect of DMARD therapy on vaccine efficacy

As with most vaccines in the rheumatologic setting, studies have not been large enough to evaluate changes in efficacy related to DMARD usage. Immunogenicity outcomes are achievable in such studies, and it is clear that rituximab[14 18 45–47] and MTX[11 14 48–51] reduce pneumococcal vaccine immunogenicity. JAK inhibitors[30 52 53] and abatacept[25 45 46] appear to modestly

Table 2 Vaccination schedule recommendations for patients with rheumatic diseases

	Vaccination recommendation	Recommended modification of DMARD therapy relative to vaccine timing based on guidelines and best available evidence*, as compatible with disease activity
Influenza	Yearly quadrivalent vaccination for all patients.†‡§ Patients older than 65 should receive the high-dose quadrivalent vaccine.† May consider high-dose vaccine for all immunocompromised patients.*[42 44]	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose.§ MTX: consider holding for 2 weeks after vaccination.*[22 23]
Pneumococcal	Recommended for all immunosuppressed patients.†‡§ Give one dose of PCV13 followed by PPSV23 at least 8 weeks later. Give a second PPSV23 dose 5 years after the first PPSV23 dose.†	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose.§ MTX: consider holding MTX for 2 weeks after vaccination.*
Herpes zoster	Recombinant zoster vaccine for adults over age 50.†¶ Use live Zoster vaccine where recombinant is not available. Consider in all high-risk patients with rheumatic disease.†§	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose.*
Hepatitis B	All non-immune adults at risk for HBV infection.†‡§**	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose.§
Human papilloma virus	As per general population guidelines, especially for patients with SLE.§‡	Rituximab: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose.§
Tetanus	As per general population and consider for all rituximab-treated patients.§	Rituximab: vaccinate before starting rituximab.§
Yellow fever	Avoid for immunocompromised patients.†§	N/A, contraindicated
SARS-CoV-2	All patients as per the general population.[101]	ACR guidance summary[101]: Rituximab: as long as possible after the last dose, 2–4 weeks before the next dose. MTX: hold for 1 week after each mRNA dose; hold for 2 weeks after single-dose vaccine. Mycophenolate mofetil and JAK inhibitors: hold for 1 week after each vaccine dose. Abatacept subcutaneous: hold 1 week before and 1 week after the first vaccine dose, no interruption for the second vaccine dose. Abatacept intravenous: time the first vaccine dose 4 weeks after abatacept and postpone next infusion by 1 week; no adjustment for the second vaccine dose Cyclophosphamide: time cyclophosphamide 1 week after each vaccine dose. TNF, IL-6R, IL-1, IL-17, IL-12/23, IL-23, oral calcineurin inhibitors, belimumab††, azathioprine, sulfasalazine, leflunomide, hydroxychloroquine, apremilast, intravenous immune globulin (IVIG) and glucocorticoids <20 mg/day††: no modification.

*Authors' recommendations based on best available evidence.
†2021 Advisory Committee on Immunisation Practices recommendations.[12]
‡2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis.[40]
§2019 European League Against Rheumatism recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases.[41]
¶Per CDC guidelines, adults with immunocompromising conditions were not included in initial clinical trials and therefore no recommendations regarding vaccination age for this population was made. However, this may change in the future.
**Risk factors include: persons at risk through sexual exposure (sex partners of hepatitis B surface antigen positive persons, sexually active persons not in a long-term monogamous relationship, persons seeking evaluation or treatment for a sexually transmitted disease, men who have sex with men), persons with a history of current or recent injection drug use, persons at risk for infection by percutaneous or mucosal exposure to blood (household contact or sexual partner who is hepatitis B surface antigen positive, resident or staff of a facility for the developmentally disabled, healthcare or public safety workers with anticipated risk for exposure to body fluids, patients with end-stage renal disease, persons with diabetes mellitus aged <60 or those over age 60 at the discretion of the treating physicians), travellers to endemic areas, patients with chronic liver disease or hepatitis C infection, incarcerated persons and patients with HIV.
††Data published since guideline development suggests that lower doses of prednisone and belimumab may adversely impact the SARS-CoV-2 mRNA vaccine immunogenicity.[84]
ACR, American College of Rheumatology; CDC, Center for Disease Control; DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; PCV13, pneumococcal conjugate vaccine 13-valent; PPSV23, pneumococcal polysaccharide vaccine 23-valent; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

reduce immunogenicity, while other biologics (TNF, IL-6, IL-12/IL-23 and IL-17 inhibitors) do not impair vaccine immunogenicity.[14 31 54–56]

A meta-analysis reported that rituximab-treated patients had a pooled OR for non-seroconversion (inability to mount a twofold increase in antibody concentrations postvaccination) ranging from 4.91 (95% CI: 2.32 to 10.40) to 13.06 (95% CI: 2.39 to 71.34) depending on the pneumococcal serotype.[11] The effect of MTX is less than that of rituximab; pooled ORs for non-seroconversion ranged from 2.0 (95% CI: 1.06 to 3.77) to 5.41 (95% CI: 2.09 to 13.98) depending on the serotype.[11]

Interpretation of data from abatacept studies is complicated by concomitant MTX and/or a lack of controls. In one uncontrolled study of patients on subcutaneous abatacept (most of whom were also on MTX) vaccinated with PPSV23, 34 (74%)/46 patients developed protective antibody titres, consistent with expected response.[25] However, another study of 17 patients on intravenous abatacept vaccinated with PCV7 (13 of whom were receiving concomitant MTX) found a lower likelihood of a greater than equal to twofold increase in postvaccination antibody titre compared with patients on tocilizumab or controls.[45] Lastly, in a pneumococcal booster study, the booster

strategy improved antibody response in 23 abatacept-treated patients (half of whom were on MTX); however the antibody response was lower than in healthy controls.[46]

JAK inhibitors appear to have a modest impact on the rate of satisfactory responses to pneumococcal vaccinations (defined as a greater than equal to twofold increase in antibody concentrations in ≥6 serotypes), at least to PPSV23 where there is comparative data published.[30 53] A placebo-controlled study of patients with RA vaccinated after 4 weeks of tofacitinib or placebo found that those on tofacitinib were less likely to develop a satisfactory antibody response compared with placebo (45.1% vs 68.4%, −23% difference (95% CI: −36.6% to −9.6%)), particularly if they were also on MTX (31.6%).[30] Temporary interruption in tofacitinib for 1 week prevaccination and 1 week postvaccination modestly improved PPSV23 response when compared with continuous tofacitinib, but this did not reach significance (84.6% vs 75.0%, −9.6% difference (95% CI: −24.0% to 4.7%)).[30] A final uncontrolled study of 106 baricitinib-treated patients (89% of whom were also on MTX) vaccinated with PCV13 found that approximately two-third of patients received a satisfactory antibody response[53]; these proportions were similar to another study evaluating PCV13 responses in healthy controls and patients with RA not using DMARDs.[50]

Low-dose glucocorticoids taken concomitantly with other DMARD therapy have not been found to impact pneumococcal vaccine responses,[53 57 58] while high-dose glucocorticoids may adversely impact pneumococcal vaccine immunogenicity.[59] Among patients with inflammatory diseases vaccinated with the PPSV23, 57% of non-responders were taking prednisone >20 mg/day compared with 22% of vaccine responders (p=0.07).[59] In an uncontrolled baricitinib study where approximately 30% of participants were taking concomitant low-dose corticosteroids (mean dose: 6.2 mg/day), PCV13 response rates were similar in those taking corticosteroids versus those not taking corticosteroids (71% (95% CI: 53.4% to 83.9%) vs 67% (95% CI: 55.2% to 76.5%)).[53] Similarly, in a study of patients on MTX with or without infliximab, concomitant low-dose glucocorticoids (prednisone equivalent <10 mg/day) did not adversely impact vaccine response.[58]

Recommendations

The EULAR, ACR and CDC all recommend pneumococcal vaccinations for patients with rheumatic disease taking DMARD therapy.[40 60 61] Patients should receive a dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 vaccine should be given 5 years after the first one. PCV13 followed by a booster of PPSV23 improves pneumococcal antibody responses for patients on conventional synthetic DMARDs and partially improves responses for patients on abatacept but may not improve vaccine response for those on rituximab.[46]

Patients should be given their first dose of a pneumococcal vaccine ideally before starting DMARD therapy. Patients on rituximab should receive the required vaccine dose at least 2 weeks before their next dose of rituximab is due. Although extrapolating from influenza studies and observational data raises the idea that holding MTX at the time of vaccination could improve pneumococcal vaccine response, this idea has yet to be studied.

HERPES ZOSTER VACCINATION

Background

There are two approved herpes zoster vaccines—the recombinant zoster vaccine (RZV) (Shingrix) and the live zoster vaccine (ZVL) (Zostavax). In non-head-to-head studies in the general population, the RZV appears more effective such that the ZVL is no longer marketed in the USA, although it is still used in many parts of the world.[62] Response to zoster vaccine is measured by a humoral varicella zoster virus IgG and/or cell-mediated varicella zoster virus-specific T-cell enumeration. Although both measures correlated with vaccine efficacy, cell-mediated responses correlate more strongly with the risk of future shingles.[63]

Effect of DMARD therapy on vaccine efficacy

Few studies have evaluated the immunogenicity of zoster vaccines in patients with rheumatic disease.

Hundred and twelve patients with RA on MTX were vaccinated with the ZVL and then randomised to start tofacitinib or placebo 2–3 weeks postvaccination. Patients in both groups had similar postvaccine responses.[52] In this study, approximately 40% of patients treated with placebo and 47% of patients treated with tofacitinib were taking concomitant glucocorticoids (mean dose: 7.1 and 5.9 mg/day prednisone or equivalent, respectively). ZVL vaccine responses were similar in those taking glucocorticoids and those not taking glucocorticoids.[52] TNF inhibitor-treated patients vaccinated with the ZVL developed 30% increases in humoral and cell-mediated responses relative to a placebo vaccine, which are about half the response observed in initial pivotal trials among healthy subjects.[64] Zoster vaccines have not been studied in patients with rheumatic disease on rituximab, however, among patients with haematologic malignancies on anti-CD20 therapies (alone or in combination with other chemotherapies), 4 doses of the RZV produced significant T-cell responses.[65] Zoster vaccine immunogenicity data for patients currently taking JAK inhibitors, abatacept and other biologics have not been reported.

Safety in patients with rheumatic diseases

While the ZVL vaccine is contraindicated in immunocompromised patients, given the theoretical concern of potential local or disseminated vaccine-strain varicella with vaccination, available data suggest it is safer than initially thought. In the study of MTX and tofacitinib above, there was one case of cutaneous vaccine dissemination in a patient on MTX randomised to start tofacitinib, however, this patient lacked primary immunity to varicella (ie, they did not have chickenpox as a child) and were not a candidate for the live vaccine.[52] Among 633 United States Medicare patients inadvertently vaccinated while on biologics, no cases of shingles occurred in the 6 weeks postvaccination.[10] Six hundred patients on TNF inhibitors (with or without MTX and prednisone) randomised 1:1 to receive the ZVL versus placebo and found no cases of varicella infection or zoster within the subsequent 42-day risk period of highest interest.[64] These data suggest that the ZVL may be given safely to those using TNF inhibitors with/without MTX and/or prednisone if the RZV is not available.

The recombinant vaccine is not live and is likely safe in patients with rheumatic diseases, however, phase III clinical trials excluded patients on immunosuppressive therapy. There has been theoretical concern that the adjuvant in the RZV may cause a flare of underlying inflammatory disease. The first retrospective review of 403 patients with rheumatic disease vaccinated with the RZV found a 7% incidence of disease flare within 12 weeks of receiving a vaccine dose; this incidence was considered to be similar to expected rates from clinical trials.[66] However, a second retrospective review of 359 patients with rheumatic diseases found that 16% had a flare of their disease within 12

weeks of receiving a vaccine dose.[67] The differences in these results may be related to a difference in flare definition, however neither was prospective or controlled. A post-hoc analysis of clinical trials (NCT01165177 and NCT01165229) pooled data from nearly 2000 patients (approximately half received vaccine) with self-reported inflammatory disease who were not treated with DMARDs. This analysis found similar high rates of vaccine efficacy and no new safety concerns, however, it is likely that these self-reported individuals had either mild or no disease given their lack of DMARD therapy.[68] Future prospective, controlled studies are necessary to adequately evaluate safety and efficacy of this vaccine in the rheumatology setting.

Recommendations

The CDC recommends the RZV for all patients aged 50 and above.[12] The European Medicines Agency recently approved the RZV for adults over age 18 with immunocompromising conditions,[69] however, very little data exist in this age group and guidelines are not yet available for the use of this vaccine in patients with rheumatic diseases. The ACR recommends use of the ZVL for patients with RA over age 50,[40] and EULAR recommends zoster vaccination in high-risk patients,[41] however, neither of these guidelines address the newer RZV. Given that immunocompromised patients with rheumatic diseases are at increased risk of zoster,[6 70] future guidelines may be expanded to recommend the RZV for high-risk patients at a younger age (eg, 18 and older).

SARS-COV-2 VACCINATION

Background

A growing number of SARS-CoV-2 vaccines are in use worldwide, including mRNA, adenoviral vector, protein subunit and inactivated virus vaccines.[71] We will focus our discussion on two mRNA vaccines and two adenoviral vector vaccines, which have been most widely studied in patients with rheumatic diseases. In phase III trials, the BNT162b2 (Pfizer/BioNTech) mRNA vaccine was 95% effective (95% CI: 90.3% to 97.6%)[72] and the mRNA01273 (Moderna) vaccine was 94.1% effective (95% CI: 89.3% to 96.8%)[73] in preventing symptomatic COVID-19 infection following the second dose. Phase III trials found the Ad26.COV2.S (Janssen/Johnson & Johnson) single-dose vaccine to be 66.9% effective (95% CI: 59.0% to 73.4%)[74] and the ChAdOx1 nCoV-19/AZD1222 (University of Oxford/AstraZeneca/Serum Institute of India) vaccine to be 70.4% effective (95% CI: 54.8% to 80.6) following the second dose.[75]

SARS-CoV-2 vaccine immunogenicity can be measured by humoral IgG to spike protein (not nucleocapsid protein) or cellular T-cell reactivity via interferon (IFN)-γ response to SARS-CoV-2 peptide. Antibody responses are reported as 'seroconversion' (newly positive antispike protein IgG), or by postvaccination antibody titres. The role of T-cell responses to SARS-CoV-2 vaccines are not fully understood, however emerging evidence suggests that T-cell responses may confer protection[76 77] even in the absence of humoral response.[78 79] However, we do not yet know how immunogenicity cut-offs correlate with efficacy, whether reduced absolute titres may still be adequate titres, or whether immune responses wane over time, making SARS-CoV-2 immunogenicity studies difficult to fully interpret.

Effect of DMARD therapy on SARS-CoV-2 vaccine efficacy

Early data in this setting are largely consistent with that from other vaccine studies. Data suggest that rituximab,[80–84] glucocorticoids,[82 84] MTX,[82 84 85] abatacept,[84] mycophenolate mofetil[84] and JAK inhibitors[82] impair SARS-CoV-2 vaccine responses in many patients. The mRNA vaccine mechanism and potential impact of DMARD therapy is described in figure 1.

The largest observational study to date evaluated the BNT162b2 (Pfizer/BioNTech) mRNA vaccine in 686 patients with rheumatic diseases. Compared with controls where 100% seroconverted to vaccination (ie, newly positive anti-spike IgG), seroconversion rates were significantly lower for patients on rituximab (39% seroconverted, p<0.0001), mycophenolate mofetil (64% seroconverted, p<0.0001), abatacept (71% seroconverted, p<0.0001), JAK inhibitors (90% seroconverted, p=0.02), MTX (92% seroconverted, p=0.02) and glucocorticoids (mean dose: 6.7 mg/day, 77% seroconverted, p<0.0001), while other DMARDs (leflunomide, hydroxychloroquine, TNF, IL-6 and IL-17-inhibitors) did not significantly impact seroconversion.[84] A logistic regression further identified anti-CD20 therapy (adjusted OR: 0.13, p<0.001), glucocorticoids (adjusted OR: 0.48, p=0.02), abatacept (adjusted OR: 0.14, p<0.001) and mycophenolate mofetil (adjusted OR: 0.1, p=0.0013) as independent predictors of a poor vaccine response.[84] Another prospective study of 133 patients with immune-mediated inflammatory diseases on various DMARD therapies and 53 controls vaccinated with mRNA vaccines found that rituximab significantly reduced mRNA vaccine immunogenicity, JAK inhibitors and MTX moderately reduced antibody titres, and other therapies (TNF, IL-12/IL-23 and integrin inhibitors) had a modest impact on antibody formation.[82]

Risk factors for a poor humoral response on rituximab include a shorter duration between rituximab dose and vaccine, and lack of B-cell reconstitution.[81 86] Rituximab-treated patients vaccinated 6 months after their last rituximab dose had a seropositivity rate around 20%, and those vaccinated 1 year after the last rituximab dose had rates around 50%.[84] Despite a reduced humoral response, early data suggest that rituximab-treated patients may still mount a normal cellular vaccine response, such that the net impact on clinical protection is not clear.[86]

MTX appears to reduce some aspects of the SARS-CoV-2 vaccine response.[82 84 85] In a New York cohort of patients with immune-mediated inflammatory disease, 72% of MTX-treated patients had adequate humoral antibody titres (defined as IgG to spike protein >5000 units) compared with 92.3% of patients with rheumatic disease not on MTX and 96.1% of healthy controls (p=0.023).[85] Patients on MTX also had reduced activated CD8 + T-cell response but a preserved CD4 + T-cell response.[85] In the Furer *et al* cohort of 176 MTX-treated patients, 84% of all MTX-treated patients and 92% of patients on MTX-monotherapy seroconverted, compared with 100% of controls (p<0.05).[84]

TNF inhibitors appear to reduce SARS-CoV-2 postvaccination titres,[82 87 88] but do not seem to substantially impact rates of seroconversion[83 84 87 88]—although antibody cut-offs for seroprotection are not defined. Among 865 infliximab-treated patients with inflammatory bowel disease given a single vaccine dose of the BNT162b2 mRNA vaccine or the ChAdOx1 nCoV-19 adenoviral vaccine had lower antibody concentrations and seroconversion rates compared with those on vedolizumab.[88] However, in the 27 patients who were studied after a second vaccine dose of the mRNA vaccine, there was no difference in the rate of seroconversion (85% vs 86%, p=0.68).[88] Similarly, in the Furer *et al* cohort, 172

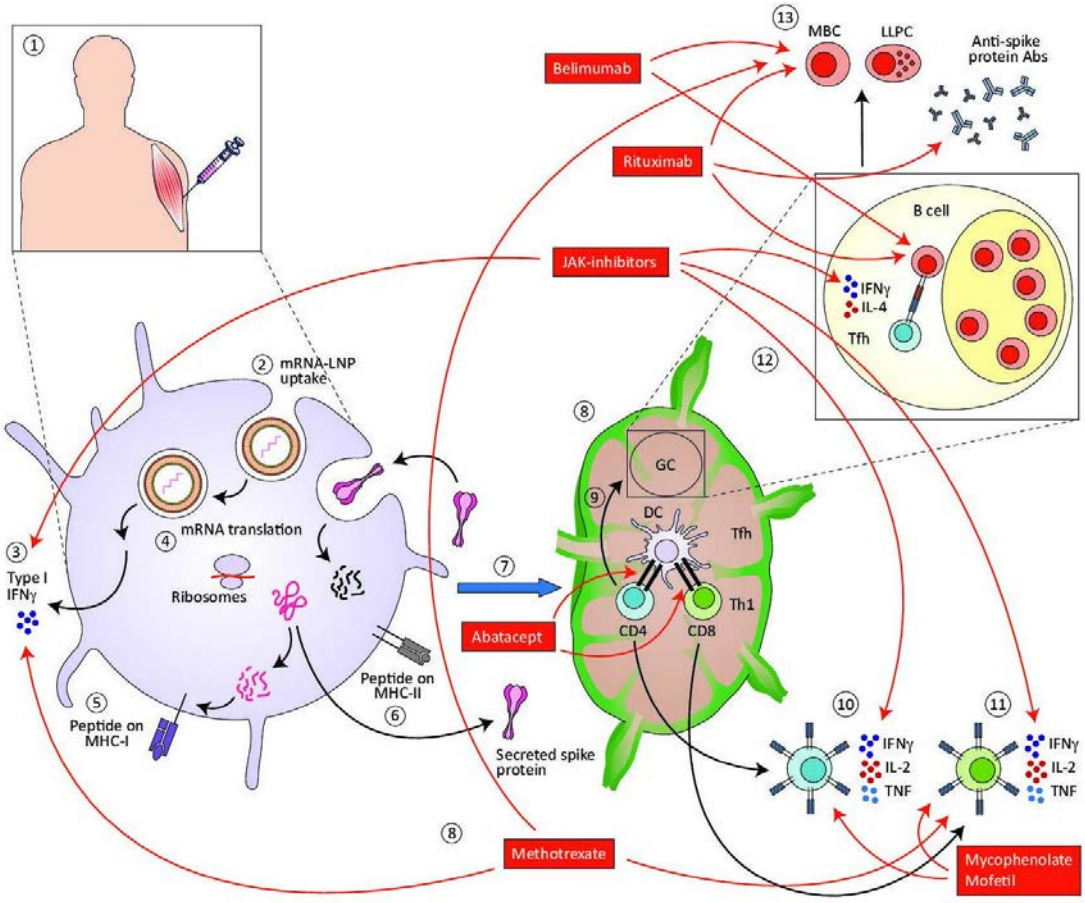

Figure 1 Mechanism of the mRNA SARS-CoV-2 vaccine and potential impact of DMARD therapy: (1) the mRNA vaccine is given as an intramuscular injection; (2) LPN coating the mRNA allow uptake into APCs[135]; (3) mRNA is recognised by Toll-like receptors/retinoic acid-inducible gene-I, triggering a type I IFN response; (4) mRNA is translated by ribosomes into peptides; (5) peptides are processed by the proteasome and presented on MHC-I or (6) post-translationally modified into secreted proteins, which can then be taken up by APCs and presented by MHC-II; (7) DCs are trafficked to lymph nodes where they (8) prime CD4 + and CD8+ T cells; (9) CD4 + T cells differentiate into Tfh cells, which form GC or (10) Th1 cells; (11) CD8 + T cells become circulating cytotoxic T cells; (12) in the GC, Tfh cells interact with B cells, resulting in (13) MBC and LLPCs secreting anti-spike protein Abs.[135 136]Low-dose MTX impacts expression of cytokines,[137] B cell and CD8 + T-cell responses, with apparent preservation of CD4 + response.[85] Mycophenolate mofetil reduces B and T lymphocyte proliferation.[138] Abatacept is a soluble fusion CTLA-4 IgG, which prevents T-cell costimulation.[139] JAK inhibitors reduce signalling by numerous cytokines, of particular importance in mRNA vaccines response are IFN-γ, IL-4 and IL-2 signalling.[140] Rituximab depletes B cells by targeting CD20, which is expressed by early B cells but not mature plasma cells.[141] Belimumab binds soluble BLyS, reducing B-cell survival.[142] SARS-CoV-2 mRNA vaccine mechanism depictions are modified from figures attributed to Cagigi/Loré[135] and Bettini/Locci,[136] licensed under CC by 4.0. Abs, antibodies; APCs, antigen-presenting cells; BLyS, B lymphocyte stimulator; CTLA, cytotoxic T-lymphocyte-associated protein 4; DCs, dendritic cells; GC, germinal centres; IL-4, interleukin-4; IFN, interferon; JAK, Janus kinase; LLPCs, long-lived plasma cells; LPN, lipid nanoparticle; MBC, memory B cells; MHC, major histocompatibility complex; MTX, methotrexate; Tfh, T follicular helper.

patients on TNF inhibitors fully vaccinated with BNT162b2 mRNA vaccine showed no significant difference in seroconversion rates compared with healthy controls.[84] Whether reductions in quantitative humoral responses are of clinical significance is unknown.

JAK inhibitors likely reduce antibody titres and have a mild effect on seroconversion, although the clinical importance of these observations is unknown and data are scant. The 10 patients on JAK inhibitors in the Deepak *et al* cohort had a greater than sixfold reduction in titres compared with controls (95% CI: 2.9 to 15.3, $p<0.05$.)[82] However, in the Furer *et al* study, among 21 patients on JAK inhibitor monotherapy and 24 on combination therapy, 19 (90%) and 22 (92%), respectively seroconverted, neither of which were significantly different from controls.[84]

Safety in patients with rheumatic diseases

Because of its substantial immunogenicity, there is concern that the SARS-CoV-2 vaccine may induce flares in patients with inflammatory diseases. This concern is supported by reports of thrombocytopaenic purpura[89–92] and myocarditis/pericarditis[93–95] after vaccination. There have additionally been observational reports of new-onset immune-mediated disease[96] and/or disease flares after SARS-CoV-2 vaccination,[96 97] which must be balanced against the risk of immune-mediated disease resulting from SARS-CoV-2 infection itself.[98–100]

The Furer *et al* cohort of rheumatic disease patients documented two fatalities postvaccination; one ANCA-vasculitis patient developed cutaneous vasculitis with subsequent fatal sepsis 3 weeks after the second vaccine dose and the second had a history of cardiovascular disease and died of a myocardial infarction 2 months after the second vaccine dose. Other

adverse events of note were two cases of uveitis, one case of pericarditis, six cases of herpes zoster, and one case of herpes labialis, while risks of typical side effects were similar to the controls.[84] Small prospective studies thus far have not found an increased in underlying inflammatory disease activity measures after SARS-CoV-2 vaccination,[84 87] however, more prospective data are needed to understand the safety of these vaccines and risk of disease flare in patients with rheumatic diseases.

Recommendations

The ACR has provided detailed recommendations for management of DMARD therapy in the setting of the SARS-CoV-2 vaccine (table 2).[101] EULAR is also developing guidelines for SARS-CoV-2 vaccines in patients with rheumatic diseases, which should be available in the near future. All patients with rheumatic diseases should receive the SARS-CoV-2 vaccine as per general population recommendations.

HEPATITIS B VACCINATION

Background

There are three different single-antigen recombinant HBV vaccines available worldwide and several combination vaccines; however, the most common HBV vaccine is a yeast-derived single-antigen vaccine. HBV vaccine immunogenicity is measured by anti-HBV surface antibody, where a titre of ≥10 IU/L is considered to be seroprotective.[102]

Effect of DMARD therapy on vaccine efficacy

TNF and IL-12/IL-23 inhibitors have been found to reduce HBV vaccine immunogenicity,[103–105] while most other medications have not been extensively evaluated.

TNF inhibitors reduce HBV vaccine immunogenicity,[103–105] although there may be differences among TNF inhibitors, with the lower antibody response rates for infliximab and higher response rates for etanercept.[105] Ustekinumab was evaluated in one study of 25 patients where vaccine responses were moderately reduced.[105] A recent trial of a high-dose HBV vaccine in DMARD-treated patients resulted in higher antibody response rates (anti-HBs titre over 10 IU/mL) when compared with a standard-dose vaccine, however this result did not reach significance (61.1% vs 49.3%, p>0.05).[105]

Recommendations

In the USA, HBV vaccination is recommended for adults at high risk (table 1).[12 61 106–108] Ideally patients who require HBV vaccination should be vaccinated prior to starting DMARD therapy, particularly for high-risk patients starting rituximab.[109]

HPV VACCINATION

Background

Three HPV vaccines are approved; however, the 9-valent vaccine is the only HPV vaccine currently available in the USA. Women with rheumatic diseases on immunosuppressive therapies are at increased risk of HPV and cervical cancer; this has been particularly well described in systemic lupus erythematosus (SLE) but is seen in other inflammatory diseases.[110–115] HPV vaccine immunogenicity is measured by seroconversion to subtypes contained in the vaccine, although a minimum threshold for seroprotection is not defined.

Effect of DMARD therapy on vaccine efficacy

MTX and TNF inhibitors have been evaluated in patients with juvenile idiopathic arthritis, juvenile dermatomyositis, inflammatory bowel disease and SLE; in these patients, MTX and TNF inhibitors do not appear to impact postvaccination seroconversion rates.[116–119] Patients with SLE on combination mycophenolate mofetil and low-dose glucocorticoids show moderately reduced seroconversion rates for HPV6 and HPV18, but not for other subtypes.[118] Other DMARD therapies have not been evaluated in patients with rheumatic diseases.

Recommendations

The Center for Disease Control (CDC) recommends HPV vaccination for all patients (regardless of sex) at age 11 or 12 up through age 26.[12] No specific changes in medications are recommended for the HPV vaccines. It is important to remember that HPV vaccines are given as a series and the treating rheumatologist should ensure that the entire series have been completed.

TETANUS VACCINATION

Background

The tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine is a single-dose vaccine. Tetanus toxoid is a T-cell-dependent antigen. Tetanus vaccine immunogenicity is typically measured by antitetanus toxoid IgG concentrations 4 weeks postvaccination, where an antibody concentration of ≥0.10 IU/mL is typically considered seroprotective, however, an endpoint of fourfold increase in antibody concentration is also sometimes used.[120]

Effect of DMARD therapy on vaccine efficacy

Rituximab reduces response to the tetanus vaccine, however, the degree of this reduction is inconsistent between studies.[18 121] Studies of abatacept,[122 123] JAK inhibitors[53 120] and TNF inhibitors[121 124] suggest a modest impairment in immunogenicity. IL-6,[55] IL-17[55] and IL-12/IL-23[54] inhibitors have not been shown to impair tetanus vaccine immunogenicity.

Rituximab may have less of a profound impact on tetanus immunogenicity than other vaccines, possibly because most patients have previously had tetanus vaccine and may have residual tetanus-specific memory B cells. Patients with RA on rituximab + MTX and MTX monotherapy were able to mount similar rates of humoral response, defined as a greater than equal to fourfold rise in antitetanus IgG (39.1% vs 42.3%, 95% CI: −25.7 to 19.2).[18] However, another study found that rituximab was associated with lower rates of protective antibodies titres (≥0.1 IU/mL) compared with other patients with inflammatory disease or controls (73% vs 96%–100%) and only 9% of rituximab-treated patients had a greater than equal to fourfold rise in antibody titres.[121]

A study of patients with inflammatory bowel disease on TNF inhibitors found lower antibody titres relative to those on thiopurines or healthy controls (p<0.001), though average titres were still in the protective range.[124] Other data have shown similar antibody response rates in TNF-treated patients relative to healthy controls.[121] An uncontrolled study of subcutaneous abatacept found satisfactory tetanus vaccine response in 219 juvenile patients with idiopathic arthritis (regardless of MTX or concomitant glucocorticoids),[122] while a smaller study of 20 adults vaccinated 2 weeks after a single dose of intravenous abatacept found approximately 10% lower rates of protective antibody development relative to controls.[123] Delaying the tetanus vaccine to 8 weeks after abatacept improved response

rates close to that of healthy controls.[123] Studies of JAK inhibitors are uncontrolled, making it difficult to estimate the drug effect. However, relative to expected responses in the general population, baricitinib plus MTX-treated patients with RA show reduced antitetanus antibody concentrations,[53] while tofacitinib-treated patients with psoriasis mount a seemingly satisfactory response.[120] In a study of baricitinib and tetanus vaccination, concomitant glucocorticoids did not appear to have an adverse effect on rates of adequate humoral response; 52% (95% CI: 34.8% to 68%) of those taking glucocorticoids versus 39% (95% CI: 28.9% to 51.1%) of those not taking glucocorticoids.[53]

Studies of patients with psoriasis on ustekinumab[54] and ixekizumab[55] did not find any change in postvaccination tetanus antibody response relative to untreated controls. Tocilizumab similarly does not appear to hamper antibody response to the tetanus vaccine.[125]

Recommendations

Adults and adolescents should receive a Tdap followed by boosters of tetanus and diphtheria toxoids (Td) every 10 years or when indicated due to a wound, although a booster may be either Td or Tdap.[12] Tetanus vaccination should ideally be done prior to starting rituximab therapy.

YF VACCINATION

Background

The YF vaccine is recommended to immunocompetent persons who live or travel to endemic areas.[61 126] However, this vaccine is live and is contraindicated in immunosuppressed patients including those receiving biologics and JAK inhibitors.[41] YF vaccine immunogenicity is measured by postvaccination neutralising antibody titres.

Effect of DMARD therapy on vaccine efficacy

Because the YF vaccine is live, few studies have addressed the immunogenicity of this vaccine in patients with rheumatic diseases. A study from Brazil evaluated 31 patients who were inadvertently revaccinated (patients had primary immunity from a previous vaccine) while on biologics; these patients had lower, yet adequate antibody titres.[127] Another 17 patients on infliximab + MTX achieved satisfactory antibody levels in all but one patient.[128] Among 15 patients on MTX, all achieved seroprotection.[129] Patients on corticosteroids (mean: 7 mg/day, range: 5–20 mg/day), 18/34 of whom were vaccine naive, also appeared to have satisfactory titres.[130]

Safety in patients with rheumatic diseases

Small studies suggest that the vaccine may be safer than previously thought for patients on MTX,[127 129 131] infliximab[127 128] and corticosteroids <20 mg/day.[130] A retrospective Swiss study of 92 patients on immunosuppressive medications (16 on MTX, 40 on corticosteroids, small numbers on other medications) who received the YF vaccine developed similar rates of side effects as healthy controls (controls had a similar proportion of patients with a primary YF vaccine history) and no serious adverse events.[131] A prospective study of 15 patients on MTX (≤20 mg/week) receiving a primary YF vaccine found slightly increased rates of YF RNA viraemia in MTX-treated patients relative to controls ($p>0.39$), however these levels were never of clinical significance.[129] In the study from Brazil above, 31 patients revaccinated on biologics had no adverse events.[127]

Recommendations

The YF vaccine should be avoided in patients who are immunosuppressed. In travels or patients in endemic areas at very high risk, patients and their providers may consider holding immunosuppressive therapy for vaccination. The typical requirement for doing this would be to hold for a sufficient time to allow for the medication to wash out and its biologic effect to dissipate depending on half-life, then vaccinate and then wait 2–4 weeks before resuming medication.

CONCLUSION

Vaccinations are critical in the care of patients with inflammatory diseases, especially for those on DMARD therapy, yet DMARD therapy can impair vaccine response. This issue is only becoming more important with the emergence of novel pathogens and resultant innovative vaccines. In this review, we have summarised the available data regarding DMARDs and vaccine responses. While the impact of DMARD therapy on vaccines is variable, there are consistent themes. Rituximab substantially reduces antibody response to vaccines, although T-cell responses may be preserved. MTX and abatacept reduce the immunogenicity of many vaccines. TNF and JAK inhibitors typically reduce absolute postvaccination antibody titres, though most patients (particularly those on TNF inhibitors) still achieve seroprotective levels. Other anticytokine therapies, including IL-6, IL-12/IL-23, and IL-17 inhibitors do not appear to have a measurable impact on vaccine immunogenicity.

Vaccine immunogenicity studies are limited by inconsistency in immunogenicity measures and heterogeneity of control groups. More data are needed for the SARS-CoV-2, HBV, HPV and zoster vaccines, and for less-common medications such as belimumab and newer anticytokine therapies. Lastly, few clinical trials have directly evaluated strategies to overcome this issue, such as timing vaccines around DMARD dosing, or utilising drug holidays. As our arsenal of DMARD therapy and vaccines grow, more clinical trials will be needed to assess the impact of DMARD therapy on vaccines, and to test strategies to optimise vaccine response.

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Message from the new EULAR President and Steering Group

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ABSTRACT

The last decade witnessed the ascendancy of rheumatology to become one of the most dynamic and progressive across the fields of medicine. During the COVID-19 pandemic our discipline emerged at the forefront of molecular medicine with the rapid uptake of immune-modulatory therapeutics and depth of immune pathogenesis understanding contributing fundamentally to the COVID-19 response. The European Alliance of Associations for Rheumatology (EULAR) played a fundamental and vital role in this response in guiding rheumatic and musculoskeletal disease (RMD) therapeutics, vaccine use and even treatment innovations in the context of COVID-19 itself. Given this remarkable contribution, it is timely to reflect on EULAR—what is it and for what does it stand? At its core, EULAR represents people with RMDs, including their national societies, health professionals in rheumatology and scientific societies of rheumatology across the European nations. Our mission is to reduce the burden of RMDs on individuals and society and improve the treatment and prevention of RMDs. In this message from the new EULAR President and Steering Group, we present the most relevant activities of EULAR, its strategic aims and the concept of the EULAR family, a fantastic team of people working together across the three pillars of medical, health professional and patient societies.

The last decade witnessed the ascendancy of rheumatology to become one of the most dynamic and progressive across the fields of medicine. As pandemic struck, so too our discipline emerged at the forefront of molecular medicine with the rapid uptake of immune modulatory therapeutics and depth of immune pathogenesis understanding contributing fundamentally to the COVID-19 response. EULAR, the European Alliance of Associations for Rheumatology, played a fundamental and vital role in this response in guiding rheumatic and musculoskeletal diseases (RMDs) therapeutics, vaccine use and even treatment innovations in the context of COVID-19 itself. Given this remarkable contribution, it is timely to reflect on EULAR - what is it and for what does it stand? At its core, EULAR represents people with RMDs (PARE), including their national societies, health professionals in rheumatology (HPR) and their associations and scientific societies of rheumatology across the European nations. Our mission is to reduce the burden of RMDs on individuals and society and improve the treatment and prevention of RMDs. EULAR has evolved significantly in the last 5 years, driving excellence in rheumatology education, research, promoting implementation of research advances into daily care and fighting for recognition of the needs of people with RMDs with a reimagined political advocacy programme. This progress arose substantially from our adherence to, and achievement of, the principles laid out in our current EULAR strategy set through to 2023. Accordingly, we are working now on the development of the new strategy for the period 2024–2028—in this new phase, EULAR will build on this firm foundation as we set ever more ambitious goals.

Reflection on each of these core activities is illustrative. The EULAR School of Rheumatology provides live courses and meetings, online courses and webinars, publications, bursaries, grants and certificates of the highest quality that have become a global standard. We offer resource and opportunity to various rheumatology populations including undergraduates, physicians, researchers, patients and HPR. In recent pandemic times, EULAR education rapidly pivoted to capitalise on continuous innovation and technological advances to maintain delivery of cutting-edge education, in a new online interactive structure built on the most modern educational models.

Delivery of the highest clinical standards is built not only on education but also on provision of clear frameworks for quality of care in practice. As such, EULAR treatment recommendations and taskforces addressing prevention, diagnosis, classification and treatment of RMDs have substantially contributed to the improvement in the lives of people with RMDs across Europe and beyond. Implementation science will increasingly become a core part of these efforts to ensure that the 'theory and evidence are delivered in practice'. Crucially, these EULAR taskforces also set a research agenda. Significantly, we founded the EULAR Research Centre in 2020, with the aim of building capacity for collaborative translational, clinical and epidemiological/population research in rheumatology across Europe. The centre in turn will support and grow our core research capabilities to close key knowledge gaps highlighted in the EULAR RheumaMap, published in 2017 and updated in 2020. The RheumaMap calls to a broad audience including political classes, charitable and public funders and industry to invest substantially in rheumatology research in the next decade and highlights especially the value that will accrue in individual lives currently blighted by RMDs, healthcare economies and worldwide-related societal costs. Moreover, the EULAR research centre is designed to work in close partnership with Foundation for Research in Rheumatology, which directly funds

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research in Europe and in due course, we hope, will engage in the wider global space to collaborate and enable international research collaborations and interactions around the world.

Communicating cutting edge research and delivering the state of the art of knowledge to our constituencies are also achieved via the Annual European Congress of Rheumatology. This has become the primary platform for the exchange of scientific and clinical information in Europe and fosters extensive interactions among physicians, scientists, people with RMDs, HPR and representatives of the pharmaceutical industry worldwide. Since 2000, the EULAR Congress has been held in June, every year, in one of the major cities in Europe. Pandemic times required migration to the virtual world to remarkable success—more than 18000 delegates in 2020 and 17000 in 2021 attended. Over the years, the EULAR Congress has gained a reputation as the most innovative platform for the rheumatology community; in this spirit, we will now move to hybrid congress models that offer flexibility, adherence to zero-carbon ambitions and increased equity of access for delegates with flexible attendance models. Crucially, we will embrace the state of the art in the modalities of congress experience. This is timely since EULAR will shortly celebrate its 75th anniversary and the 2022 Congress will offer outstanding celebrations of the EULAR jubilee.

Despite the medical advances alluded to above, rheumatology remains too often 'the bridesmaid' on the political stage. A substantially revised approach to EULAR Advocacy has been transformative and now EULAR commands close attention among political authorities in the European Union and with national governments across the EULAR countries. EULAR Advocacy works to ensure that policies, regulations and legislation in Europe are focused on the burden of RMDs on individuals and society. Numerous initiatives are enacted at the European and national level with increasing impact in an iterative programme to drive ever greater visibility and action as a result.

Above all, at our heart is the 'EULAR family'—the fantastic team of people working together across the three pillars of medical, health professional and patient societies. In prior times, EULAR may have appeared opaque reflecting its inherent complexity. A radical revision of our structures and governance rules in the last 3 years has created an inclusive organisation that truly seeks to engage with our member organisations and the wider rheumatology community—encapsulated in the launch of individual memberships imminently. Any person in the community who is willing to participate in our EULAR family can be involved in its initiatives, with individuals appointed or voted to positions of responsibility, based on their unique skills and perspectives and independent of gender, age or geographic origin. In particular, in the last 2 years, EULAR has directly faced the important concept of gender equality with work ongoing. All of the above is founded on meritocracy, an important element in any volunteer-led organisation.

Not only is our structure evolving but also our scale. In-housing many of our activities into EULAR House in Zurich will render us highly efficient in the times to come—value accrued was demonstrable during the recent pandemic. With the expansion of our admirable secretariat, EULAR is now ideally placed to rapidly adapt to life, facing new key challenge, including the unexpected post pandemic. We seek new initiatives, strategies, innovation and to work in new contexts retaining our fundamental aim of combatting the RMDs and their impact. This has never been more important than now when we transition to a new hybrid world, capitalising on virtual technology for our clinical consultations, medical communications, education and research activities—these efficiencies however must be balanced with the essential humanity that binds us together and on which we draw for inspiration and mutual support in the practice of clinical medicine and science and the lived experience of the RMDs. EULAR will embrace this new reality and prosper within it.

In closing, we would like to thank the members of the EULAR pillars who dedicate many hours of their daily work to the EULAR Family, to colleagues on the EULAR board for their continuous commitment in making EULAR successful and to the EULAR office and executive directors for their engagement and superb support. Mostly we thank the extraordinary community that is rheumatology in Europe—we wish you safe and exciting times.

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Preclinical models of arthritis for studying immunotherapy and immune tolerance

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ABSTRACT

Increasingly earlier identification of individuals at high risk of rheumatoid arthritis (RA) (eg, with autoantibodies and mild symptoms) improves the feasibility of preventing or curing disease. The use of antigen-specific immunotherapies to reinstate immunological self-tolerance represent a highly attractive strategy due to their potential to induce disease resolution, in contrast to existing approaches that require long-term treatment of underlying symptoms.

Preclinical animal models have been used to understand disease mechanisms and to evaluate novel immunotherapeutic approaches. However, models are required to understand critical processes supporting disease development such as the breach of self-tolerance that triggers autoimmunity and the progression from asymptomatic autoimmunity to joint pain and bone loss. These models would also be useful in evaluating the response to treatment in the pre-RA period.

This review proposes that focusing on immune processes contributing to initial disease induction rather than end-stage pathological consequences is essential to allow development and evaluation of novel immunotherapies for early intervention. We will describe and critique existing models in arthritis and the broader field of autoimmunity that may fulfil these criteria. We will also identify key gaps in our ability to study these processes in animal models, to highlight where further research should be targeted.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that results in the destruction of the bone and cartilage of the joints. The disease is thought to be driven by genetic predisposition and environmental factors, leading to a loss of immunological self-tolerance, autoimmunity and arthritis (figure 1).

It is widely accepted that the combination of arthralgia and the presence of antibodies (indicating loss of tolerance) to citrullinated proteins (ACPAs) and or IgM rheumatoid factor (RF) is appropriate to identify individuals with high risk of developing RA.[1–4] Approximately 30%–40% of subjects at risk will develop RA within 1 year. Several factors might indicate even higher risk: (1) high levels of ACPA (>three times of the upper level of normal) and/or RF (although RF is probably less important), (2) human leucocyte antigen (HLA) susceptibility alleles, such as shared epitope, (3) evidence of synovitis based on imaging (generally ultrasound and MRI), (4) smoking and (5) obesity. Based on all these factors individuals with up to 50%–60% risk to develop RA within 1 year might be identified.[5–7] Disease progression to RA is associated with decreasing potential for remission.[8] Treatment in the pre-RA phase might be associated with complete suppression of clinical signs and symptoms and the potential for the re-establishment of tolerance.[9]

Current treatments for RA consist of glucocorticoids, conventional and targeted synthetic and biological disease-modifying antirheumatic drugs (DMARDs). However, DMARDs decrease inflammation and ameliorate the radiological progression of the disease without altering the underlying pathology. The focus of recent autoimmune disease research has been to reinstate immunological self-tolerance. An 'immunological reset' with antigen-specific immunotherapy may ultimately allow for drug-free remission in RA, in essence curing the disease.

Arthritis research has employed a number of animal models which vary in their design and method of disease induction as well as the stage in the disease process they represent. The benefits of these models and their contributions to research have been discussed extensively in other reviews.[10–13] Significantly not all models of RA are appropriate for the study of antigen-specific, tolerising immunotherapy.

Here, we focus on models that are suited to the study of initiating events in pre-RA (table 1) and are therefore well placed for identifying therapeutic targets for tolerance induction and for the resulting testing and development of new therapies. Importantly, we identify key questions about arthritis and how these models may contribute to our understanding of different immunological processes and antigen-specific immunotherapies.

Can animal models help us understand loss of tolerance leading to autoimmunity?

Breach of self-tolerance is a central and early step in the development of autoimmune disease. While the list of self and post-translationally modified antigens that are recognised by the host immune response is increasing,[14] it remains unclear why responses are directed at these particular proteins, what are the circumstances that drive autoimmune responses to these antigens and why they evade mechanisms of central and peripheral tolerance in RA. Underlying factors associated with RA susceptibility include

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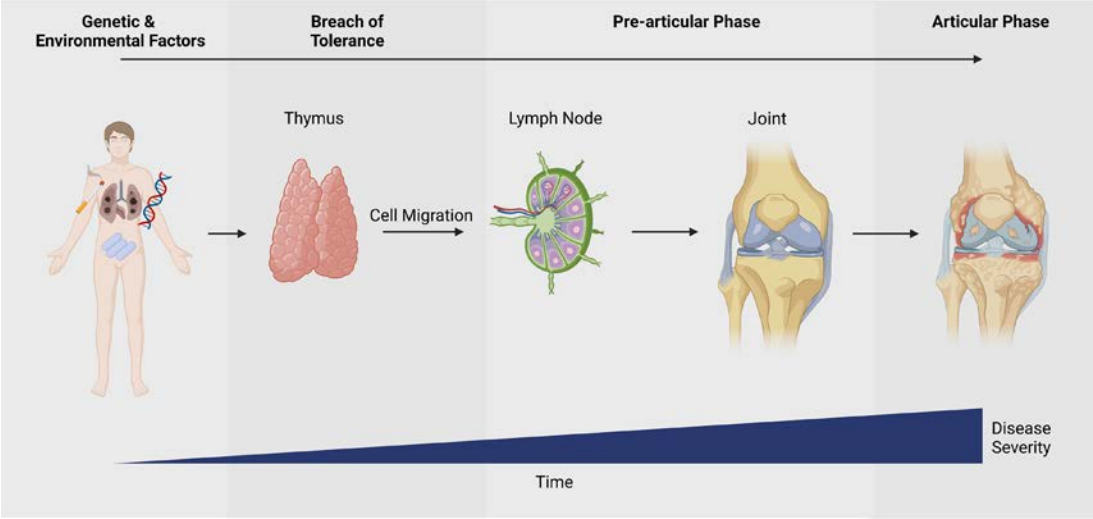

Figure 1 Disease progression of rheumatoid arthritis - created with BioRender.com.

genetic predisposition as well as environmental factors including smoking, various infections, lung inflammation, periodontitis and changes in the microbiome, which contribute to the breach of self-tolerance at mucosal interfaces well before the development of joint inflammation.[15–18] Animal models can play a critical role in identifying and isolating the environmental and genetic mechanisms that promote loss of tolerance. For example, in animal models with genetic predisposition to autoimmunity, such as the ZAP-70-mutant SKG mouse, in which altered T cell receptor (TCR) signalling leads to modified thymic selection, either an environmental stimulus or additional genetic lesion is required to initiate arthritis. Thus germ-free SKG mice fail to develop peripheral arthritis with a beta-glucan trigger, but they do develop spondylitis.[19 20] SKG mice in a specific pathogen-free environment develop spontaneous arthritis when crossed to ZAP-70-deficient mice.[21] Equally, models such as collagen-induced arthritis (CIA) or proteoglycan (PG)-induced arthritis (PgIA) require specific, susceptible, genetic strains of mice for induction of autoimmunity.[22] It is worth nothing that while SKG mice have been instrumental for understanding underlying disease mechanisms, they have not been useful to date for studying antigen tolerisation strategies as few self-antigens have been elucidated.[23]

In the CIA or PgIA models, a known antigen is administered to animals in the context of a powerful adjuvant, such as Freund's complete adjuvant or dimethyldioctadecylammonium. This antigen is commonly a heterologous protein that closely resembles the endogenous protein of the animal, although models using autologous antigen have been demonstrated to also effectively induce arthritis in mice.[24 25] In these models, the adjuvant creates an environment for immunogenicity of the antigen, inducing antibodies cross reacting with heterologous and endogenous antigen, leading to a loss of tolerance.[26] While these mechanisms are well understood in CIA and PgIA models, they are unlikely to fully reflect how tolerance is breached in patients with RA, which is more complex, without a single initiating autoantigen with adjuvant, and involving the need for an ageing immune system to balance self-tolerance with immune control of micro-organisms. Other models of antigen-induced arthritis (AIA) using molecularly distinct antigens may help answer these questions (figure 2). In ovalbumin (OVA)-induced arthritis (OIA) or AIA, the eliciting antigen (OVA or methylated bovine serum albumin, respectively) is not an autoantigen; however, breach of self-tolerance occurs. This is instigated through the intra-articular injection of antigen into mice previously immunised with the same antigen and may employ the use of adoptively transferred antigen-specific T cells as in the OIA model. Following this challenge, there is a large influx of neutrophils and macrophages into the joint, resulting in the generation of B and T cells that recognise a range of unrelated autoantigens in addition to the initiating antigen (bystander activation).[27 28] These latter two models allow closer analysis of the conditions that lead to autoimmunity as the bystander response to autoantigen can be considered 'spontaneous'. Using this approach, the key role of cognate antigen (OVA) recognition in the joint and surrounding tissue was identified. Administration of either an inflammatory agent alone (lipopolysaccharides) or OVA subcutaneously is not sufficient to elicit autoimmunity.[29 30] Further studies defined the role played by endogenous conventional dendritic cells (DC) in promoting breach of tolerance, as well as the regulatory role of plasmacytoid DCs.[31 32] Future studies of these models will help define the range of autoantigens that are recognised in joint inflammation and, more importantly, when and why these particular host antigens are recognised and how they promote the process of epitope spreading. In this respect, it is important to note that immune recognition of post-translational modifications of endogenous proteins such as citrullination have been observed at low levels in some models,[29] although there have been questions about the reproducibility of these results as well as the absence of appropriate controls.[33] Whether ACPA are directly pathogenic in RA is still unclear. However, studies aimed at tolerising the T cell response to citrullinated antigens in both animals and humans may help define whether regulation of this response influences disease outcome.

While some models above contribute to our understanding of why breach of tolerance and autoimmunity develops, there remains considerable scope for improvement. Animal models offer the opportunity to perform reductionist approaches that allow dissection of the complex contributory genetic and environmental factors that lead to breach of tolerance. However, the mechanisms driving disease events in animal models do not necessarily replicate those occurring in human RA, for example, respiratory mucosal involvement, complex genetic background and contributory environmental factors, in addition to the long duration of disease. Furthermore, no spontaneous models faithfully reproduce human RA. Technologies such as animals

Table 1 Preclinical arthritis models suitable for the development of tolerogenic therapies

Species	Induction of disease	Endogenous or exogenous antigen	Incidence rate (%)	Autoresponses involved	Is model synchronised?	Clinical course	Benefits for tolerance studies	Limitations for tolerance studies
Human	Spontaneous	Unknown	1% of population	Generation of autoantibodies (CII, ACPA, RF) and autoreactive T cells. Formation of immune complexes	–	Genetic susceptibility or environmental exposure, Breach of tolerance, prearticular phase, articular phase, chronic	–	–
Mouse (BALBc or C57BL/6J)	Immunisation with ovalbumin in mice that have ovalbumin specific T cells	Exogenous leading to endogenous response	80–100	Generation of autoantibodies (CII, ACPA, RF) and autoreactive T cells. Formation of immune complexes	Yes	Breach of tolerance, prearticular phase, acute but can be made chronic with further challenge	Congenic markers distinguish between OVA specific and endogenous T cells. True breach of tolerance. Autoreactivity only occurs with articular challenge	Inflammation is self resolving. Only polyarthritic with further challenge
Mouse (BALB/cAnNCrl)	Immunisation with Human cartilage proteoglycan aggrecan	Endogenous	100	Generation of autoantibodies (PG, ACPA, RF) and autoreactive T cells	Yes	Breach of tolerance, prearticular and articular phase, chronic	Tetramers are available to characterise antigens specific T cells.	Can only be used in BALB/cAnNCrl mice purchased from Charles River
Rat (various) or Mouse (BALBc, DBA/1, C57BL/10 or C57/BL6*)	Immunisation with bovine, murine or chicken collagen II	Exogenous/ Endogenous	70–100	Generation of autoantibodies (CII, ACPA, RF) and autoreactive T cells	No	Breach of tolerance, prearticular and articular phase, chronic	Tetramers are available to characterise antigens specific T cells. Useful for studying effect of tolerance on both B and T cell responses.	Difficult to perform in C57BL/6 J mice which limits genetic manipulation
Mouse (HLA-DR1 on C57BL6xB10 background	Immunisation of genetically predisposed mice with bovine or mouse collagen II	Exogenous/ endogenous	70–100	Generation of autoantibodies (CII, ACPA, RF) and autoreactive T cells	No	Breach of tolerance, prearticular and articular phase, chronic	Tetramers are available to characterise antigens specific T cells. Uses HLA associated with human RA. TCR skewed to DR1 restricted collagen	Require mixed background mice as well as DR1 gene. Breeding can be challenging
Rat (DA) or mouse† (CBA/Igb, DBA/1 or BALBc)	Immunisation with the adjuvant pristane	Endogenous due to adjuvant exposure	50–80	Generation of autoantibodies (CarP, RNPs, RF) and autoreactive T cells	Yes	Prearticular and articular phase, chronic	Strongly T cell dependent	Mostly limited to rats so genetic manipulation difficult. Expensive.

*Must use chicken type II collagen.
†Delayed onset.
ACPA, antibodies (indicating loss of tolerance) to citrullinated proteins; CarP, carbamylated protein; CII, type II collagen
; OVA, ovalbumin; PG, proteoglycan; RF, rheumatoid factor; RNP, ribonucleoprotein.

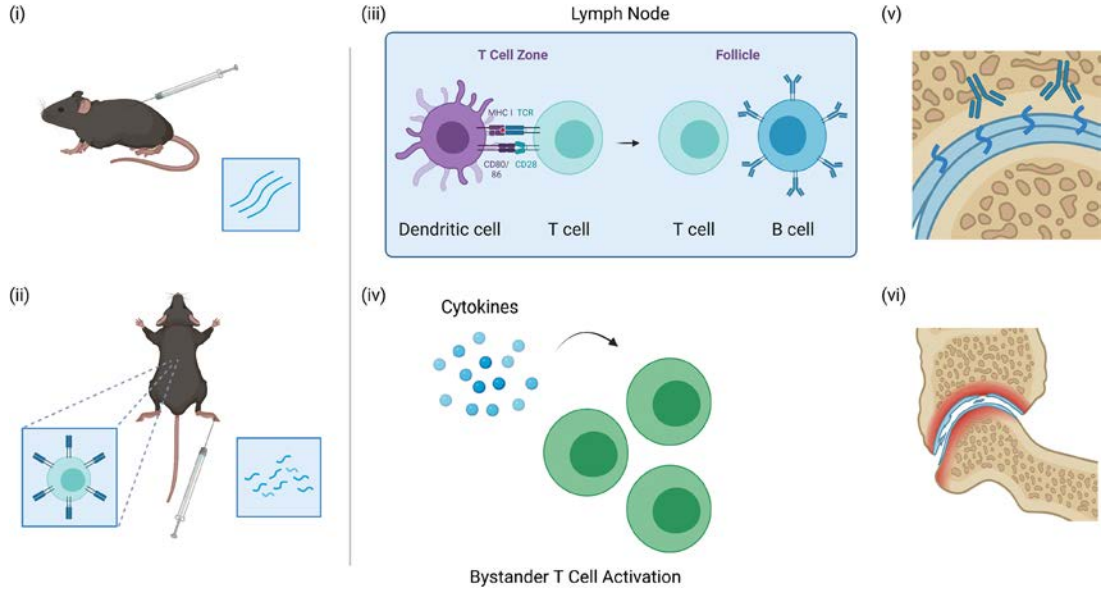

Figure 2 CIA and AIA models of arthritis. (i) CIA mice are injected with heterologous or autologous collagen in the presence of an adjuvant. (ii) in AIA models, mice are first immunised with an unrelated antigen in the presence of an adjuvant and then rechallenged with the same antigen in the joint. These models may employ the use of TCR transgenic T cells. (iii) The antigens in both models are initially presented by dendritic cells to CD4 T cells within the T cell zone of the lymph nodes. These CD4 T cells then interact with B cells within the follicle to produce antibodies. (iv) In the AIA models, the inflammation within the joint to the exogenous antigen triggers the activation of bystander T cells resulting in the targeting of joint antigens. (v) In both models, antigens within the joints become targeted by the immune response. (vi) This results in the destruction of cartilage and bones within the joints - created with BioRender.com. AIA, antigen-induced arthritis; CIA, collagen-induced arthritis; TCR, T cell receptor

expressing fluorescent reporters can be used to identify where and when key molecules are expressed, while cell-specific and tissue-specific gene knockouts can identify their mechanistic contributions to autoimmunity. These studies can be performed with the opportunity for the full temporal development of autoimmunity to be investigated, including assessment of where and when key therapeutic windows arise.

Can animal models help us understand the progression from asymptomatic autoimmunity to joint infiltration and bone erosion?

The development of autoimmunity in RA and the transition into clinical disease remains a poorly understood process. Changes in innate immune reactivity and altered T cell and B cell regulation result in the development of autoantibodies targeting post-translationally modified proteins. These perturbations in immune cell activity indicate loss of tolerance and eventually culminate in the development of a synovial lesion that contains large numbers of infiltrating T cells, B cells, macrophages and fibroblasts.[34]

As this transitionary period generally occurs slowly over many years, different aspects of the immune response, particularly within the joints and lymph nodes, are difficult to study longitudinally in patients. Although animal models are unable to fully recapitulate human disease, their selective application has offered many insights into the development of autoimmunity and the complex interplay of immune cells in different tissues at various stages of disease. Importantly, as these models can be used in combination with technologies that would be otherwise impractical or unethical for use in patients, they allow for the study of discrete aspects of the disease that cannot be researched using other methods.

The ability to identify, manipulate and track specific cell populations is particularly useful in animal models, as has been shown in research examining the roles of autoreactive CD4 T cells in the development of early arthritis. The PgIA model has been used to demonstrate that TCR signalling strength dictates the fate of T cells, with those with weaker signals developing into T follicular helper cells (Tfh) which stimulate human PG-specific antibodies, cross-reactive with mouse PG.[35] Since autoreactive T cells driving autoimmunity may have escaped central and peripheral tolerance mechanisms due to low TCR affinity, the fact that autoreactive T cells in RA mostly recognise modified self, which bind HLA with higher affinity, offers insights into the activation and persistence of Tfh and other effector cells driving autoimmune disease progression.

T cell migration studies, using multiphoton microscopy and lymph node sequestering drugs[36] have also demonstrated that the majority of aggrecan-specific T cells are not involved in the pathogenesis of synovial inflammation directly, but rather exert their effects in the lymphoid organs where they provide B cell help for systemic autoantibody production.[37–39] Similar work using a partially humanised CIA model in HLA-DR1 isotype (HLA-DR1) mice, in which chimeric human/mouse major histocompatibility complex (MHC) class II molecules comprise the peptide-binding domain from human DR and the CD4-binding domain derived from mouse I-E,[40 41] has shown that T cells expressing an RA-relevant HLA-class II allele mount a response to the dominant epitope of collagen II. In this model, at the time of first clinical arthritis symptoms, specific effector CD4 T cells were undetectable in the synovial fluid and rare in the blood, but persisted in the lymph nodes.[42]

Taken together, data in PgIA and CIA models suggest that after the initial antigen-specific CD4 +T cell priming event in the lymphoid organs, disease development is dependent on B cells, which can present antigen and produce antibodies, and is perpetuated by CD4 Tfh cells which provide further B cell help for antibody-mediated joint destruction.[43 44] Methods that disrupt Tfh and B cells within the lymph node may therefore offer a potential target for new immunotherapies.

Aside from T cells, animal models also implicate many other immune cells in arthritic disease development and regulation, including B cells,[45] plasmacytoid DCs[31] and synovial fibroblasts.[46] Animal models offer major insights into immune cell dysfunction in arthritis. As new tolerogenic therapies are developed, antigen-driven animal models will be essential tools to understand how treatments impact immunological processes and will be key to understanding how these therapies function to restore immunological tolerance.

How does the diversity of the TCR repertoire influence models?

TCR repertoire diversity is achieved on two levels: a genetic level involving selecting, editing and combining the various TCR genes, and on a cellular level involving thymic selection and outgrowth of certain clones in both acute and chronic immune responses. The strong association of autoimmune diseases, including RA, with certain HLA alleles is well documented.[47–49] Thus, it is plausible that thymic selection and peripheral antigen encounter could influence the composition of the mature T cell repertoire in persons susceptible to RA and in patients with RA.[50 51] Indeed, the outgrowth or enrichment of certain T cell clones has been demonstrated in RA, both in the naïve[52] and antigen-experienced T cell compartments[53–56] suggesting that both thymic selection and antigen-driven responses skew the TCR repertoire in patients with RA. Similarly in the CIA model in DBA/1 mice, the *IAq* allele is required for development of the disease due to high affinity binding of the collagen II dominant epitope to I-Aq after processing of collagen II protein, driving activation of autoreactive T cells.[57 58]

Moreover, TCR repertoire diversity in patients with RA differs depending on the tissues sampled. For instance, the repertoire was found to be more restricted in the synovial compartment compared with peripheral blood in patients with RA,[53 54 59 60] indicating that tissue sites may influence the retention or accumulation of CD4 T cells possibly in an antigen-specific manner. TCR diversity has also been found to evolve with RA chronicity. In some cases, the TCR repertoire was more restricted in early RA and diversified with the progression of the disease,[54] while in other cases the TCR repertoire was found to become more restricted with time.[61] Additionally, changes in the TCR repertoire can also indicate patient response to therapeutics. For instance, patients treated with tumour necrosis factor inhibitors showed a reduction in clonal expansion in T cells expressing certain TCRβ variable region (TCRBV) genes,[62] while responders and non-responders to methotrexate display differences in TCRBV gene expression profiles in the circulating CD4 T cell repertoire.[63]

The differences in TCR repertoire diversity reported at various stages of RA development and between different tissue sites highlights how assessment of TCR repertoire diversity has the potential of being an informative indicator of disease state and predictor of effective therapeutic regimens. However, patient to patient variability in clonal responses and the conflicting evidence of repertoire changes with disease progression accentuate our lack of understanding of how TCR repertoire diversity develops in RA and how it evolves with disease progression. Thus, animal models of arthritis can help elucidate development of the TCR repertoire as they provide a setting in which different disease stages can be observed more easily and allow for spatial and temporal assessment of TCR diversity.[62 63] In addition, mouse models, such as CIA, with known dominant epitope, restricting I-A and HLA-DR molecules and responding T cells that can be identified with pMHC tetramers, offer a major advantage for T cell tolerance studies.

Models already exist that incorporate the influence of thymic selection on susceptibility to develop arthritis. For example, C57BL/6N.Q mice are more susceptible to CIA compared with C57BL/6 mice due to differences in MHC restriction[64 65] and changes in T cell positive and negative selection in the SKG transgenic mice result in spontaneous development of arthritis.[23] Studies examining aspects of TCR repertoire diversity have been conducted using the CIA model of arthritis and have also reported a skewed or restricted TCR repertoire and the prevalence of certain TCRβ chains were found to be strain dependent.[66–69] The dominance of these chains were also relevant to the pathology as administration of depleting antibodies specific to the dominant Vβ chains were found to significantly reduce the incidence of CIA. One study using the HLA-DR1 mouse/CIA model found CD4 T cells of limited clonality in the joint with a highly selective subset of the TCR repertoire.[70] These CD4 T cells bind to the dominant collagen II epitope and, although they comprise a minor population, they may play a major role in disease pathogenesis. A recent study investigated differences in the composition of the TCR repertoire in joints and their draining lymph nodes with the progression of OIA.[71] The authors reported a disparity in TCR repertoire diversity between the draining lymph nodes and joints with the progression of inflammatory arthritis, with the lymph nodes displaying greater repertoire diversity than the joints at later stages of the disease. The results of the study highlight two main therapeutic implications; first, that tolerogenic therapies may be more effective at the very early stages of arthritis when the TCR repertoire is more restricted and, second, that TCR repertoire of joint-draining lymph nodes could possibly foreshadow TCR repertoire diversity of the joint, and thus be a marker of disease severity and guide effective therapeutic interventions. Significantly, animal models provide the opportunity to test these hypotheses, and rationalise the application of antigen-specific immunotherapy in disease.

Are particular models more suitable for studying specific immunotherapeutic approaches?

There is a wide range of animal models available for arthritis research but not all models are well suited for studying tolerogenic immunotherapies. As these therapies can take many different forms it is essential that models are selected with consideration given to the method of tolerance induction. Optimising model selection will strengthen the data garnered from these studies and should improve the translation of this research into effective clinical treatments.

In the pathogenesis of RA, DCs act as key players in the development of autoimmunity as they, along with medullary thymic epithelial cells, present self-antigens to T cells in the thymus impacting negative selection, and in the periphery they are able to prime naive autoreactive T cells to initiate autoimmune models.[72] However, DCs are also capable of inducing and maintaining peripheral tolerance by blocking T cell expansion, inducing T cell deletion or anergy. One promising cell-based approach is targeting autoreactive T lymphocytes by the production of tolerogenic DCs (TolDCs). The tolerogenic function of DCs can be promoted by the exposure to different anti-inflammatory cytokines or by in vitro treatment with an NF-kB inhibitor. TolDCs act by different mechanisms including the secretion of immunomodulatory mediators, reduction of MHC and costimulatory molecules or the expression of immune-modulatory/

immune-inhibitory molecules.[73] Preclinical data informing current clinical trials of TolDC immunotherapy in RA were derived from the 'classical' RA models, namely CIA[74–76] and AIA models.[77] Humanised mouse models of RA show several advantages in testing tolerogenic therapy by enabling direct translation to humans through introduction of human transgenes or by the selective transfer of human autoantigens or cells/tissue into immunodeficient mice.[78] However, limitations include relatively poor expression of the human HLA transgene, and the need for induction of inflammatory arthritis with heterologous antigen, which limit interpretation of antigen presentation and efficacy of tolerising immunotherapies.[79]

The induction of regulatory T cells (Treg) by peptide-based therapies have been developed for the treatment of a number of autoimmune diseases including RA,[80] multiple sclerosis (MS) and Graves' disease.[81–83] In this treatment, known tolerogenic peptides bind directly to MHC II on DCs.[84] These DCs then interact with CD4 T cells to induce regulatory T cells that suppress T cell activation. As this therapy is based on peptide presentation, HLA-DR transgenic mice have supported the design of tolerogenic T cell epitopes and testing of tolerogenic strategies[85–87]; however, important lessons have been learnt. For example, introduction of a human HLA allele does not guarantee that an HLA-DR transgenic mouse will respond to an epitope known to be dominant in humans.[88] This implies that mice have a 'hole' in their T cell repertoire for certain HLA-restricted T cell epitopes which can be overcome by creation of mice expressing both HLA-DR and TCR molecules from relevant patients.[85 89] Furthermore, design work with individual peptide epitopes has shown that they must mimic naturally processed epitopes when bound to MHC II in order to induce tolerance through induction of IL-10 secreting regulatory T cells.[90 91] This research confirms the importance of HLA-DR mice for the development and testing of peptide-based therapies in RA.

In addition to antigen-specific immunomodulatory therapy targeting DCs or T cells in situ, chimeric antigen receptor (CAR)-Treg cell therapy, in which Tregs are engineered to target specific proteins in a MHC independent manner,[92 93] is being expanded to include autoimmunity in light of promising results from clinical trials, and product registration of CAR-T in oncology.[94] In the context of RA and the HLA-DR1 model, it has been reasoned that engineering CAR-Tregs to specifically target an antigen in the joints of patients with RA may promote their migration to the site of abnormal inflammation, inducing a localised and protective immunosuppressive response. Accordingly, a CAR directed against citrullinated vimentin, a cytoskeletal protein, which is expressed in the synovial tissue of the majority of patients with RA, has been developed.[95] This group is working to transduce this CAR into Tregs in order to assess functional activity in vitro and therapeutic potential in vivo of CAR-Treg transfer in the CIA model. Another approach in development is the generation of CAR CD8 CTL presenting antigenic peptide to specifically target and eliminate autoreactive CD4 T cells (Rosloniec, unpublished); these will also be tested in the HLA-DR1 humanised mouse model of CIA. While the CAR-Treg approach is advantageous in that it offers specific targeting and imparts no HLA restriction, its drawback is the requirement for a specific antigen for recognition, which is a design issue in RA due to the number of potential autoantigens involved in disease progression. Strategies invoking bystander tolerance or patient stratification based on putative autoantigen involvement and disease stage may facilitate therapeutic selection of CAR-T cell therapy to complement immunomodulatory approaches such as antigen-specific immunotherapies, as have been used in solid tumours in vivo in mice[96]

One of the oldest and most widely explored tolerogenic therapies is antigen feeding. In this therapy, small amounts of a specific antigen are administered orally to restore a state of homeostasis and tolerance to self-peptides in the adaptive immune system. This method has been used extensively with antigen-induced models, particularly CIA. Multiple experiments demonstrated that feeding collagen II prior to disease induction was protective against CIA in rats.[97 98] Unfortunately, subsequent clinical trials with patients with RA showed conflicting results,[99–101] with greater success observed with administration of lower antigen doses leading to the generation of active suppression via Tregs rather than anergy or clonal deletion.[102] Due to inconsistencies between trials, this therapy was not pursued in RA. The disparity between animal models and clinical studies may lie in the lack of knowledge about the initiating autoantigen in RA, as collagen II is just one of many possible autoantigens involved in disease progression. Similarly, the timing of clinical trials of antigen feeding may be too late when autoimmunity has already progressed to disease. In addition, differences in rodent and human immune responses have to be considered.[103] Despite these setbacks, antigen-induced CIA, OIA and AIA models are certainly useful to understand the mechanisms of how tolerance is induced from an immunological perspective. They may also offer insights into how antigen dosing and the timing of intervention affects disease outcomes.

DC targeting with antigen in the context of suppressing their activation is an emerging immunotherapy that is gaining popularity. DC targeting recapitulates models in which transgenic antigen targeted to 'resting' DCs promotes long-lasting peripheral tolerance through mechanisms of T cell deletion or regulation.[104] Nanoparticles such as liposomes encapsulating disease-specific peptides along with immunomodulatory drugs, such as curcumin or calcitriol to suppress NF-kB activation required for DC activation, are taken up by DCs that interact with antigen-specific CD4 T cells to suppress disease progression.[105] In the PgIA model, tolerising liposomes were found to significantly suppress disease severity.[106] Peptide/calcitriol liposomes were found to exert their effects primarily through the deletion of high affinity antigen-specific autoreactive CD4 T cells and through anergy induction in the residual antigen-specific T cells. Delivery of the tolerising liposomes after the onset of disease also significantly reduced disease severity, even though arthritis is predominantly driven by autoantibody and complement-driven mechanisms in established disease.[107] In contrast to pretreatment, the liposomes in this experiment were found to exert their effects through the expansion of FoxP3 +and IL-10-producing Tregs. Interestingly, this model suggests that the mechanisms of tolerance induction are dependent on the timing of liposome administration.

Will current animal models identify where and when to intervene?

One of the major strengths of animal models of RA is that they allow for in-depth investigation of molecular and cellular processes at all different disease stages, that is, from initiation to chronic inflammation. They, therefore, also provide a powerful tool for studying immunotherapies, addressing important questions relating to the timing, route and frequency of administration and therapeutic effects. For example, using a rat allotransplantation model it was found that the timing and frequency of mesenchymal stem cell administration was crucial for graft survival, with multiple administrations having the best

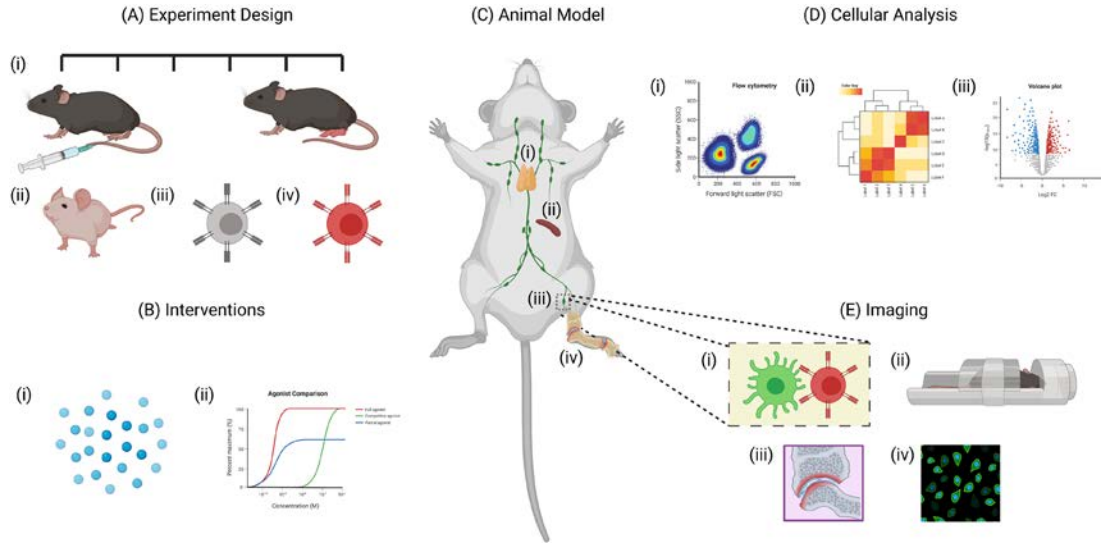

Figure 3 Benefits of using animal models for studying rheumatoid arthritis. Animal models allow researchers to study various aspects the disease that would otherwise be impractical to study in human patients. (A)(i)The experimental design of animal models allow researchers to monitor disease progression at various time points. Specific aspects of the disease can also be examined through the use of (ii) transgenic animals, (iii) TCR transgenic T cells and (iv) fluorescently labelled cells. (B) Interventions including (i) antigen-specific immunotherapies and (ii) drug treatments can also be studied in detail. (C) Tissues including the (i) thymus, (ii) spleen, (iii) lymph nodes and (iv) synovial tissue can be collected from animals at any time point. (D) This allows for detailed analysis of various cell populations using techniques such as (i) flow cytometry, (ii) RNA sequencing and (iii) cytokine assays. (E) Another major advantage of animal models is the use of live imaging techniques including (i) intravital imaging using multiphoton microscopy and (ii) whole tissue imaging using techniques such as MRI scanners. Similarly, tissues collected from culled animals can be imaged by (iii) histology or (iv) immunofluorescence - created with BioRender.com.

outcome in terms of the number of circulating Tregs.[108] Similarly, administration of IL-4-transduced DC in CIA mice via the intravenous or intraperitoneal routes led to higher numbers of DC migration to the spleen and correlated with enhanced therapeutic effects as compared with the subcutaneous administration route.[109]

The disease stage is particularly important for immunomodulatory tolerance induction strategies, which use Tregs. The function, survival and stability of these cells is highly influenced by inflammation and tissue-specific factors which will vary depending on the stage and activity of the disease.[110] Functional adaptation of FoxP3 +Tregs, also referred to as Treg plasticity, is an important process that occurs during protective immune responses. For example, exposure of Tregs to polarising cytokines directs expression of appropriate chemokine receptors that allow Tregs to home to and regulate the relevant site of inflammation. However, chronic exposure of Tregs to inflammatory mediators, as might occur, for example, in active RA, can backfire by destabilising FoxP3 expression and turn Tregs into pathogenic effector T cells. Indeed, it was shown that synovial fibroblast-derived IL-6 converted FoxP3 Tregs into Th17 cells with potent osteoclastogenic function in a CIA mouse model.[111] This has important implications for Treg-based therapies, whether it is through adoptive transfer of Tregs, induction of FoxP3 +Tregs via adoptive transfer of tolerogenic DCs or in vivo expansion of existing Tregs with low dose IL-2, which shows promise in lupus as well as other autoimmune diseases.[112] To avoid a detrimental conversion of Tregs, further investigation is required to optimise the timing of administration of tolerogenic immunotherapies, the potential for coadministration of anti-inflammatory drugs that could prevent Treg conversion (eg, anti-IL-6), and strategies and conditions that support or induce stable type 1 (Tr1) Treg from memory T cells.

Conversely, it is important to consider potentially adverse effects of existing RA medications on tolerance induction. For example, mouse models have shown that the calcineurin inhibitor ciclosporin A interferes with induction of allograft tolerance,[113] and Cox-2 inhibitors (a subclass of non-steroidal anti-inflammatory drugs) inhibit oral tolerance to dietary antigens.[114] The inhibitory effect of ciclosporin A is most likely caused by inhibition of Treg expansion and function.[115–117] Testing the *in vivo* effects of relevant RA drugs on performance of tolerogenic therapeutics in preclinical animal models is important to determine the most suitable patient group for recruitment to clinical trials, and which DMARDs might help or hinder the tolerogenic response.

Another important question is where protolerogenic therapies should act. There is ample evidence that peripheral tolerance is chiefly induced in secondary lymphoid tissues—the same site as for priming of tissue-specific T cell clones. For example, immune tolerance to inhaled or oral antigens relied on CCR7-dependent migration of DCs to the relevant draining lymph nodes,[118 119] and induction of allograft tolerance through treatment with IL-10-producing DCs also depended on CCR7-mediated homing of these DCs to the lymph node.[120] It is not surprising that secondary lymphoid tissues play an important role in both immunogenic and tolerogenic immune responses, given that DCs (both mature and immature 'tolerogenic' DCs) as well as naïve T cells and Tregs home to these locations, providing the optimal architecture relevant for DC/T cell interactions. However, it is still uncertain whether this precludes the possibility that tolerance could be induced in different locations, for example, ectopic lymphoid structures at sites of inflammation (eg, in the rheumatoid joint) as with infiltrating Tregs that control tissue-destructive tumour-infiltrating lymphocytes in tumour sites.[121] Understanding at which sites tolerance induction is most effective or even possible is critical to determine and to develop technologies for the most optimal routes of tolerogenic antigen (eg, TolDC) administration. Addressing these questions in humans is a major challenge. Although studies are

underway to compare different routes of TolDC administration (intradermal vs intranodal) in the RESTORE study in patients with MS,[122] and intradermal versus intra-articular versus intranodal in the AuToDeCRA2 study in patients with RA (Isaacs and Hilkens, unpublished), partially humanised animal models could aid in investigating these questions in more depth. For example, animal models provide an excellent tool for the longitudinal tracking and visualisation of interactions between different cell populations in vivo, including PET combined with vascular or lymphotracking dyes and CT or MRI, as well as multicolour fluorescence imaging. In some circumstances, these can be translated to clinical trials. Animal models can therefore be hugely beneficial in getting important clues on when and where to intervene, allowing for the improved, informed design of future clinical trials in patients with RA.

CONCLUSION

Although there have been many criticisms of animal models due to the poor translatability of data from preclinical models to clinical trials,[123] currently these models remain essential to develop curative therapy in RA. Understandably not all aspects of human disease can be fully recapitulated in animal models including the long transition from breach of tolerance to autoimmunity as well as the extensive interplay of genetic and environmental factors that trigger the onset of disease. Despite these drawbacks, when proficiently applied in combination with different technologies, and selected to reflect appropriate points in disease progression, animal models are critical tools in mechanistic arthritis research and remain essential for the development of curative therapies (figure 3).

A key point is that of reverse translation. As new antigen-specific immunotherapies are developed, it is critical that data from clinical studies further inform model selection. This will allow for a targeted approach to research in animal models, where bioassays or technologies can be improved for future trials, and to identify the immunological mechanisms underlying human disease and therapeutic responses. Used in this way, animal models will facilitate the development and testing of new therapeutic agents to reinstate immunological self-tolerance.

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2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis

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ABSTRACT

Background An important but often insufficient aspect of care in people with inflammatory arthritis (IA) is empowering patients to acquire a good understanding of their disease and building their ability to deal effectively with the practical, physical and psychological impacts of it. Self-management skills can be helpful in this regard.

Objectives To develop recommendations for the implementation of self-management strategies in IA.

Methods A multidisciplinary taskforce of 18 members from 11 European countries was convened. A systematic review and other supportive information (survey of healthcare professionals (HCPs) and patient organisations) were used to formulate the recommendations.

Results Three overarching principles and nine recommendations were formulated. These focused on empowering patients to become active partners of the team and to take a more proactive role. The importance of patient education and key self-management interventions such as problem solving, goal setting and cognitive behavioural therapy were highlighted. Role of patient organisations and HCPs in promoting and signposting patients to available resources has been highlighted through the promotion of physical activity, lifestyle advice, support with mental health aspects and ability to remain at work. Digital healthcare is essential in supporting and optimising self-management and the HCPs need to be aware of available resources to signpost patients.

Conclusion These recommendations support the inclusion of self-management advice and resources in the routine management of people with IA and aim to empower and support patients and encourage a more holistic, patient-centred approach to care which could result in improved patient experience of care and outcomes.

Key messages

What is already known on this subject?

- The ability to self-manage in inflammatory arthritis (IA) represents an essential component of care that goes beyond drug therapy and which supports the patient in managing the practical, physical and psychological impacts of disease.
- Self-management is a multicomponent complex intervention that represents an unmet need in the care of people with IA.

What does this study add?

- These recommendations, based on evidence and expert opinion, confirm the beneficial effects of different components of self-management and provide guidance on embedding self-management interventions into the routine clinical care of people with IA.
- This work highlights the value of patient organisations in providing support and structured guidance for people with IA and the need to demonstrate and document the effectiveness of specific self-management interventions.

How might this impact on clinical practice?

- Adherence to these recommendations will lead to improved patient care and outcomes in people living with IA and will encourage a more active patient role in the management of disease.

INTRODUCTION

In people living with inflammatory arthritis (IA), as well as other rheumatic and musculoskeletal diseases (RMDs) and chronic conditions, an important aspect of care is the ability to understand the disease and deal with the practical, physical and psychological impacts that come along with it.[1 2] This extends beyond drug therapy and places emphasis on the ability to self-manage as an essential component of care.[3] Comorbidities including cardiovascular disease and common mental health conditions represent important, yet often poorly addressed aspects of IA despite their impact on disease outcomes.[4 5] Addressing physical as well as psychological comorbidities is therefore crucial and more likely to be achieved if more holistic approaches to patient care are adopted, including,

for example, signposting, where appropriate, to other members of the multidisciplinary team (MDT).[6] These members include, aside from rheumatologists, nurses, physiotherapists, occupational therapists, podiatrists, psychologists, nutritionists and any other healthcare professionals (HCPs) involved in the care of patients with IA.[2] All these important aspects of disease which can place a high burden on the individual and their immediate family necessitate the incorporation of supported self-management in the routine clinical care of people living with IA. For self-management to be effective however, it is imperative that HCPs (for the purposes of this work, reference to HCPs includes rheumatologists as well as allied health professionals) are given adequate guidance and professional training. This has a significant positive impact on their engagement in clinical self-management support and patient centredness, as well as on their overall confidence to support self-management.[7] Patient organisations also play a role in the provision of supported self-management resources. Acknowledging all these important aspects of care, a taskforce supported by the European Alliance of Associations for Rheumatology (EULAR) was convened to embed recommendations alongside the standard medical care of IA that encourage supported patient self-management and concordance with treatment.

The overarching aim of the taskforce was to formulate recommendations for the implementation of self-management strategies in patients with IA, including but not limited to rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. The target audience was HCPs including all members of the MDT and patients. There were three key objectives: (1) to develop EULAR recommendations for the implementation of effective self-management strategies facilitated by HCPs in IA concurrently with and complimentary to the delivery of standard medical care, (2) to enable all members of the rheumatology MDT to be able to provide and signpost a continuous and appropriate measure of support to enable better self-management of patient with IA and (3) to improve the patient's 'journey' and experience during their care, disease outcomes and quality of life.

METHODS

The 2014 updated EULAR standardised operating procedures were followed throughout the execution of this work.[8] Following approval by the EULAR Executive Committee, the convenors (AB, EN) and methodologist (LC) led a taskforce of 18 members from across 11 European countries. Taskforce members came with a background and expertise in rheumatology, nursing, occupational therapy, psychology, self-management, exercise physiology and physiotherapy. The taskforce also included patient representatives with lived experience of IA from People with Arthritis/Rheumatism across Europe. Expert discussions took place primarily through two taskforce meetings, the first, face-to-face and the second, via a virtual online platform.

In preparation for the first meeting, an initial scoping review and a survey (available on request) were undertaken to explore, respectively, effective interventions in IA and self-management resources in RMDs across Europe. During the first meeting, the scope of this work, definitions for self-management and overarching principles (OAPs) were discussed. Furthermore, unmet need and key clinically relevant questions were identified in relation to self-management in IA and sources of best practice examples explored.

In preparation for the second meeting and, as guided by the first meeting, clinical questions were converted by the steering group (AB, EN, LC, AM, EJFS) into epidemiological questions that were addressed through systematic literature review (SLR) (under submission) undertaken by the taskforce fellows (AM, EJFS). The aim of the SLR was to identify the best evidence for the implementation of self-management interventions in IA and to describe individual components and effects. The review was conducted according to the Cochrane Handbook[9] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] Patient organisations affiliated with EULAR and HCPs across Europe were also approached via direct email communication requesting information and experience/feedback on examples of self-management resources in IA, to supplement the information retrieved from the SLR.

At the second meeting, the taskforce members formulated the OAPs and recommendations based on evidence from the SLR, survey, email communication with patient organisations/HCPs and best practice examples, guided by their expert opinion and through a process of discussion and voting. Consensus was accepted in the first round if >75% of the members voted in favour of keeping it in. In the second and third rounds, after refinements, the level of agreement (LoA) was voted on a 0 to 10 scale (0='do not agree at all' to 10='fully agree') anonymously. The second round was voted through Zoom polls during the second meeting and the third round through SurveyMonkey, afterwards. The mean and SD of the LoA was presented along with the percentage of taskforce members with an agreement ≥8. An indication of the level of evidence (LoE) based on the evidence retrieved from the SLR was discussed for each of the formulated recommendations, to facilitate discussions. At the meeting, the LoE and strength of recommendation were assigned for each of the final drafted recommendations using the standards of the Oxford Centre for Evidence Based Medicine.[11]

Finally, a research agenda was formulated based on discussions around identified unmet need and gaps in evidence.

RESULTS

The taskforce discussed existing definitions for self-management and reached consensus on three OAPs and nine recommendations (table 1), guided by the results of the SLR, the surveys to patient organisations and HCPs relating to self-management resources, across EULAR countries (online supplemental file) and best practice examples (can be provided on request). In total, 12 patient organisations were approached of which 9 responded, representing eight different countries. A total of 13 HCPs were approached and 100% replied from 13 different countries.

Definition

The definition and concept of self-management varies widely in the published literature and the context in which it is used.[12] The taskforce aligned mostly with the well-established definition of self-management provided by Barlow *et al*[13] whereby self-management is defined as 'the ability of the individual to manage symptoms, treatment, lifestyle changes and psychosocial and cultural consequences of health conditions'. In this definition, two major components were highlighted: (1) self-management is aimed at achieving independence and (2) ideally, self-management

Table 1 EULAR overarching principles (OAPs) and recommendations for the implementation of self-management strategies in patients with inflammatory arthritis (IA)

	LoE (1–5)	SoR (A–D)	Level of agreement (0–10)	
			Mean (SD)	% with score ≥8
OAPs				
A. Self-management implies taking an active role in learning about one's condition and in the shared decision-making process about one's health and care pathway.	n.a	n.a	9.5 (0.6)	100
B. Self-efficacy (personal confidence to carry out an activity with the aim of achieving a desired outcome) has a positive effect on various aspects of living with IA.	n.a	n.a	9.6 (0.7)	100
C. Patient organisations often provide valuable self-management resources and collaboration between healthcare professionals (HCPs) and patient organisations will therefore benefit patients.	n.a	n.a	9.4 (1.0)	88
Recommendations				
R1. HCPs should encourage patients to become active partners of the team and make them aware of HCPs and patient organisations involved in all aspects of the care pathway.	5	D	9.5 (1.1)	87
R2. Patient education should be the start point and underpin all self-management interventions.	1A	A	9.5 (0.8)	93
R3. Self-management interventions that include problem solving and goal setting and, where relevant to the individual and available, cognitive behavioural therapy should be incorporated into routine clinical practice to support patients.	1A	A	9.1 (1.4)	93
R4. HCPs should actively promote physical activity at diagnosis and throughout the disease course.	1A	A	9.9 (0.3)	100
R5. Lifestyle advice based on evidence should be given to better manage common comorbidity and patients should be guided and encouraged by their healthcare team to adopt healthy behaviours.	5	D	9.6 (0.6)	100
R6. Better emotional well-being leads to better self-management; therefore, mental health needs to be assessed periodically and appropriate intervention should be made if necessary.	5	D	9.4 (1.3)	93
R7. HCPs should invite discussion with patients about work and signpost to sources of help where appropriate or where needed.	5	D	9.6 (0.5)	100
R8. Digital healthcare can help patients to self-manage and should be considered for inclusion in supported self-management where appropriate and available.	1B	A	9.3 (1.0)	93
R9. HCPs should make themselves aware of available resources to signpost patients to, as part of optimising and supporting self-management.	5	D	8.7 (1.2)	100

EULAR, European Alliance of Associations for Rheumatology; LoE, level of evidence (1–5; 1 indicating evidence from high-quality randomised clinical trial (RCT) data and 5 indicating evidence from expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles')[11]; n.a, not applicable; SoR, strength of recommendation (A–D; A indicating consistent level 1 studies (RCTs) and D indicating level 5 evidence or troublingly inconsistent or inconclusive studies of any level).

should be supported by others, for example, HCPs, patient organisations and family. The taskforce proposed to emphasise the important contribution that patient organisations can make in supporting self-management for the purpose of this work and any future reference on the topic, something that has been largely overlooked and left out of most definitions to date.

Overarching principles

The taskforce identified key themes considered to apply across all recommendations, formulated and agreed as three OAPs.

1. Self-management implies taking an active role in learning about one's condition and in the shared decision-making process about one's health and care pathway.
   Driven by the self-management definition above, it is important that patients take an active role in understanding their condition and engage in acquiring self-management skills and coping strategies, as well as in shared decision-making, as part of their care. Effective supported self-management encompasses the ability to monitor one's condition and to put into action the cognitive, behavioural and emotional responses necessary to maintain a satisfactory quality of life.[14–17] This way, a dynamic and continuous process of self-regulation is established. The importance of targeting and educating HCPs on self-management strategies and available resources, to ensure their ability to provide optimal support to patients, has been strongly emphasised.
2. Self-efficacy (personal confidence to carry out an activity with the aim of achieving a desired outcome) has a positive benefit on various aspects of living with IA.
   Good self-efficacy and coping skills benefit and reduce health and financial burden to the individual as well as the health service, benefitting society overall.[18 19] Self-efficacy, supported by the existing literature, implies a process as well as an outcome[20] since it is also an important outcome of self-management interventions.[1]
3. Patient organisations often provide valuable self-management resources and collaboration between HCPs and patient organisations may therefore benefit patients.
   There are numbers of best practice examples which include self-management resources in Europe, with important benefits for patients. Aside from practical advice and physical support, patient organisations can provide support with mental health issues, self-isolation and loneliness,[21] which commonly feature in patients with IA. HCPs should take responsibility for addressing these issues in people living with IA and signpost to patient organisations. The taskforce acknowledges that variation exists both in healthcare delivery and the resources that patient organisations can offer. In some countries such as the UK, patient organisations invite HCPs to become medical advisors to the organisation and also provide free membership to all HCPs. Their medical advisors actively contribute educational articles for their magazines and to patient-related campaigns, educational activities

and others. There is a close relationship that encourages cross-talk and collaboration that can be of huge benefit to patients.

Recommendations

R1. HCPs should encourage patients to become active partners of the team and make them aware of HCPs and patient organisations involved in all aspects of the care pathway

For patients to take a more active role in their health, it is important that they are introduced to all members of the MDT involved in all aspects of their disease. Patient organisations can provide an invaluable source of information and resources to support patients. Yet, there seems to be a general lack of awareness of the self-management resources (and potential value) provided by many patient organisations (eg, in terms of patient education/disease knowledge, advocacy and other resources) and hence referral to these resources by HCPs. Some patients already engage in self-management and reach out to patient organisations for support. We acknowledge that patient organisations or at least well-developed patient organisations are not always available in many parts of Europe. Where available, patients should be signposted to relevant patient organisations in parallel with all other care and treatment they may be receiving.[22 23] Where not available, we recommend using existing sources of information from the websites of other patient organisations and generally from trusted internet information sites, books and any other educational material that may be easily accessible online or via other routes.

R2. Patient education should be the start point and underpin all self-management interventions

Specific interactive education was among the most studied intervention across 19 randomised clinical trials (RCTs) based on the findings of the systematic review informing this taskforce (under submission). Self-management is considered a complex intervention as it contains many interacting techniques, thus making it difficult to identify the most effective components.[18] Patient education is considered crucial, but not sufficient, in the context of self-management and is included in a majority of interventions.[24–30] Patient education has been shown to improve treatment adherence, based on clinical trial evidence, although patient sample and follow-up time were both limited.[26] The taskforce considers treatment adherence (and discussions addressing this) to be part of the patient education plan.[31] Patient organisations reinforce the information and messaging about adherence and the impact of peer reinforcement around adherence is very powerful.

EULAR has produced recommendations for patient education for people with IA addressing when and by whom patient education should be offered, as well as modes and methods of delivery, theoretical frameworks, outcomes and evaluation.[32] We advocate the use of these recommendations when it comes to patient education, recognising that patient education is an integral part of supported self-management for people with IA throughout the course of their disease.

R3. Self-management interventions that include problem solving and goal setting and, where relevant to the individual and available, cognitive behavioural therapy (CBT), should be incorporated into routine clinical practice to support patients

There are various self-management interventions. These include problem solving[27 29 30 33–39] and goal setting,[27 29 30 33 34 37 39] as well as cognitive behavioural therapy (CBT),[28 33 35 37–41] supported by several SLRs and RCTs. The three interventions highlighted in this recommendation were therefore supported by strong evidence in their role in self-management. We advocate that they are promoted and provided where available and are relevant to patients, to enhance their ability to manage their disease confidently.[42] CBT is a psychosocial intervention, often delivered by psychologists/psychotherapists, but also by some nurse specialists who have done a course in CBT and this further highlights the important role of the MDT. Referral to CBT can be initiated by any HCP involved in the care of the patient, if any doubt, in liaison with an expert delivering the intervention.

R4. HCPs should actively promote physical activity at diagnosis and throughout the disease course

Ample evidence from the existing literature supports the use of physical activity in IA and demonstrates its beneficial effect on several outcomes.[43–49] Existing EULAR recommendations on physical activity[50] emphasise its importance in disease management, based on proven effectiveness, feasibility and safety. Physical activity should thus form an integral part of standard patient care and be actively promoted and tailored to the individual's circumstances, throughout their disease course. HCPs should be aware of the benefits of physical activity and advocate this as an important component of self-management. Any HCP should be able to promote the benefits of being physically active and take regular exercise and initiate a referral for physical therapy if deemed appropriate. If discussion is required with a physiotherapist or other physical exercise expert regarding the need and type of physical activity appropriate for an individual, then HCPs should know whom to approach for this. While there is a considerable amount of evidence for the beneficial effects of exercise, there is a general lack of emphasis on this aspect of care. Most interventions in regard to exercise relate to referral to a physiotherapist. However, the taskforce emphasises the importance and potential of exercise programmes and information provided by patient organisations and other community programmes, for example, classes which might include physical activities such as aquarobics, swimming, dancing, yoga and pilates.[51]

R5. Lifestyle advice based on evidence should be given to better manage common comorbidity and patients should be guided and encouraged by their healthcare team to adopt healthy behaviours

A number of modifiable lifestyle factors in IA can affect outcome.[52] For example, the negative effects of smoking[53] as well as high body mass index[54] impact on inflammation and disease activity are now well established, as is the increased risk of cardiovascular disease.[55] Lifestyle approaches should complement medical treatments, as also supported by a EULAR taskforce dedicated to providing recommendations on specific lifestyle interventions for the management of RMDs (currently ongoing). This taskforce considers such interventions to be a core part of self-management and advocates that patients receive support to adopt healthy behaviours including guidance on what constitutes a healthy, balanced diet, the benefits of exercise and quitting smoking, among others. Where specialised input is needed, for example, on nutrition, the input from dieticians should be sought where possible, acknowledging that dieticians are not always 'standard' members of the MDT so external support might be required. Such interventions are expected to have a positive impact on comorbidities and extra-articular manifestations, as well as the IA itself and should be accompanied by relevant investigations such as lipid profile testing, blood pressure monitoring and sleep hygiene.[4 6 56 57] The addressing

of comorbidities and initiation of relevant investigations may be undertaken by primary care physicians, rheumatologists or other HCPs such as nurses, involved in the patient's care and as part, for example, of an annual review clinic. Some centres have their own pro formas for screening of comorbidities or lifestyle factors, for example, smoking, and these can be helpful as part of the screening process and facilitate the process for any member of the MDT.

R6. Better emotional well-being leads to better self-management; therefore, mental health needs to be assessed periodically and appropriate intervention be made if necessary

Poor mental health leads to worse outcomes in IA.[58–60] CBT and other psychosocial interventions[43 61–64] should be offered where available and tailored according to individual needs. Addressing mental health issues can help mitigate self-isolation and feelings of loneliness and can result in better self-management.[59 65] Examples of questionnaires that could be used to measure patients' emotional well-being feasibly in routine clinical practice include the mental health component of the SF36[66] and the Patient Health Questionnaire (PHQ-9).[67] The taskforce acknowledges that many patient organisations provide forums for networking and peer support programmes which can improve emotional well-being. Furthermore, we acknowledge that patients requiring more specialist assessment and support for mental health issues should be signposted as necessary, for example, to psychology and/or psychiatry.

R7. HCPs should invite discussion with patients about work and signpost to sources of help where appropriate or where needed

EULAR's current strategy states that 'by 2023, EULAR's activities and related advocacy will have increased participation in work by people with RMDs'.[68] The greatest proportion of people with IA are of working age at the time of diagnosis and work represents a major contributor to financial independence, self-esteem, purpose in life and overall quality of life.[2 69 70] Therefore, it is crucial to the taskforce that HCPs address work-related aspects and signpost the patients to useful resources and support them to stay in work and maintain their independence.[71] Occupational therapists and occupational health experts can provide helpful advice and resources in relation to the workplace.

R8. Digital healthcare can help patients to self-manage and should be considered for inclusion in supported self-management, where appropriate and available

Electronic patient records and other digital resources such as mobile health apps are becoming increasingly available in healthcare delivery.[72] Mobile health technologies in particular can support self-management and allow people to take a more active role in their health.[72 73] Patient-reported outcome domains as deemed relevant and important by patients could also be considered with digital healthcare. EULAR recommendations provide guidance on important aspects that should be considered for the development, evaluation and implementation of existing and new apps.[74] The taskforce recommends referring to EULAR guidance on the above.

R9. HCPs should make themselves aware of available resources to signpost patients to, as part of optimising and supporting self-management

The taskforce highlighted the need for HCPs to be made aware of available resources for patients with IA, including those provided by patient organisations, to promote and support self-management interventions. At the same time, the taskforce recognised that just as there's variation in healthcare resources, there is also variation in what patient organisations can offer.[75]

DISCUSSION

This EULAR taskforce has produced three OAPs relevant to nine agreed recommendations for the implementation of supported self-management strategies in patients with IA. OAPs and recommendations were met with strong consensus among experts in the task force.

The concept of self-management to some may imply needing to deal alone with a chronic condition.[76] Receiving adequate support from a variety of sources is crucial.[77] A key role of HCPs is also to enable access to and to signpost to supported self-management resources. Many HCPs will need to make themselves aware of how to most effectively provide and signpost to these different resources. The taskforce highlighted the importance of honesty and building trust as important elements for establishing open communication between patients and HCPs.[78–81] Adequate time should be given to patients, as well as family and carers to discuss concerns and management options.[82 83] Forward planning should be based on goal setting and what matters to patients, as supported by the existing literature.[27 29 30 33 34 37 39] Furthermore, it was recognised that context, in other words, health system, culture or local resources, vary across settings and that nothing can be implemented without a clear familiarity and understanding of the local context. It is therefore important to understand and appreciate individual circumstances and social context when it comes to patient care, to maximise chances of implementing proposed care and supported self-management plans.[84 85] For example, potential barriers to effective engagement with self-management could include poor health literacy and cultural or personal barriers, for example, for the latter, language barriers and low education. These should be identified where possible to maximise the support given to patients and to enhance their overall participation in self-management strategies. In some countries, patient organisations are particularly influential and with well-developed, active websites, support lines, educational material and some even with self-management programmes already established and made available to patients, families and carers. We encourage the use of social media such as Facebook, Twitter, websites and advertisements, for example, on national TV/radio to promote these resources.

Exploration of various definitions of self-management by the task force indicated that more holistic definitions of self-management reflecting the 'individual's ability to manage symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition' were more warmly received.[3] The taskforce additionally highlighted the important contribution that patient organisations can make in supporting self-management, an aspect that has been largely left out of definitions to date. The latter is supported by additional sources of evidence informing this task force including direct communication with chief executives of patient organisations and best practice examples (available on request). However, the taskforce noted that the constitution of patient organisations varies considerably from large professional expert organisations led by paid chief executive officers and staff governed by boards of trustees to very small organisations which are primarily volunteer led. This means that the resources provided by patient organisations also vary.

Patient education has been identified as a crucial component that should underpin all self-management interventions.

Effective patient education should be the responsibility of both the HCPs and the patients themselves. Patient education has been shown to improve treatment adherence,[26] something that this taskforce recognises as an important part of patient education. Furthermore, patient outcomes including effective disease knowledge, healthcare management and self-efficacy have been shown to improve with patient education.[24–30]

The vision of the taskforce is that patient–HCP communication, the setting of meaningful and achievable goals and shared decision-making are seen as core components of self-management. This aligns well with EULAR's current quality-of-care strategy that by 2023, EULAR will deliver pre-eminent comprehensive quality of care frameworks for the management of people with RMDs. One of the main quality-of-care objectives is to provide a 'package' that will enable greater uptake of the advice given in the recommendations, in other words emphasis on implementation aspects.[68] In this regard and in relation to the nine recommendations, the taskforce recognised the importance of:

1. Raising awareness and educating HCPs on self-management strategies and available resources, to ensure ability to provide optimal support to patients.
2. Efforts to increase awareness and strengthen collaborations between patients, patient organisations and HCPs.
3. Signposting patients to good evidence-based information, also provided by many patient organisations.
4. Patient education as a crucial component of self-management, while acknowledging that being educated around various aspects of the disease does not necessarily imply implementation of meaningful changes.

It was particularly highlighted that training of HCPs, for example, on CBT, can improve their skills to deliver interventions and can be of great benefit to patients.[28 33 35 37–41] The taskforce emphasised the need and importance of members of the MDT to be encouraged to work as a team towards implementation of the specific recommendations. Knowledge sharing should form a core part of these MDT meetings. Additionally, individual needs and variation in national health systems, availability of local resources and patient organisation offerings should be considered as part of the implementation. Finally, it is important to keep in mind that for self-management to be effective, the mode of delivery of various interventions should be considered in the setting of disease and severity, individual social circumstances and available resources. Referral to occupational health, occupational therapy patient organisations for resources related to work issues and other support should be considered where indicated and available.

With the recognition of all the above, unmet need has been identified and a research agenda has been proposed (box 1) for future work on the subject. An important focus has been the value of patient organisations and information and other resources they can provide to support people with IA, as well as the need to demonstrate and document the effectiveness of specific self-management interventions. It is particularly challenging for patient organisations to demonstrate the value of what they do, however, this does not remove the need for them to make real effort to demonstrate the impact of their resources. The taskforce identified, as part of the educational agenda, that there is scope for using best practice self-management programme examples to encourage and support other less-developed patient organisations and healthcare systems to work towards developing similar patient resources. Furthermore, in current clinical practice there is a strong emphasis on achieving clinical markers that are of importance to HCPs, for example, lowering of disease activity, whereas this taskforce is advocating that more focus should be given to goals that are more meaningful to the patients in the context of their everyday lives. In this respect, we recommend raising awareness among HCPs of the importance of the biopsychosocial determinants of health.

Box 1 Research agenda

Self-management in inflammatory arthritis (IA)—identified unmet need and suggested focus for future research.

1. To demonstrate the effectiveness of specific self-management interventions in IA and their impact on disease activity.
2. To study specific patient-reported outcome domains potentially affected by self-management including pain, fatigue, sleep, emotional and physical well-being, disability, quality of life and self-efficacy and explore a core outcome set.
3. To elucidate the cost-effectiveness of specific self-management interventions and programmes delivered.
4. To study the role of patient organisations and explore the impact of these organisations and the resources and support they provide for people with IA.
5. To investigate the impact of remotely delivered self-management interventions compared with face-to-face interventions.
6. To explore how the European Alliance of Associations for Rheumatology community could implement strategies to support and enable less established patient organisations to adapt best practice examples to suit their local circumstances.

CONCLUSIONS

In conclusion, EULAR recommendations are now available for the implementation of self-management strategies in patients with IA. A dissemination strategy is currently underway to enhance the uptake of these recommendations, through national organisations, patient organisations and educational programmes.

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EULAR points to consider for conducting clinical trials and observational studies in individuals at risk of rheumatoid arthritis

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ABSTRACT

Background Despite growing interest, there is no guidance or consensus on how to conduct clinical trials and observational studies in populations at risk of rheumatoid arthritis (RA).

Methods An European League Against Rheumatism (EULAR) task force formulated four research questions to be addressed by systematic literature review (SLR). The SLR results informed consensus statements. One overarching principle, 10 points to consider (PTC) and a research agenda were proposed. Task force members rated their level of agreement (1–10) for each PTC.

Results Epidemiological and demographic characteristics should be measured in all clinical trials and studies in at-risk individuals. Different at-risk populations, identified according to clinical presentation, were defined: asymptomatic, musculoskeletal symptoms without arthritis and early clinical arthritis. Study endpoints should include the development of subclinical inflammation on imaging, clinical arthritis, RA and subsequent achievement of arthritis remission. Risk factors should be assessed at baseline and re-evaluated where appropriate; they include genetic markers and autoantibody profiling and additionally clinical symptoms and subclinical inflammation on imaging in those with symptoms and/or clinical arthritis. Trials should address the effect of the intervention on risk factors, as well as progression to clinical arthritis or RA. In patients with early clinical arthritis, pharmacological intervention has the potential to prevent RA development. Participants' knowledge of their RA risk may inform their decision to participate; information should be provided using an individually tailored approach.

Conclusion These consensus statements provide data-driven guidance for rheumatologists, health professionals and investigators conducting clinical trials and observational studies in individuals at risk of RA.

INTRODUCTION

It is now clear that the onset of rheumatoid arthritis (RA) is preceded by a complex preclinical phase.[1] While the early arthritis paradigm (ie, early identification and treatment) has revolutionised the outlook of RA, interventions targeting the preclinical phase may unleash an even greater therapeutic leap. In the preclinical phase, 'at-risk' individuals, many of whom have genetic or environmental predispositions, develop autoantibodies and/or symptoms and eventually progress to clinical arthritis and classifiable RA.[2] Over the last decade, longitudinal observational studies of prospective at-risk cohorts have identified risk factors and biomarkers, which have enabled a better understanding of RA pathobiology and also prediction of the onset and timing of clinical arthritis.[3–5] In this way, symptomatic at-risk populations may now be risk stratified for future RA development.[6 7] Building on this work, clinical trials investigating therapeutic intervention in at-risk individuals with the aim of RA prevention have been conducted.[8 9] Several more are now either underway or in preparation; all are targeting at-risk populations with the aim of RA prevention. While sharing a common goal, these trials are strikingly heterogeneous; different at-risk populations have been included with different eligibility criteria, biomarkers, interventions and outcomes. The heterogeneity is a natural consequence of the infancy of the field but may present unwelcome challenges in interpreting the relevance and validity of the findings. As this field grows exponentially, it is critical that all future efforts are optimally aligned; at-risk individuals are difficult to identify, recruit and monitor but provide invaluable opportunity for insights into the pathobiology of RA and new avenues for prevention that must be maximised.

The current EULAR task force was convened with the goal of providing data-driven guidance and consensus for use by current and future investigators in this important area of rheumatology research.

METHODS

An international multidisciplinary task force was convened with the aim of defining points to consider for conducting clinical trials and studies in individuals at risk of RA (co-convened by KM and PE). The task force included 13 academic rheumatologists from Europe and North America with specific expertise in this area. There were two project methodologists/epidemiologists (DA and AK). The task force also included one health professional (HP),

two rheumatologists from the EMerging EULAR NETwork (EMEUNET) and two patient representatives from the people with arthritis / rheumatism across Europe (PARE) network of patient research partners. In developing the points to consider, the task force followed the most recent EULAR standardised operating procedures for the development of recommendations.[10] The project was fully approved by the EULAR executive committee.

At the first meeting (October 2019 in Amsterdam, the Netherlands), the task force discussed the background and focus of the project and defined the objectives. Four key questions to be addressed by systematic literature reviews (SLRs) were then prioritised by a group voting process, supervised by the methodologists. The SLR was performed by the fellow and co-convenor (KM) and the allied health professional (AHP) (HJS) with support from one of the EMEUNET members (DAR), a librarian (Joel Kerry) and a research fellow from Leeds (Andrea Di Matteo). Based on the findings of the SLRs, a draft of the points to consider and research agenda was prepared by the fellow (KM), AHP (HJS), the methodologists (DA and AK) and the convenor (PE).

At the second meeting (held in April 2020, by video conference due to the COVID-19 pandemic), the SLR results and the draft of the points to consider and research agenda were presented to the task force. Following group discussions, during and after the meeting, the task force agreed on the final consensus statements which encompassed 1 overarching principle, 10 points to consider and 1 research agenda. Task force members were then asked to anonymously rate the overarching principle and points to consider on a scale of 0 (absolutely disagree) to 10 (absolutely agree) to assess the level of agreement (LoA). The research agenda was extensively discussed between members and consensus was achieved on the points to be included. Comments from external industry stakeholders (Marie Brazil, Francesco De Leonardis and Jens Gammeltoft Gerwien) on the final consensus statements were proactively elicited and further considered during the writing of the manuscript.

RESULTS

Systematic literature review

The task force agreed on the following four questions to be addressed by the SLR:

1. In clinical studies involving individuals at risk of RA, which populations should be included and what study endpoints should be used?
2. In individuals at risk of RA, is there a core set of risk factors and how frequently should they be measured?
3. In individuals at risk of RA, does risk-factor-driven intervention alter risk of progression?
4. Is there a benefit in informing individuals at risk of RA about their risk of developing RA and offering preventive treatment?

It was acknowledged that questions 3 and 4 were focused on potential interventions. The task force felt these questions would inform the design of clinical trials and studies in this area and would be important to include; question 3 would inform which potential interventions should be selected by investigators, while question 4 would inform recruitment strategies, communication approaches and feasibility of future studies.

To address these questions, four separate literature searches were conducted (see online supplemental materials for details). For each search, the relevant keywords were used in Medline, Embase, Pubmed and Central databases. Abstracts from January 2018 onwards were included. Meta-analyses were included, but all other reviews and study protocols were excluded. Manually searched articles either from the references of selected manuscripts or identified by task force members were also included.

The task force agreed on 1 overarching principle, 10 points to consider (table 1) and 1 research agenda. When deciding overarching principles, discussion focused on the at-risk populations being recruited, data collection, study design and outcomes. Consideration was given to principles included in the 10 points to consider, to ensure specific guidance included in these points was not repeated. It was agreed that only one overarching principle should be put forward and this should specify key features, which should be collected from all at-risk populations.

Industry stakeholders received the initial draft of the manuscript and made comments and edits mainly around text wording, communication of content and structure. For example, statements were clarified with explanatory text where needed. The industry stakeholders helped ensuring that the manuscript would be relevant and accessible to potential industry partners who may be involved in future clinical trials and studies in this area. Industry bias was avoided as representatives were chosen to provide personal views based on their individual expertise and experience only (two in clinical research and trials and one in basic and translational science).

Overarching principle

All clinical trials and observational studies in individuals at risk of RA should include the epidemiological and demographic characteristics of the at-risk population being studied (LoA 10)

The task force recognised the different populations of at-risk individuals currently being studied in prospective cohorts internationally. While individual studies may prioritise the investigation of specific risk factors or a specific intervention in these populations, the task force agreed that certain population characteristics should invariably be measured. These are the core epidemiological and demographic characteristics of age, sex, body mass index (BMI), ethnicity, smoking status and family history of RA. Recording these core characteristics enables direct comparison and where possible integration of datasets from multiple cohorts.

Points to consider

1. For clinical trials or observational studies, individuals at risk of RA should be identified according to their clinical presentation. Within each clinical presentation, subpopulations should be identified based on the presence of specific risk factors (LoA 9.75)

Several different populations of individuals at risk of RA are being included in prospective clinical studies and interventional trials. The population differences largely reflect the available infrastructure, local populations and research interests of the various centres involved. Individuals usually present to healthcare professionals because of their clinical symptoms and signs, and the evolution of clinical features also reflects the natural history of RA development. Therefore, the task force felt it appropriate for at-risk populations to be categorised according to their clinical presentation. The task force decided against categorising at-risk populations based on just 'symptoms' and 'signs', as clinical signs (eg, joint tenderness) may be present in the absence of clinical synovitis. The term 'arthralgia' was avoided in categorisation as not all at-risk individuals with musculoskeletal (MSK) symptoms have arthralgia, with some presenting with non-specific symptoms instead. The task force proposed three broad categories, which underpin disease progression:

Table 1 Overarching principle and points to consider for conducting clinical trials and observational studies in individuals at risk of RA

		LoE LoA
Overarching principle		
1	All clinical trials and observational studies in individuals at risk of RA should include the epidemiological and demographic characteristics of the at-risk population being studied	5 10
Points to consider		
1	For clinical trials or observational studies, individuals at risk of RA should be identified according to their clinical presentation. Within each clinical presentation, subpopulations should be identified based on the presence of specific risk factors	5 9.75
2	In clinical trials and observational studies of individuals at risk of RA, the development of clinical arthritis or progression to RA (according to 2010 ACR/EULAR Rheumatoid Arthritis Criteria) should be considered as study end-points	2b 9.85
3	The development of subclinical inflammation on US and/or MRI should also be considered as an end-point in at-risk populations without subclinical disease	2b 8.65
4	In at-risk populations with clinical arthritis (ie, PR and UA patients), interventional studies should include disease remission (on/off therapy) as an end-point	1b 9.55
5	In clinical trials or observational studies of individuals at risk of RA, risk factors should be assessed in a population-specific manner, and should include, or be a composite of, core and emerging risk factors	5 9.7
6	Risk factors should be assessed at baseline and repeated assessment considered according to the specifics of the study population and intervention	5 9.75
7	Clinical trials should evaluate the ability of a specific intervention to modify the risk factor itself (as well as the risk of progression to RA)	5 9.65
8	In individuals at high risk of RA (eg, with early clinical synovitis), drug intervention should alter progression to RA or the outcome of RA therapy	1b 9.5
9	In clinical trials and observational studies, individuals should be informed about their risk of developing RA using an approach tailored to the individual participants	5 9.5
10	Individuals should be informed about their risk of progression to RA, as this may modify their decision to participate, or not, in clinical trials and observational studies	2b 9.85

LoA; mean LoA of taskforce members. 1a systematic review of randomised controlled trials (RCTs); 1b, individual RCT; 2a, systematic review of cohort studies; 2b, individual cohort study (including low quality RCT); 3a, systematic review of case–control studies; 3b, individual case–control study; 4, case series (and poor-quality cohort and case–control studies); 5, expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.
ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; LoA, level of agreement; LoE, level of evidence; MRI, magnetic resonance imaging; PR, palindromic rheumatism; RA, rheumatoid arthritis; UA, undifferentiated arthritis; US, ultrasound.

asymptomatic, MSK symptoms without clinical arthritis and early clinical arthritis.

Asymptomatic at-risk individuals

Asymptomatic at-risk individuals are typically identified through either family relationships or population screening for the presence of informative autoantibodies.[11–13] With these approaches, asymptomatic individuals are presumed to exhibit genetic or environmental risk factors without clinical symptoms or signs of arthritis. The influence of genetic and environmental risk factors in asymptomatic individuals who exhibit autoantibodies has not been well characterised across prospective cohorts. The first-degree relatives (FDRs) of people with RA are a population with genetic risk who may be feasibly identified from the general population (via the affected RA proband). FDRs are currently being studied in multiple research cohorts both to understand the pathobiology of RA and to investigate the influence of specific risk factors on disease progression in this population.[14–19] Considering risk factors in FDRs, serum autoantibodies and other serum biomarkers have been the best characterised. Serum anti-citrullinated protein antibodies (ACPA) are enriched in FDRs[20] and associated with arthritis development.[17] Multiple serum cytokines and chemokines are associated with ACPA and disease progression in FDRs.[21 22] Conversely, omega-3 fatty acid levels appear to have an inverse relationship with anti-cyclic citrullinated protein (anti-CCP) antibodies in those with genetic risk.[23 24]

In addition to FDRs from the general population, specific geographical populations also carry a heightened genetic risk of RA. Indigenous North Americans (INA), also referred to in the research literature as Indigenous Peoples, North American Natives, First Nations, First Nations Peoples, North American Indians, Aboriginals or Aboriginal peoples, have been the best characterised.[25 26] Many of these populations exhibit high RA prevalence rates of predominantly seropositive, severe disease,[27] familial clustering of cases[19] and unfavourable disease outcomes. Although likely a significant factor, the increased risk may not be solely due to genetics, environmental factors, access to appropriate rheumatology care or a combination of these factors are also likely to be important. Studies of genetic risk in American Indians of Alaska and First Nations Peoples of Central Canada have shown that the shared epitope (SE) encoding allele HLA-DRB1*1402, which is almost unique to Indigenous Peoples, is a particularly important risk factor.[28] Non-human leukocyte antigen (HLA) genes in these populations also appear to play a role.[29]

Longitudinal studies in FDRs of indigenous populations have demonstrated a high prevalence of serum ACPA (~10%) and rheumatoid factor (RF) (~15%). Although associated with arthritis development, ACPA levels fluctuate over time and not uncommonly revert to a seronegative state.[30] Also, ACPA IgG variable domain glycosylation is a strong predictor of future RA development, in such populations.[31]

Overall, the task force agreed that FDRs, individuals who screen positive for ACPA and genetically predisposed indigenous populations are important asymptomatic at-risk populations that should be studied. Within these populations, serum autoantibodies and other serum biomarkers enable identification of important subpopulations.

At-risk individuals with MSK symptoms without clinical arthritis

Several different symptomatic at-risk populations without clinical arthritis are being studied. These include ACPA-positive individuals with MSK symptoms,[7 32] seropositive (ACPA and/or RF) individuals with arthralgia[33] and individuals with clinically suspect arthralgia (CSA).[34 35]

In these individuals, subpopulations may be defined based on serum autoantibodies, serum biomarkers, clinical symptoms and

subclinical inflammation on imaging. In ACPA-positive individuals with MSK symptoms, a high anti-CCP level and the presence of RF are strongly associated with arthritis development.[7] A high ACPA level is also associated with disease progression in ACPA-positive individuals without arthritis, but less well-defined clinical symptoms.[36 37] In patients with seropositive arthralgia, the presence of anti-CCP antibodies, a high level of anti-CCP antibodies, the extent of the ACPA repertoire and dual positivity to anti-CCP and RF are all associated with arthritis development.[6 33 38 39] ACPA and RF positivity are also associated with arthritis development in individuals with CSA.[35 40] Anti-carbamylated antibodies have also been shown to be associated with arthritis development in patients with seropositive arthralgia.[41] Serum and cellular biomarkers (T cell subsets) have predictive value in ACPA-positive individuals with MSK symptoms[42] and seropositive arthralgia.[43 44] The presence of certain clinical symptoms such as small joint tenderness and early morning stiffness are relevant for risk stratification in ACPA-positive individuals with MSK symptoms and patients with seropositive arthralgia.[6 7] In patients with CSA, difficulty making a fist and a positive 'squeeze test' are associated with subclinical inflammation on MRI particularly tenosynovitis[45 46] and is predictive of arthritis development.[45] A set of clinical features in individuals at risk of RA were defined by a recent EULAR task force.[34]

In ACPA-positive individuals with MSK symptoms, patients with seropositive arthralgia and patients with CSA, subclinical inflammation on imaging has been characterised on ultrasound (US) and MRI. Intra-articular inflammation (grey scale and power Doppler signal) is the most relevant on US,[47 48] whereas tenosynovitis is the most specific and predictive feature for arthritis development on MRI.[49 50]

The task force agreed that serum autoantibodies (especially ACPA), serum and cellular biomarkers, clinical features and subclinical inflammation on imaging should all be used to characterise subpopulations in symptomatic at-risk individuals without clinical arthritis.

At-risk individuals with early clinical arthritis

Two important populations with early clinical arthritis who are at risk of progression to RA are patients with undifferentiated arthritis (UA) and palindromic rheumatism (PR). Both have been studied extensively in prospective cohorts. For both conditions, clinically relevant subpopulations may be defined based on the presence of serum autoantibodies,[51–54] serum biomarkers, clinical features[54] and subclinical inflammation on imaging.[55–57] In both PR and UA, these factors may be used for risk stratification (discussed below).

2. In longitudinal studies of individuals at risk of RA, the development of clinically evident arthritis, or progression to RA (according to 2010 ACR/EULAR Rheumatoid Arthritis Criteria), should be considered as study end-points (LoA 9.85)

Most longitudinal studies in at-risk populations have been performed in cohorts of individuals who have MSK symptoms without clinical arthritis (as described in point 1). The development of clinically evident arthritis is the most frequently studied primary end-point in longitudinal studies in ACPA-positive individuals with MSK symptoms, patients with seropositive arthralgia and patients with CSA. In many cases, individuals who develop clinical arthritis will also meet ACR/EULAR classification criteria for RA.[58] This criterion is often included as a separate secondary end-point in studies. Investigators of a large Mexican longitudinal cohort study of relatives of RA probands (including FDRs) defined the development of clinical inflammatory arthritis (IA) as the primary end-point[17] as have others.[59] Longitudinal studies of INA have used development of RA as the primary end-point.[30 60]

Longitudinal studies of at-risk populations with clinical arthritis (ie, UA and PR) have specified the development of RA (either 2010 ACR/EULAR Criteria or previously accepted criteria) as the primary end-point. For PR, all such longitudinal studies have used the 1987 (or older) criteria due to age of the studies.[51–53 61–65] In these studies, the primary end-point represents a clear transition from a relapsing–remitting phenotype to a persistent arthritis. In studies of patients with UA, the population is described as having undifferentiated or unclassified arthritis or early IA not meeting classification criteria for RA.[66–76] In each case, the definition of UA is based on having clinical arthritis but not meeting the specified classification criteria for RA. Therefore, the RA classification criteria used are critical to the interpretation of the findings. The task force acknowledged that many of the patients with UA included in studies, which have not used the most recent classification criteria, are likely to have met the updated 2010 criteria, which is more sensitive for early disease.

3. The development of subclinical inflammation on US and/or MRI should also be considered as an end-point in at-risk populations without subclinical or clinical disease (LoA 8.65)

In at-risk populations without clinical or subclinical joint disease, the development of pathological subclinical inflammation on imaging is a significant step as it represents a transition from systemic autoimmunity to local articular inflammation, and is associated with imminent clinical arthritis. To reflect this, some longitudinal cohort studies stipulate the development of imaging-detected synovitis as the primary study end-point.[77] Subclinical synovitis on US also influences clinical decision-making in at-risk individuals with MSK symptoms.[78] The task force, therefore, felt it appropriate that the development of subclinical inflammation on imaging should be considered as an end-point distinct from the development of clinical arthritis (see table 2 for definitions of arthritis). The most appropriate imaging modality and protocol to use for detection of subclinical inflammation in at-risk populations are a subject for future research and were beyond the scope of the current task force.

4. In at-risk populations with clinical arthritis (ie, patients with PR and UA), interventional studies should include disease remission (on/off therapy) as an end-point (LoA 9.55)

Several interventional studies have been performed in patients with UA. Some have specified disease remission as the primary study end-point.[68 79 80] In addition, others have included disease remission as a secondary end-point,[81–84] with the primary end-point instead being the development of classifiable RA. Of those studies stipulating disease remission as an end-point, the majority tested short-term induction therapy, that is, the ability to achieve drug-free remission (DFR). In the PRObable rheumatoid arthritis: Methotrexate vs Placebo Treatment (PROMPT) trial, van Dongen *et al* investigated 12 months of

Table 2 Definitions of arthritis

Asymptomatic	The absence of arthralgia or other musculoskeletal symptoms Symptoms not exclusively musculoskeletal, such as fatigue may be present
Subclinical inflammation on imaging	The presence of signs of joint inflammation on high-resolution imaging in the absence of clinical arthritis
Clinical arthritis	The presence of inflammatory joint swelling on clinical examination

induction therapy with methotrexate (MTX) in patients with UA and stipulated DFR at 30-month follow-up as a study end-point. There was no significant difference in DFR rates in the MTX and placebo arms.[82] However, in a subanalysis of high-risk patients only (Leiden prediction score ≥8), DFR at 30 months was achieved in 36% of the MTX arm compared with 0% in the placebo arm (p=0.027), although in a total of only 22 patients.[81] In the Stop Arthritis Very Early (SAVE) trial, the primary end-point was disease remission at 12 weeks and 15 weeks after a single intramuscular injection of methylprednisolone or placebo. DFR was achieved by 32/198 (16.2%) of the treatment group and 33/185 (17.8%) of the placebo group (p=0.68).[79] In a recent observational study, data were used from the Induction therapy with MTX and prednisolone in Rheumatoid Or Very Early arthritic Disease (IMPROVED) study to specifically investigate predictors of DFR at 1 year in a subgroup of patients with UA who achieved remission and tapered all therapy at 8 months, according to a predefined protocol.[80] In a recent small study of infliximab (IFX; given at week 0, week 2, week 6, week 14 and week 22) versus placebo in patients with ACPA-positive UA, DFR (according to DAS28 CRP) at 1 year was observed in 50% of the IFX group versus 21.4% of the placebo group.[83]

In contrast to the above-mentioned studies, two trials have used disease remission while still on therapy as an end-point.[68 84] The first was a trial of IFX in patients with poor-prognosis UA who relapsed after a single corticosteroid injection, and the second a study of MTX compared with placebo. There was no difference in remission rates in the IFX study, whereas in the more recent MTX study, the proportion of patients who achieved Boolean remission after 1 year was greater in the MTX group compared with the placebo group.[84]

In a recent interventional study performed in a PR cohort, a predefined disease modifying anti-rheuamtic drug (DMARD) escalation protocol was used to bring flares under control with the aim of achieving disease remission.[85] Complete or partial remission was achieved in 76/106 (82.6%) of patients, while 16.3% of patients were able to discontinue medications and achieve DFR. Disease remission (defined as the absence of flares for ≥1 month) on therapy was also the primary end-point in a study of rituximab (RTX) in PR.[86] All of the 33 patients with seropositive PR in this study eventually achieved remission, although some required four cycles of RTX to do so. Neither of these studies were controlled trials.

5. In clinical trials or observational studies of individuals at risk of RA, risk factors should be assessed in a population-specific manner. Risk factors should include, or be a composite of, core and emerging risk factors (LoA 9.7)

Risk factors for the development of RA have been investigated using both large retrospective case–control studies and prospective cohort studies in predefined at-risk populations. The advantage of the former is the availability of large datasets from national and international registries, which allow the influence of specific genetic or environmental risk factors in the background population to be accurately quantified. However, to investigate the influence of specific risk factors in at-risk populations (as opposed to the general population), as well as the effects of risk factors that operate in a stage-specific manner, prospective cohort studies have proven most valuable.

Several different risk factors have been investigated in prospective cohort studies in well-defined at-risk populations. The task force agreed that risk factors are population specific, for example, symptom complexes and imaging are only relevant in at-risk populations who have symptoms. Therefore, risk factors should to be assessed according to the at-risk population, which is being included in a particular study or trial. Within each population, some risk factors have a strong evidence base, while others have a more limited evidence base. It was, therefore, felt that 'core' and 'emerging' risk factors may be defined based on the current evidence base. The task force agreed that core risk factors should, where feasible, always be assessed in a clinical trial or observational study (table 3).

Table 3 Core and emerging risk factors for arthritis according to different at-risk populations

At-risk population	Core risk factors for arthritis	Emerging risk factors for arthritis
Asymptomatic at-risk individuals	Genetic risk factors Serum ACPA and/or other autoantibodies	Serological biomarkers
MSK symptoms without arthritis	Genetic markers Serum autoantibody profiling (including ACPA/RF) Subclinical inflammation on imaging (US and MRI) Clinical symptoms (EMS duration, joint tenderness and symptom duration)	Serological and cellular biomarkers Mucosal inflammation/ dysbiosis
Early clinical arthritis	Genetic markers: serum autoantibody profiling (including ACPA/RF) Subclinical inflammation on imaging (US and MRI) Clinical symptoms (EMS duration, joint tenderness and symptom duration)	Serological and cellular biomarkers Mucosal inflammation/ dysbiosis

ACPA, anti-citrullinated protein antibodies; EMS, early morning stiffness; MSK, musculoskeletal; RF, rheumatoid factor; US, ultrasound.

Asymptomatic at-risk individuals

Studies in large prospective cohorts of individuals with genetic risk factors for RA or identified in population screening have demonstrated that the additional presence of ACPA and other autoantibodies are significant risk factors for arthritis development. Anti-CCP-positive relatives (mainly FDRs) of RA probands are at much higher risk of developing RA compared with their seronegative counterparts (positive predictive value (PPV) of 64% for RA development at 5 years in CCP+/RF + relatives).[17] Similarly, 30% of anti-CCP+/RF + relatives of INA developed RA after a median of 3-year follow-up.[30] Before the availability of ACPA testing, a seminal study of over 2000 healthy INA monitored biannually for up to 19 years revealed a highly significant association between RF level and RA development (p<0.001, controlling for age and sex).[60]

Genotype also confers additional risk of ACPA and RA in FDRs of INA populations. The combination of HLA-DR SE and the non-SE allele DRB1*0901 is associated with ACPA and earlier age of RA onset in these FDRs.[87] IgG ACPA glycosylation also appears to be strongly predictive of the future development of RA in INA FDRs.[31]

The core and emerging risk factors, which should be assessed in this population, are summarised in table 3.

At-risk individuals with MSK symptoms but without clinical arthritis

Several risk factors for the development of clinical arthritis and RA have been identified in ACPA-positive individuals with MSK symptoms, patients with seropositive arthralgia and patients with CSA. Autoantibodies (especially ACPA), clinical symptoms and imaging markers have the strongest evidence base.

The importance of ACPA status has been confirmed in various international cohorts, including a UK ACPA+ cohort with new

non-specific MSK symptoms,[7] a Dutch seropositive (CCP+/RF+) arthralgia cohort[33 38] and a Dutch CSA cohort.[40] The heightened risk conferred by high-tire ACPA is reflected in the highest weighting given to this risk factor in two clinical prediction rules for arthritis development.[6 7] Anti-carbamylated protein (anti-CarP) antibodies also appear to confer additional risk of arthritis development in ACPA/RF + at-risk individuals, independent of ACPA status.[41] However, the level of risk does not appear to be as pronounced as that related to ACPA.

Certain clinical features are associated with an increased risk of arthritis development. Of these, prolonged early morning stiffness (EMS) duration is a cardinal symptom. Prolonged EMS duration is an important risk factor for arthritis in ACPA+ individuals with MSK symptoms (EMS >30 min)[7] and patients with seropositive arthralgia (EMS >60 mins),[6] and has been included in clinical prediction rules. EMS is also one of the components included in the agreed definition of CSA[34] and is associated with arthritis development in unselected patients presenting with arthralgia.[88] Joint tenderness (especially of the small joints) was also associated with arthritis development in ACPA+ individuals with MSK symptoms[7 36] in two cohorts. Other symptom complexes were associated with progression to arthritis in seropositive arthralgia—duration of symptoms less than 1 year, intermittent symptoms and history of joint swelling.[6] These symptoms were not prognostic in the UK ACPA+ cohort, perhaps because all individuals had new-onset symptoms and patients with PR were specifically excluded.

Abnormalities on high-sensitivity US and MRI (and positron emission tomography in one study[89]) also signify an increased risk for arthritis development in at-risk individuals. These abnormalities reflect the presence of intra-articular and extracapsular subclinical inflammation, in at-risk individuals who have symptoms without clinically evident arthritis. Several studies have identified the presence of subclinical US synovitis (power Doppler and grey scale) as a risk factor for arthritis development both at joint and patient level.[47 48 90 91] Recent data suggest US tenosynovitis is associated with arthritis development in ACPA+ individuals with non-specific MSK symptoms and no subclinical synovitis on baseline US.[77 92] In those with symptoms, the development of US synovitis appears to be a relatively late event, reflecting imminent clinical arthritis,[93] especially as more joints become involved.[94]

MRI studies in ACPA+ individuals with MSK symptoms and patients with CSA have identified tenosynovitis as both the most prevalent abnormality and the strongest MRI risk factor for arthritis development.[35 50 95] Tenosynovitis was the only MRI abnormality associated with arthritis progression at patient level in a study of 98 ACPA+ individuals with MSK symptoms (HR 4.02 (1.91–8.44), p=0.002).[95] Similarly, tenosynovitis was the only MRI risk factor independently associated with arthritis development in a prospective study of 150 patients with CSA (HR 8.39 (3.38–20.81), p<0.001). There is also an increased prevalence of hand interosseous tendon inflammation in ACPA+ individuals with MSK symptoms.[96] These studies highlight the importance of extracapsular inflammation (which MRI is particularly sensitive for) as a risk factor for disease progression.

Other clinical, cellular and serological risk factors for arthritis development have also been identified in this population, although current evidence for these factors is based largely on single unvalidated studies. Elevated BMI has been associated with arthritis development in some patients with seropositive arthralgia[97] and ACPA+ at-risk individuals (some FDRs and some with MSK symptoms).[98] Studies in the Dutch seropositive arthralgia cohort have shown that the number of peripheral blood B cell receptor clones,[99] serum apolipoprotein A1[100] and serum 14-3-3n levels[101] are all associated with arthritis development. Loss of bone mineral density was associated with arthritis development in a prospective study in patients with CSA.[102] Peripheral blood T cell subsets were also associated with arthritis development in ACPA+ at-risk individuals.[42] The peripheral blood B cell signature[103] and type I interferon signature[104] have also been shown to be predictive of arthritis development in patients with seropositive arthralgia.

Early clinical arthritis

Clinical features, imaging findings and autoantibody profile are also important risk factors for the development of RA in patients classified as having UA. These data are largely based on prospective analyses of UA cohorts, with patients with early arthritis included on the basis of failure to meet now outdated versions of RA classification criteria. As such, it is likely that a significant proportion of these patients would now, based on current criteria,[58] classify as early RA. Several risk prediction tools, combining clinical features, autoantibodies and/or imaging risk factors, have been proposed in UA cohorts.[66 69–71 73 105–107] Many of the risk factors are the same as those described above for individuals with MSK symptoms without clinical arthritis; prolonged EMS duration,[69 105 106] ACPA and/or RF,[66 69 71 73 105 106] and power Doppler (PD) signal on US[105] have all been shown to predict progression of UA to RA. However, elevated CRP/ESR,[69 105] longer disease duration,[73 105] greater number of swollen and/or tender joints[69 73] and radiographic erosions[69 70] are risk factors for progression specific to patients with early clinically apparent arthritis. Autoantibody profile (ACPA and RF) and flares involving the hands and wrists are also risk factors for RA development in patients with PR.[51 52]

Subclinical inflammation on US and MRI has been identified as a risk factor for RA development in several UA cohorts.[108–113] The presence of US synovitis (gray-scale (GS) and/or PD) is predictive of progression from early UA to RA.[110–112 114] However, tenosynovitis in the hands and feet[113] on US and MRI also appears to be associated with disease progression.[109 112] Of the studies investigating the role of autoantibody profiling in UA, ACPA status and level (high level most predictive) are the most consistently predictive of disease progression.[67 72 74]

There has been considerable interest in the putative role of mucosal inflammation and dysbiosis in initiating and driving disease progression in at-risk individuals.[15 115–119] The potential importance of this was recognised by the task force. Although limited data were identified reporting these as specific risk factors for arthritis development,[120] the task force felt that these factors should be considered in future studies and clinical trials.

Considering the available data, the task force proposed that specific core and emerging risk factors should be assessed in symptomatic at-risk populations, that is, at-risk individuals with symptoms (but no clinical synovitis) and individuals with early clinical arthritis (table 3).

6. Risk factors should be assessed at baseline and repeated assessment considered according to the specifics of the study population and intervention (LoA 9.75)

The majority of studies investigating risk factors in prospective at-risk cohorts have taken only a single baseline measurement of the risk factor(s). While this provides valuable information on the overall influence of risk factors on the development of arthritis, a single measurement cannot address whether and to what extent risk factors change over time, nor the relationship

between different risk factors over time. For example, some risk factors may be more relevant in the asymptomatic at-risk phase, while others may become more relevant in symptomatic individuals when the onset of clinical arthritis is imminent.

In line with this, recent data suggest the prevalence and overall burden of subclinical joint inflammation on US imaging increases over sequential assessments prior to arthritis development in ACPA+ individuals with MSK symptoms.[93 94] This suggests that US subclinical inflammation is most relevant in those with imminent arthritis. There is a paucity of longitudinal, repeated assessments of other risk factors, particularly the evolution of clinical symptoms or cellular/serological markers. Investigators may seek to understand the influence of interventions on risk factors (ie, surrogates of disease progression), as well as arthritis development. An understanding of the stability of risk factors will be critical to designing such studies. The task force felt that this was an area which should be prioritised in future clinical trials and longitudinal studies.

7. Clinical trials should evaluate the ability of a specific intervention to modify the risk factor itself, as well as the risk of progression to RA (LoA 9.65)

Clinical trials in individuals at risk of RA have primarily focused on the prevention of progression to clinical arthritis or RA. Given increasing evidence for the role of specific risk factors in driving disease progression (as detailed above), the task force felt that evaluation of the ability of interventions to modify an individual's underlying risk factors should be prioritised in future study designs. This would be important for two reasons: first, to better understand the relative influence of specific risk factors on disease progression and second, it would represent an important step towards personalising different types of preventive intervention (eg, pharmacotherapies, lifestyle modifications or a combination) by understanding their suitability to target specific risk factors, which may be enriched in different at-risk populations.

Published studies suggest modification of risk factors in this way is feasible; improvement in RA-autoantibody levels has been reported in interventional trials in both patients with seropositive arthralgia and patients with UA.[8 121] In the Abatacept study to determine the effectiveness in preventing the development of rheumatoid arthritis in patients with Undifferentiated inflammatory arthritis and to evaluate safety and tolerability (ADJUST) trial, induction therapy with abatacept (ABT) in patients with UA was associated with a reduction in anti-CCP level. MRI osteitis scores also improved with ABT therapy and this benefit was sustained 6 months after treatment withdrawal.[121]

8. In individuals at high risk of RA (eg, with early clinical synovitis), drug intervention should alter progression to RA or the outcome of RA therapy (LoA 9.5)

Clinical trials have shown that in patients with UA, drug intervention can reduce or delay progression to RA and improve the outcome of therapy.[81 82 84 121–123] There is particularly strong evidence for a beneficial effect of MTX in UA.[81 82 84] The Dutch PROMPT study showed a delay in development of RA when MTX and placebo (12 months induction treatment) were compared in unselected patients with UA, although there was no overall difference in progression to RA at 30 months.[82] There was also no difference in disease remission rate at 30 months. However, when considering only the patients with anti-CCP-positive UA, 93% of the placebo arm progressed to RA compared with only 67% of the MTX arm ($p<0.001$) indicating a preventive effect. Furthermore, in a subsequent analysis restricted to 22 patients with 'high-risk' UA, a clear benefit of MTX was demonstrated; 6/11 (55%) of patients with high-risk UA developed RA in the MTX arm compared with 11/11 (100%) in the placebo arm, although in small numbers of patients.[81] Of the patients that developed RA in the MTX arm, this was delayed compared with placebo (median 22.5 months vs 3 months; $p<0.001$) and DFR was achieved by 4/11 (36%) in the MTX arm compared with 0/11 (0%) in the placebo arm ($p=0.031$). A separate study also showed a beneficial effect of MTX in patients with anti-CCP-positive UA; after 12 months' therapy, only 17.2% of patients in the MTX arm progressed to RA compared with 78.9% of those in the placebo arm ($p<0.001$).[84] Boolean remission was achieved in 46.4% of the MTX arm compared with 17.6% of the placebo group ($p=0.057$).

Six months of ABT therapy in patients with anti-CCP-positive UA also showed beneficial effects on radiographic and MRI disease progression and anti-CCP levels at 1 year compared with placebo.[121] Fewer patients in the ABT arm progressed to RA, but statistical significance was not reached in this small study. An important caveat, as with many of the UA studies, is that many of the included patients would now meet the updated classification criteria for RA[58] and would no longer be considered eligible for such studies.

Trials investigating the benefits of induction therapy with corticosteroids in altering disease progression in UA have produced less impressive results.[79 124] One such trial investigated the effect of three 80 mg intramuscular injections of methylprednisolone compared with placebo on disease progression (judged as the need to start DMARDs) and development of RA at 1 year. Corticosteroids delayed disease progression (76% vs 61% referred to start DMARDs at 6 months; OR 2.11, 95% CI 1.16 to 3.75, $p=0.015$) but did not prevent the development of RA.[124] Similarly, in the SAVE trial, a single 120 mg intramuscular injection of methylprednisolone produced similar disease remission rates compared with placebo at 1 year (16.2% vs 17.8% in methylprednisolone vs placebo) and similar progression to RA (45.1% in steroid arm vs 50.1% placebo arm).[79]

Studies investigating the use of tumour necrosis factor (TNF) - alpha inhibitors as induction therapy in UA have been limited; those reported have failed to show an impact in altering progression to RA.[68 83] In patients with high-risk UA, only 20% of IFX-treated patients achieved remission at 6 months, compared with 14% of placebo. All patients in the IFX arm developed RA at 1 year.[68] The majority of patients with IFX-treated UA also progressed to RA in a recent study (73% of IFX arm compared with 67% of placebo arm).[83]

The limited available studies in patients with PR suggest drug intervention may have a role in altering progression to RA in this population, although the evidence is much weaker than for UA, as appropriately designed clinical trials have not been performed. Antimalarial therapy appeared to delay the development of RA (162 months vs 56 months, $p=0.03$) in a retrospective cohort study, although there was no difference in overall rates of progression to RA.[61] Relatively low progression rates to RA were also reported in cohorts of patients with PR treated with DMARDs, although these were not controlled studies, which limits their interpretation.[65 85]

Considering the available data, the task force felt drug intervention should be considered in patients with UA with the aim of reducing disease progression and improving RA outcomes. The benefit of drug intervention in PR is less clear at present although antimalarials may be beneficial and warrant further study. There is no current evidence for the use of drug intervention in

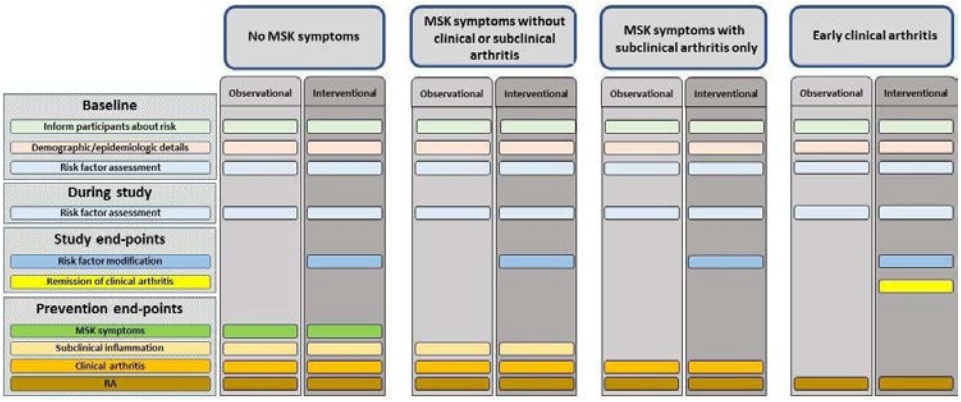

Figure 1 A summary of assessments and end-points which should be collected in clinical trials and observational studies of individuals at risk of RA, according to the at-risk population. MSK, musculoskeletal; RA, rheumatoid arthritis.

delaying disease progression in at-risk individuals without clinical arthritis.

9. In clinical trials and observational studies, individuals should be informed about their risk of developing RA using an approach tailored to the individual participants (LoA 9.5)

The task force felt it important that individuals at risk of RA are optimally engaged with strategies to identify their risk and/or potentially reduce their risk through intervention. Thematic synthesis of qualitative data and quantitative data from preventive intervention studies informed points to consider 9 and 10.

Only a few studies have explored the perspectives of individuals at risk of RA regarding risk prediction and RA prevention. There are two studies in people with MSK symptoms but without clinical arthritis (including arthralgia)[125 126] and five in FDRs.[127–132] Additionally, there is one study in people who have been diagnosed with RA[133] and another includes views from members of the public.[134]

Individuals with arthralgia (94%) report that they have benefited from being informed about their risk of developing RA.[126] FDRs are aware of their susceptibility to RA but at the same time unsure of the extent of their risk.[128] FDRs have raised concern that knowing their absolute risk would increase their anxiety and potentially affect decisions about their future and they would need additional support to understand the risk and cope with the emotional impact of this information.[128] A randomised controlled trial (RCT) comparing a web-based tool (Personalized Risk Estimator for Rheumatoid Arthritis) with standard, non-personalised RA education showed that the tool may help such individuals to better calculate disease risk.[131]

Identifying personal risk factors is important for FDRs, particularly when it comes to addressing modifiable ones such as diet.[129] An RCT conducted in FDRs without RA concluded that personalised medicine approaches increase motivation for those at risk to improve behaviours that reduce the risk of developing RA.[130]

An individual tailored approach for communication has been acknowledged by patients with RA; they have highlighted that sharing risk information with relatives may cause negative emotions, particularly because of the negative impact on quality of life that RA has[133]; as such, they would prefer to choose with whom the information is communicated.

The task force agreed that it was important for individuals participating in clinical trials and observational studies to understand their personal risk of developing RA. Communication should be tailored to the individual and additional support should be considered. This is particularly important for promoting participation and engagement in prevention studies.

10. An individual's knowledge about their risk of progression to RA may inform their decision to participate, or not, in clinical trials and observational studies (LoA 9.85)

The variable accuracy of predictive models in identifying an individual's risk of developing RA has been raised by FDRs[128] and people with CSA, highlighting difficulties in interpreting prognostic information given to them.[125] People with CSA preferred to have information on the origin of their symptoms,[125] thus exploring illness perceptions to guide treatment decisions, rather than risk percentages. How individuals receive information about their risk may, therefore, contribute to their decision to participate in interventional studies or not.

A recent study included at-risk individuals, defined on the basis of ACPA/RF positivity. In that study, those with arthralgia (≥one peripheral joint) were more likely to have had an autoantibody test to help identify the cause of their symptoms; in contrast, asymptomatic individuals were more likely to have had a test to contribute to research. Many symptomatic individuals expressed willingness to undergo additional predictive testing, including an assessment of the synovium by biopsy, if that would help further refine risk estimation. Asymptomatic individuals were less likely to consider further predictive testing.

Importantly, both groups highlighted the need for tailored, patient-understandable information to be delivered by an HP.

Prevention intervention studies are typically grouped into those that involve lifestyle and/or behaviour modification or those that involve taking medication. At-risk individuals with symptoms are more likely to consider both interventions.[126] This contrasts with FDRs who would prefer to wait until symptoms developed before considering drug interventions.[129] An understanding of personal risk is more likely to improve RA-risk-related behaviours such as dental hygiene and dietary change.[129 130] However, preventive treatment offering the largest risk reduction is not necessarily the priority for asymptomatic FDRs.[132]

The task force acknowledged that level of baseline risk typically informs study protocols for preventive interventions, either lifestyle/behaviour modification or pharmacotherapy. Hence, supporting individuals at risk of RA to understand their personal risk factors and overall level of risk is likely to help inform their decision to participate, or not, in clinical trials and observational studies.

Box 1 Research agenda

The task force agreed that future research should address the following key questions:

- Should individuals with mucosal inflammation/dysbiosis (periodontal, lung or gut) with or without genetic predisposition or serum autoantibodies be included as an at-risk group?
- Are non-musculoskeletal symptoms (eg, stress-related symptoms and fatigue) prevalent in individuals at risk of developing rheumatoid arthritis (RA)?
- Which surrogate biomarkers should be used as end-points in pilot/early phase interventional studies? And in which populations?
  - Improvement of subclinical inflammation on ultrasound (US)/MRI in symptomatic individuals?
  - Improvement of clinical features (eg, early morning stiffness duration and small joint tenderness) in symptomatic individuals?
  - Improvement of mucosal inflammation with or without dysbiosis in seropositive asymptomatic individuals?
  - Development of autoimmunity in seronegative individuals with genetic risk (including first-degree relatives)?
  - Improvements in patient reported outcomes (PROs) for symptomatic patients? And which patient reported outcomes should be used as end-points?
  - Biomarkers of inflammation/autoimmunity (emerging).
- Can at-risk populations, from the background population, be cost-effectively identified, recruited and given preventative treatment based solely on demographics (age, sex and smoking status)?
- Does subclinical inflammation on imaging represent a relevant endpoint (with distinct predictors)?
- Do the risk factors that drive RA autoimmunity and disease progression vary according to the ethnicity or geography of the population?
- Which biomarkers/risk factors change as individuals progress to inflammatory arthritis?
- In individuals at risk of RA, what is the sequence and timescale of the changes in biomarkers/risk factors?
- How frequently should we reassess an individual's risk and is this subpopulation dependent?
- Which biological pathways are linked with progression to RA?
- Should interventions be personalised to an individual's risk factors, for example, smoking cessation, treatment of periodontitis and weight loss?
- In those at high risk, should multimodal intervention be considered according to risk factors, for example, immunomodulation combined with periodontal therapy/smoking cessation/weight loss as appropriate?
- Does reduction in one or more risk factors reduce the likelihood of progression?
- Can the quantification of an individual's risk be improved, and risk scores validated?
- Are interventional studies in at-risk individuals cost effective?
- Should studies assess the long-term impacts of pre-arthritis interventions, including impacts on the RA phenotype (eg, severity, treatment response, DFR, etc), if it develops?
- Should we develop standardised methodologies to optimise acquisition and comparability of potentially relevant clinical and epidemiological data and biospecimens (eg, blood, oral, lung, gut and synovium) in studies of individuals at risk for RA?
- What is the optimum approach (including psychological support/counselling) for conveying risk of RA to these individuals?
- How do at-risk individuals assess risk versus benefit in deciding on participation in either lifestyle or drug prevention studies?
- Which risk factors do patients consider are high risk for developing RA?
- Should risk prevention strategies be tailored for differing cultural dimensions?

The task force acknowledged that points 9 and 10 follow the same theme, but convey separate messages, which justifies having two separate points. Point 9 refers to the approach to be used to inform participants about their risk. This point is centred on communication strategies, which should be considered when planning clinical trials and studies in at-risk populations. Point 10 refers to factors which may influence participation in trials and clinical studies. This point explores reasons why participation in studies may be limited and how it could be improved.

CONCLUSION

The goal of this EULAR task force was to provide the first expert consensus and guidance on the conduct of clinical trials and observational studies in individuals at risk of RA. These studies represent a new and evolving area in rheumatology research and clinical practice. Although much of the guidance is based on robust data from multiple studies, some is based on low levels of evidence and expert opinion. Therefore, guidance statements have been formulated as 'points to consider' rather than recommendations (table 1). Validation of the points to consider was beyond the scope of the task force but could be considered in a larger independent group of stakeholders in future. We acknowledge that guidance could not be provided in some specific areas, for example, at-risk individuals who develop non-articular diseases (eg, eye disease and lung disease) in the absence of arthritis. This is due to a lack of published evidence in these areas.

Several clinical trials in individuals at risk of RA are in progress and there is a growing interest from multiple stakeholders, including rheumatologists, academics, policy-makers, the pharmaceutical industry and, most importantly, patients. In many ways, these studies represent uncharted territory in rheumatology; aiming to prevent arthritis those with risk factors, rather than the conventional paradigm of suppressing the disease once it is clinically established. As such, there are many important differences and unknowns. The goal of the task force was to address these uncertainties by providing expert consensus and data-driven guidance where available to help optimise the conduct of work in this area.

The overarching principle and 10 points to consider set out a broad framework, which covers the key areas for conducting clinical trials and studies in at-risk individuals. The areas included were those prioritised by the task force. This includes the different types of at-risk populations, and how they may be distinguished based on clinical presentation, for trials and studies. For each of these populations, guidance on appropriate study end-points and trial outcomes, and the core and emerging

risk factors, which should be assessed, are provided (table 3, figure 1). Considerations for optimising participation in these studies and informing at-risk individuals about their level of risk are also included. Finally, a research agenda, agreed by the task force, has also been proposed (box 1).

These statements should help harmonise the datasets produced by future studies and facilitate collaboration in this important area. They should also improve the validity of individual trials and studies, optimising outputs from hard to recruit populations, which often require unique patient cohorts and infrastructure. It is hoped that this guidance will help galvanise future collaborative efforts in studies of at-risk individuals and RA prevention.

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EULAR recommendations for intra-articular therapies

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ABSTRACT

Objectives To establish evidence-based recommendations to guide health professionals using intra-articular therapies (IAT) in adult patients with peripheral arthropathies.

Methods A multidisciplinary international task force established the objectives, users and scope and the need for background information, including systematic literature reviews) and two surveys addressed to healthcare providers and patients throughout Europe. The evidence was discussed in a face-to-face meeting, recommendations were formulated and subsequently voted for anonymously in a three-round Delphi process to obtain the final agreement. The level of evidence was assigned to each recommendation with the Oxford levels of evidence.

Results Recommendations focus on practical aspects to guide health professionals before, during and after IAT in adult patients with peripheral arthropathies. Five overarching principles and 11 recommendations were established, addressing issues related to patient information, procedure and setting, accuracy, routine and special aseptic care, safety issues and precautions to be addressed in special populations, efficacy and safety of repeated joint injections, use of local anaesthetics and aftercare.

Conclusion We have developed the first evidence and expert opinion-based recommendations to guide health professionals using IAT. We hope that these recommendations will be included in different educational programmes, used by patient associations and put into practice via scientific societies to help improve uniformity and quality of care when performing IAT in peripheral adult joints.

INTRODUCTION

Intra-articular therapy (IAT) is a cornerstone procedure extensively performed by different health professionals around the world. IAT is a key for treating adults with joint synovitis, effusion and pain of different origins such as inflammatory arthritis and osteoarthritis (OA).[1] Common injectables include glucocorticoids (GC), local anaesthetics, hyaluronic acid (HA), autologous blood products and radiopharmaceuticals.[2–7] Regardless of their efficacy and safety tested in clinical trials, in daily practice, a myriad of aspects may influence the outcome of IATs, such as the specific arthropathy, joint location and size, the setting and the procedure as well as the postprocedure care.

There is a wide variation in the way IAT are used and delivered in patients with arthropathies.[8 9] Health professionals may have different views and habits depending on training and access to IATs, and individual patients also have their own needs and preferences.[9 10]

To the best of our knowledge, no international and multidisciplinary effort has been made to develop evidence-based recommendations when performing IAT. To address this gap, EULAR (European alliance of associations for Rheumatology) established a taskforce with the aim of developing evidence-based recommendations to help guide health professionals using IAT in adult patients with peripheral arthropathies.

METHODS

The project adhered to the updated EULAR standardised operating procedures for the development of recommendations.[11] Methods included two face-to-face meetings, a series of systematic reviews (SR) and the production of Delphi technique-based consensual recommendations.

The task force (TF) comprised a convenor (JU), co-convenor (EN), methodologist (LC), 2 fellows (SCR-G and RC-M), 12 clinical experts from six European countries (rheumatologist, orthopaedic surgeon, nuclear medicine specialist and radiologist), 2 of whom belonged to EMEUNET (VV and ENi), 1 rheumatology nurse (JdlT-A), and one patient representative (IAP).

At the first face-to-face meeting, after presenting the evidence of an overview SR on the efficacy and safety of IAT,[12] the TF established the aims and scope and defined the functions, tasks and timing of the work programme, then prepared 32 'PICO' (population–intervention–comparator–outcome) questions relating to the topic area and carried out a ranking exercise to define priorities. To address the PICO questions, a series of SR were undertaken by the fellows under the supervision of the methodologist and the convenors, while an experienced librarian helped with the search strategies. Evidence was approached hierarchically by first identifying existing SR, appraising them using the AMSTAR-2 tool[13] and subsequently identifying and appraising individual studies in the situations where an SR to address a particular PICO question was not available. The results of the SR are being published elsewhere.[12]

To understand the patient's perspectives on IAT, a 44-item survey was developed, translated into 11 languages and disseminated to patients with rheumatic disease and their carers via the EULAR people with arthritis and rheumatism associations and via social media. To understand current clinical practice, a 160-item survey was developed and disseminated to a range of healthcare professionals via EULAR professional associations and social media. The results of these surveys will be published separately.[14] At the second face-to-face meeting, we discussed the evidence obtained from the SRs and surveys and formulated individual recommendations. These tentative recommendations were discussed and consequently rephrased if necessary. Then the agreement for each recommendation was anonymously tested in a first Delphi round from 0 to 10. Recommendations with an agreement greater than 65% were included for the next round. Those that did not reach 65% agreement were discarded and not included in the second round. One month after the second meeting, the third Delphi round was run electronically using SurveyMonkey. To remain in the set of recommendations after the second round, agreement needed to be greater than 80%. Finally, the methodologist added the level of evidence and grade of recommendation to each statement, according to the Oxford levels of evidence.[15]

The manuscript draft was reviewed by all TF members and pertinent comments were included. After that, it was submitted to the EULAR executive committee for review and approval.

RESULTS

Aim, users and scope

The TF agreed to establish recommendations to guide all healthcare professionals on practical aspects when undertaking IAT in adults with peripheral arthropathies. It was agreed that they would not include recommendations about use of individual therapies in specific diseases, for which guidelines currently exist.

Evidence results

The fellows addressed 32 PICO questions (see online supplemental table 1). An overview of SR of randomised controlled trials (RCTs) was performed up to July 2020 [12] The results from the other SRs that support specific recommendations are presented with the recommendation.

For the surveys, 200 patients responded and the results suggested a number of aspects about IAT that could be improved, including, for example, wider availability of IAT, attention paid to reduce pain from the procedure and better shared decision-making (SDM) including provision of information about the procedure.[14] The health professional survey was responded by 186 professionals, 77% of whom were rheumatologists, from 26 countries.[14] The specific results that support any recommendation are presented as supporting evidence.

Overarching principles and recommendations

The overarching principles with their agreement and the recommendations together with their agreement, level of evidence and grade of recommendation are summarised in table 1

Overarching principles

IAT are recommended and widely used in the management of joint diseases.

Any treatment, including IA injectables, should be given according to the best practice.

Table 1 Overarching principles and recommendations, with agreement and level of evidence and grade of recommendation (if applicable)

Overarching principles	A (%)		
I. IAT are recommended and widely used in the management of joint diseases.	98		
II.The aim of IAT is to improve patient-centred outcomes.	100		
III.Contextual factors are important and contribute to the effect of IAT.	93		
IV.IAT should be offered in the frame of full individualised information and a shared decision-making process.	97		
V. A variety of health professionals perform these procedures routinely.	94		
Recommendations	**A (%)**	**LE**	**GR**
1.The patient must be fully informed of the nature of the procedure, the injectable, and potential benefits and risks; informed consent should be obtained and documented according to local habits.	99	4	D
► An optimal setting for IAT includes:Professional, clean, quiet, private, well-lightened room. ► Patient in an appropriate position, ideally on a couch/examination table, easy to lie flat. ► Equipment for aseptic procedures. ► Aid from another HP. ► Resuscitation equipment close-by.	85	4	D
3.Accuracy depends on the joint, route of entry, and health professional expertise; if available, imaging guidance, for example, ultrasound, may be used to improve accuracy.	93	1B-2A	B
4.During pregnancy when injecting a joint one has to take into account whether the compound is safe for mother and baby.	98	4	D
5.Aseptic technique should always be undertaken when performing IAT.	98	3	C
6.Patients should be offered local anaesthetic explaining pros and cons.	75	3–4	D
7.Diabetic patients, especially those with suboptimal control, should be informed about the risk of transient increased glycaemia following IA GC and advised about the need to monitor glucose levels particularly from first to third day.	97	1B	A
8.IAT is not a contraindication in people with clotting/bleeding disorders or taking antithrombotic medications, unless bleeding risk is high.	89	3	C
9.IAT may be performed at least 3 months prior to joint replacement surgery, and may be performed after joint replacement following consultation with the surgical team.	88	3	C
10.The shared decision to reinject a joint should take into consideration benefits from previous injections and other individualised factors (eg, treatment options, compound used, systemic treatment, comorbidities…).	93	2	B
11.Avoid overuse of injected joints for 24 hours following IAT; however, immobilisation is discouraged.	94	1B	A

A, agreement; GR, grade of recommendation; IAGC, intra-articular glucocorticoids; IAT, intra-articular therapies; LE, level of evidence.

Table 2 Eular recommendations in which IAT are mentioned

Joint/condition	EULAR recommendation
Knee osteoarthritis[86]	'Intra-articular injection of long acting GC is indicated for acute exacerbation of knee pain, especially if accompanied by effusion.' 'Hyaluronic acid (…) is probably effective in knee OA, but the size effect is relatively small, suitable patients are not well defined, and pharmacoeconomic aspects of that treatment are not well established'.
Gout[16]	'Recommended first-line options for acute flares are colchicine (…), oral corticosteroid (…) or articular aspiration and injection of corticosteroids.'
Rheumatoid arthritis[87 88]	'Monitoring should be frequent (…) therapy should be adjusted.' *Adjustment of therapy includes the optimisation of MTX (or other csDMARD) dose or route of administration, or intra-articular injections of GC in the presence of one or few residual active joints.
Hand osteoarthritis[89 90]	'Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA, but may be considered in patients with painful interphalangeal joints'.
Acute or recent onset swelling of the knee[91]	'Intra-articular steroids should not be administered unless an appropriate diagnosis has been made and contraindications have been ruled out'.

csDMARD, conventional synthetic disease-modifying antirheumatic drugs ; GC, glucocorticoids; MTX, methotrexate; OA, osteoarthritis.

Dose and approach need to be defined for each indication and joint and might not be interchangeable across indications. Table 2 shows current EULAR recommendations in which IAT are mentioned.

The aim of IAT is to improve patient-centred outcomes.

Patient-centred outcomes are those relevant to the patient, such as benefits, harms, preferences or implications for self-management. While injectables are used mainly as a treatment to improve patient-centred outcomes, they can also be used to aid diagnosis and identify the origin of pain (eg, lidocaine test may be used to rule out joint vs referred pain).[1] The objective of therapy should be among the expected outcomes based on evidence. An example of an unclear objective is to use injectables to improve function in a joint without pain. Reduction of systemic medication can be also considered a patient and health provider aim.

Contextual factors are important and contribute to the effect of IAT.

Contextual factors such as effective communication, patient expectations or the setting in which the procedure takes place, which may influence the outcome of IAT. Additionally, one should recognise the magnitude of the placebo effect associated with this route of delivery.[16]

IAT should be offered in the frame of full individualised information and a SDM process

SDM implies the involvement of patients with their providers in making healthcare decisions that are informed by the best available evidence about options, potential benefits and harms, and that consider patient preferences. If not within a framework of SDM, any recommendation may not reach the expected effect.

A variety of health professionals perform these procedures routinely.

Depending on country regulations, IAT can be carried out by general practitioners, rheumatologists, traumatologists/orthopaedic surgeons, sports medicine specialists, radiologists, nuclear medicine specialists, trained nurses, physical therapists and occupational therapists, with varying levels of formal training.[14]

Recommendations

The patient must be fully informed of the nature of the procedure, the injectable and potential benefits and risks; informed consent should be obtained and documented according to local habits.

The TF agreed to include this general statement as the first recommendation on the basis that this frequent procedure is delivered by health professionals from many countries and that patients surveyed wanted to be informed prior to consent as an essential part of the SDM process.[14] Whether informed consent should be oral or written is beyond the scope of this project, furthermore, there was no preferred option in the patient survey. Essential information to be delivered includes the nature of the procedure, the potential benefit, side effects and postinjection care.

An optimal setting for IAT includes a professional clean quiet private well-lightened room, the patient in an appropriate position, ideally on a couch/examining table, easy to lie flat, equipment for aseptic procedures, aid from another HP and resuscitation equipment close by.

Contextual effects including the setting in which clinical care is delivered may impact on the outcome of clinical interventions. We could not identify any studies to help inform what the optimal setting for undertaking IAT therapy is. However, all these aspects may enhance the contextual effect. It was agreed that the main equipment required was a couch/examining table which could be adjusted, and equipment for aseptic procedures and resuscitation equipment close by. There was a discussion about the need to have another HP present as many countries or centres do not provide assistants.[14] A retrospective case series analysis showed a 2.6% overall rate for vasovagal reactions,[17] which may justify the help of others; however, in the healthcare professional survey, the large majority of professionals said that they never or seldom had vasovagal reactions.[14]

Accuracy depends on the joint, route of entry and health professional expertise; if available, imaging guidance, for example, ultrasound, may be used to improve accuracy.

Several published SRs and RCTs report that ultrasound improves accuracy in delivery of IAT though clinical outcomes are similar to those of landmark-guided IAT.[18–21] When using anatomical landmarks (blinded injections), each peripheral joint has different routes of entry. The best approach for a certain joint cannot be recommended except for the knee in which an SR showed that the superolateral approach was more common and resulted in the highest pooled accuracy rate of 91% (95% CI 84% to 99%) in patients with different arthropathies.[22] Aspiration of synovial fluid helps ensure that the needle is in the joint.[23 24] Expertise in the procedure is important and appreciated by the patient, as highlighted in the survey, and it is clearly dependent on practice and appropriate training.[14 25]

During pregnancy when injecting a joint one has to take into account whether the compound is safe for mother and baby.

IAT during pregnancy is often performed to treat local arthritis when indicated and the benefit/risk ratio in this setting may be superior to that for systemic therapy. Most of the compounds in routine practice can be used except for radiopharmaceuticals, which are contraindicated during pregnancy.

Aseptic technique should always be undertaken when performing IAT.

The risk of septic arthritis following IAT is very low. However, while historically the risk estimates for septic arthritis postintra-articular GC varied from 0.005% to 0.0002%, a recent study showed that the current risk could be higher (0.035 %, three per 7900 procedures).[26] We have found no studies comparing different aseptic techniques during IAT on subsequent risk of infection. Surgical gloves, skin preparation with alcohol, iodine disinfectant or chlorhexidine and changing needles between drawing the drug and injecting it into the joint are indirectly supported by their benefit in other common procedures, such as blood cultures and surgery.[27 28]

Patients should be offered local anaesthetic explaining pros and cons.

The main reasons for using local anaesthetics in IA T are to reduce discomfort during the procedure and to extend pain reduction effect. Local anaesthetics may be applied on the skin, infiltrated in the subcutaneous tissue, along the needle path into the joint, or injected into the joint, alone or mixed with GC. Topical anaesthetics such as eutectic mixture of local anaesthetic cream, lidocaine 2.5% and pilocarpine 2.5% or ethyl chloride spray, can reduce pain from the needle as demonstrated in children in one RCT.[29] Several TF members suggested ethyl chloride spray, a nonsterile coolant aerosol, might increase infection risk when not applied correctly, but we failed to find any evidence for this. A high-quality SR showed that warmed local anaesthetic (37°C) reduces local infiltration pain compared with injecting at room temperature, irrespective of whether the local anaesthetic was buffered or not.[30] Anaesthetic infiltration while advancing the needle into the joint does not minimise procedural pain, as suggested in a retrospective analysis performed in US-guided hip injections for MR arthrography.[31] Several RCTs in knee and hip OA have shown that the combination of GC and local anaesthetic improves pain longer than only injecting local anaesthetic.[32 33] Some TF members raised concern about the effect of lidocaine on cartilage. We found a study, by Ravnihar *et al*, on knee cartilage obtained from biopsies, that showed no differences in chondrocyte viability and morphology and population doublings after a single injection of lidocaine, and we failed to identify in vivo evidence of cartilage toxicity.[34] One last aspect on anaesthetics would be allergic reactions. Patients should be asked about previous allergic events prior to the procedure.

Diabetic patients, especially those with suboptimal control, should be informed about the risk of transient increased glycaemia following IA glucocorticoid injection and advised about the need to monitor glucose levels particularly from first to third day.

IA GC can provoke transient hyperglycaemia, which may cause risk to patients with diabetes mellitus by raising blood glucose to hyperglycaemic levels. One SR of critically low quality, including 76 patients, showed that blood glucose levels increase during day 1–3 postinjection though no severe adverse events such as hyperosmolar hyperglycaemic state or ketoacidosis were encountered.[35] Twu *et al* prospectively analysed 70 diabetic patients requiring IA GC and observed that preinjection haemoglobin A1C had a significant effect on postinjection blood, whereas corticosteroid dose, body mass index, insulin use and the number of injections had no significant effect on the elevation of blood glucose.[36] Also, an RCT showed that extended release triamcinolone acetonide may increase glycaemia less than the standard triamcinolone acetonide (14.7 mg/dL vs 33.9 mg/dL),[37] and so it could be an alternative for poor controlled diabetic patients. Finally, although diabetes predisposes to native and prosthetic joint infection,[38–40] none of the studies on IA GC in patients with diabetics reported postprocedure infections.[35–38 41–43]

IAT is not a contraindication in people with clotting/bleeding disorders or taking antithrombotic medications, unless bleeding risk is high.

Our literature review identified 15 observational studies including 1428 patients (1425 haemophilia and 3 Von Willebrand disease) subjected to more than 10 000 procedures (all of which were performed after appropriate factor replacement) including radioisotopes, triamcinolone, HA and other products, revealed only two hemarthroses and three soft-tissue bleeds in one study; thus, IAT appears to be a low-bleeding risk procedure in patients with clotting-impairing haematological disease.[44–57] Based on seven observational studies, the estimated periprocedure bleeding risk in patients on antithrombotic drugs (antiplatelet agents, low-molecular weight heparin, warfarin or direct oral anticoagulants) was found to be between 0% and 2%.[58–63] One of the larger studies, retrospectively reviewed 640 procedures (arthrocentesis and joint injections) in 514 patients taking warfarin; they found no significant difference in early and late complications in patients receiving therapeutic warfarin (INR 2–3) compared with nontherapeutic levels (INR <2).[61] In another large retrospective study, no bleeding was reported in 1050 procedures performed in 483 patients on rivaroxaban (52%), apixaban (31%) or dabigatran (17%).[62] Several panellists suggested that local pressure to prevent bleeding may be more important after injecting deeper joints than superficial ones.

IAT may be performed at least 3 months prior to joint replacement surgery and may be performed after joint replacement following consultation with the surgical team.

We identified six SRs, one of low quality and five of critically low quality, assessing safety issues of IA GC prior and following joint replacement.[64–69] Evidence was not conclusive of an increased risk of infection with IA GC injection in the hip or knee prior to total joint arthroplasty. Three retrospective studies examined whether this was a matter of a 'safe window'. The rate of prosthetic infections 3 months after surgery was significantly larger in the groups that had injections 0–3 months prior to total hip or knee arthroplasty, but not if the injections were separated from the surgery longer than 3 months; however, the difference was not strikingly large (from 0.5% to 1.0%, with background risk from 1.04% to 2.5%).[70–72]

Another important issue is whether it is safe to inject GC in a prosthetic joint. In a retrospective medical record review that aimed to assess the risk of acute infections in patients with total knee prosthesis,[73] the authors found a 0.6% infection rate in 1845 GC IA injections performed in 736 patients (1 infection in every 625 infiltrations). A recent single-centre retrospective study showed no joint infections at a minimum of 1-year follow-up in 184 patients with total knee prosthesis (31% received two to

five GC injections).[74] Both studies pointed out that IA GC injections in prosthetic joints should be avoided in routine practice and considered by orthopaedic surgeons after strict screening of prosthetic infection.

The shared decision to reinject a joint should take into consideration benefits from previous injections and other individualised factors (eg, treatment options, compound used, systemic treatment, comorbidities…).

IATs have been tested for different doses, frequencies and intervals. However, high-quality studies that aimed to evaluate the long-term effect of repeating IA injections are scarce. There are no clear evidence-based recommendations as to the appropriate number of IA injections from a risk benefit perspective for most indications. We found two RCT in knee OA, comparing IA GC every 3 months for 2 years versus saline, one showing gain in symptoms and no deleterious effect on cartilage volume,[75] and the other showing no difference in pain and greater progression of cartilage volume loss with GC.[76] A general accepted rule, though based on no research evidence, is to avoid more than 3–4 GC injections in the same joint per year. An SR on long-term effect of repetitive IA HA showed sustained or further pain reduction with repeated courses of HA and no serious adverse effect.[77]

Avoid overuse of injected joints for 24 hours following IAT; however, immobilisation is discouraged.

Most practitioners advise restricted activities. Studies have shown that 24–48 hour postinjection immobilisation, such as bed rest, joint splinting or bandages, add no benefit compared with normal activity after IAT, even when injecting radioisotopes.[78–83] Radioisotopic radiation leakage into extrasynovial tissue may be minimised by splinting during 48 hours.[78–80]

DISCUSSION

Herein, we present the first EULAR evidence-based recommendations to help guide health professionals who perform IAT in adult patients with peripheral joint disorders. We established 5 overarching principles and 11 recommendations addressing: patient information; procedure and setting; accuracy; routine and special antiseptic care; safety and precautions in special populations; efficacy and safety of repeated joint injections; the usage of local anaesthetics and aftercare. The main challenge faced by the TF has been the complexity of the topic and the paucity and controversy of the scientific evidence.

At the first meeting, it was very clear to the TF that there was a need for developing practical recommendations prior, during and after performing IAT, as this common procedure is performed by different clinicians and has not undergone a robust expert evidence-based evaluation. This ambitious and complex project required not only a well-designed broad systematic literature review, and an expert international panel, but also feed back from a broader group of health professionals and patients. We were fully aware that many of the accepted issues had little or no scientific support. Hence, we designed the surveys for back ground information from health professionals and patients coming from EULAR member countries. The respondents' opinions were presented with the results of the SRs for each pertinent research question. This helped the TF formulate low evidence (1, 2, 4 and 6) and moderately low evidence (5, 8 and 9) recommendations.

Recommendation 6, addressing the offering of local anaesthetics had the lowest agreement. The surveys revealed that approximately 50% of the health professional never use local anaesthetic, despite the fact that, in their respective survey, patients recurrently asked for a less painful or even painless procedure.[14] The low agreement was possibly due to the lack of scientific evidence on the benefit of local anaesthetics.

Recommendations with moderate evidence were 3 and 10. Part of recommendation 3 relating to the accuracy of IA injections says that "if available, imaging guidance, for example, ultrasound, may be used to improve accuracy". This part of the recommendation was worded as an open suggestion because many units neither have ultrasound machines nor physicians trained in joint ultrasonography. Noticeably when injecting a radiopharmaceutical, imagining is important to minimise extrasynovial radiogenic tissue necrosis.[84]

The identification of evidence was hampered by the large number of questions posed, the large number of potential populations and interventions as well as time constraints. We tackled it by using nine sensitive 'theme' search strategies and then organising the studies into the different questions.

These recommendations assume that 'best practice' is the rationale for IAT and for the selection of the compound. It was out of our scope to study and to compare the efficacy and safety of the specific IATs as well as to address the indications for the different arthropathies. When looking at contextual factors that may influence outcome, such as decrease in joint pain, we found that the procedure itself has an important placebo effect.[85] This should be considered not only in daily practice but also when interpreting the results of RCTs comparing IAT with systemic therapy or in observational studies on IAT. Another general aspect encountered was that the majority of the studies identified were conducted by orthopaedic surgeons and rehabilitation specialists and fewer by rheumatologists, and that most studies dealt with IA HA in patients with knee OA, while rheumatologists predominantly use IA GC.

Despite IAT being an important procedure and widely used for more than 70 years, many aspects of IAT still need to be assessed to increase our quality of care. These may include safe and cost-effective settings and procedures; whether ultrasound diagnosis and guidance improve outcome; better RCTs, and perhaps a real-life registry of IATs, like the arthroplasty registers.

As a disclaimer, this project was carried out before the COVID-19 pandemic outbreak, so it does not include specific safety measures to prevent SARS-CoV-2 viral infection nor measures to be used when having to deliver IAT to patients with COVID-19. Health professionals and patients should follow local country regulations and recommendations relating to this matter.

We expect these first recommendations to be included in different educational programmes, used by patient associations, and put into practice via scientific societies to help improve uniformity and quality of care when performing IAT in peripheral adult joints.

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CLINICAL SCIENCE

Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort

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ABSTRACT

Introduction In light of the SARS-CoV-2 pandemic, protecting vulnerable groups has become a high priority. Persons at risk of severe disease, for example, those receiving immunosuppressive therapies for chronic inflammatory cdiseases (CIDs), are prioritised for vaccination. However, data concerning generation of protective antibody titres in immunosuppressed patients are scarce. Additionally, mRNA vaccines represent a new vaccine technology leading to increased insecurity especially in patients with CID.

Objective Here we present for the first time, data on the efficacy and safety of anti-SARS-CoV-2 mRNA vaccines in a cohort of immunosuppressed patients as compared with healthy controls.

Methods 42 healthy controls and 26 patients with CID were included in this study (mean age 37.5 vs 50.5 years). Immunisations were performed according to national guidelines with mRNA vaccines. Antibody titres were assessed by ELISA before initial vaccination and 7 days after secondary vaccination. Disease activity and side effects were assessed prior to and 7 days after both vaccinations.

Results Anti-SARS-CoV-2 antibodies as well as neutralising activity could be detected in all study participants. IgG titres were significantly lower in patients as compared with controls (2053 binding antibody units (BAU)/mL ±1218 vs 2685±1102). Side effects were comparable in both groups. No severe adverse effects were observed, and no patients experienced a disease flare.

Conclusion We show that SARS-CoV-2 mRNA vaccines lead to development of antibodies in immunosuppressed patients without considerable side effects or induction of disease flares. Despite the small size of this cohort, we were able to demonstrate the efficiency and safety of mRNA vaccines in our cohort.

Key messages

What is already known about this subject?

- Data on the efficacy and safety of mRNA vaccines in patients with immunosuppressive therapies is not available so far.

What does this study add?

- In our cohort, mRNA vaccines against SARS-CoV-2 showed a considerable immunogenicity in patients.
- Side effects in patients were comparable with controls with systemic side effects being less frequent.
- No flares of the underlying inflammatory condition could be observed in the context of the vaccination.

How might this impact on clinical practice or future developments?

- The data in this study indicate that mRNA vaccines against SARS-CoV-2 are immunogenic and safe in patients with chronic inflammatory diseases.

INTRODUCTION

The SARS-CoV-2 pandemic continues to threaten the health of patients worldwide. Patients receiving immunosuppressive medication, for example, in the context of transplantation or chronic inflammatory diseases (CID), are considered to be at a higher risk of severe manifestations of COVID-19. Generally, patients receiving immunosuppression are considered to have an increased risk for infections. However, registry data appear to indicate that in the context of SARS-CoV-2 not every immunosuppressed patient has an increased risk of severe COVID-19. Indeed, biological therapies have been identified as decreasing the risk for hospitalisation due to COVID-19 in cohorts of patients with rheumatic diseases, chronic inflammatory bowel diseases and psoriasis.[1–5] The most important factors associated with a higher risk of hospitalisation and death across multiple indications and forms of immunosuppression were found to be older age, high underlying disease activity as well as high glucocorticoid dosages (at dosages equivalent to prednisolone ≥10 mg).[1 6 7] Additionally, B cell depleting drugs, that is, rituximab, might represent a risk factor.[8] Until now, there is

insufficient registry data for other drugs commonly used to treat patients with CID in terms of increased risk of severe COVID-19.[1 9 10] However, patients have minimised their risk by sheltering in place early and reducing infection contacts (own unpublished data).

Several drugs used in the management of CID have been analysed as potential treatments for COVID-19, especially in attenuating the so-called cytokine storm, some of which have shown considerable benefit.[11]

Vaccination against SARS-CoV-2 is now a reality for the most vulnerable and continues to spread to encompass patients receiving immunosuppressive therapies. However, patients with a higher risk being older, taking more steroids and having high underlying disease activity are known to respond less to vaccines.[12–15] Additionally, patients with CID and those taking anticytokine therapies or immunosuppression were excluded from the phase III trials for all vaccines approved by the European Medicins Agency (EMA) and US Food and Drug Administration (FDA).[16–18]

The scarce data available on vaccine response under immunosuppression for other vaccines leaves many open questions in relation to SARS-CoV-2 vaccination.[15 19]

As shown for several vaccines in patients with chronic inflammatory diseases and transplanted patients, antibody titres post-vaccination may be decreased depending on the vaccine and the treatment (although this is not always the case).[15 19 20] In relation to SARS-CoV-2, it is currently unclear how immunosuppression for CID affects vaccine response. There are also additional concerns regarding reactivation of the inflammatory disease by new mRNA vaccines.

We therefore provide for the first-time data comparing the immunogenicity and safety of SARS-CoV-2 mRNA vaccines in patients with CID undergoing immunosuppressive therapy compared with healthy controls in a monocentric observational study.

MATERIAL AND METHODS

Healthy individuals as well as the majority of patients with CID were recruited from healthcare workers of the University Medical Center in Kiel and other surrounding hospitals. Aged patients were recruited from the patient cohort of the rheumatology outpatient department in Kiel. Healthy controls and patients were vaccinated based on the occupational exposure risk or age associated risk at official vaccination centres. The vaccination was not part of the study.

Forty-two healthy controls and 26 patients with CID were enrolled into this non-randomised trial. All volunteers were eligible for early vaccination according to German federal regulations and received mRNA vaccines from either BioNtech/Pfizer or Moderna. Five Patients were immunised with COVID-19 vaccine Moderna; all others received Comirnaty. Vaccines were given to the participants with an interval of 35 days between the two doses. Patients older than 80 years were immunised twice with a 21-day interval.

Monitoring for disease activity (disease activity score 28 (DAS28), Patients Global Assessment (PGA) and Physician Global Assessment (PhGA)) was performed at baseline (before first vaccination), 7 days after the first vaccination, on the day of the second immunisation and 7 days thereafter plus any other time point in between if disease flares were experienced. Routine laboratory monitoring was performed at each time point. Side effects were monitored by online surveys and medical history taking 14 days after secondary vaccination.

IgG antibodies against SARS-CoV-2 were quantified by ELISA according to manufacturer's protocol (EUROIMMUN QuantiVac), and neutralising antibodies were measured using an ELISA-based neutralisation test system according to manufacturer's protocol (cPass system, kindly provided by medac).[21] Additionally, anti-SARS-CoV-2 IgA titres were quantified according to manufacturer's instruction (Aeskulisa, Aeskulap)

Antibody testing were normally performed on day 0, the day of secondary immunisation and day 7 after secondary immunisation.

Statistical analysis was performed using GraphPad Prism. Mann-Whitney tests was used for statistical analysis, and p values below 0.05 were considered significant.

RESULTS

Demographics

Healthy controls were 69.2% women with a mean age of 37.5 years (±13.4; range 22–61). All were healthcare professionals. No participant previously had SARS-CoV-2-infection before vaccination.

The CID patient cohort consisted of 64.3% women with a mean age of 50.5 years (±15.8; range 24–89). Again, the majority were healthcare workers and none had been infected with SARS-CoV-2 prior to vaccination. Table 1 contains detailed CID patient information (inflammatory diseases and therapies).

SARS-CoV-2 mRNA vaccines show immunogenicity in patients with CID

Neutralising antibodies and total anti-SARS-CoV-2 IgG were detected in all patients with CID and healthy controls after the second vaccination. No non-responders were detected in any group. None of the participants displayed considerable antibody titres before the first vaccination, indicating no prior infection.

While the healthy control group showed a mean anti-SARS-CoV-2-IgG titre of 2685 BAU/mL (±1102, 793–3840), patients with CID exhibited significantly lower levels of specific immunoglobulins against the SARS-CoV-2 spike protein (mean 2053 BAU/mL±1218, 98.2–3840) 7 days after the secondary immunisation (p=0.037). Nevertheless, all patients presented with an antibody titre above the ELISA cut-off (figure 1A and B). When comparing groups by age range however, this difference was not significant anymore (figure 1G).

Patients with CID also had lower levels of neutralising antibodies, with a mean inhibitory activity level of 96.04% detected in healthy controls (±1.551, 91–97), whereas patients presented with a mean inhibitory level of 87.42% (±17.94, 37–97; p=0.0442) (figure 1C, D and H).

Of interest, SARS-CoV-2 IgA antibodies were detectable in nearly all patients and healthy controls 7 days after secondary immunisation. Again, patients with CID had lower specific IgA levels compared with healthy controls (mean 24.52±30.48 U/mL vs 47.65±45.12 U/mL; p=0.0035). One patient with CID had no detectable specific IgA, while an additional two patients and three healthy controls showed IgA levels below the cut-off (E and F).

Comparing the largest therapeutic groups (TNF blockade vs conventional disease-modifying antirheumatic drugs (cDMARDs) vs anti-interleukin 17) showed no significant difference between those therapies (online supplemental figure 1).

Patients with CID had a marginal propensity towards mild vaccine side effects compared with healthy controls

Side effects as documented by an online survey were comparable in both groups. Mild systemic side effects such as fatigue and myalgia were more frequent in the CID patient cohort relative

Table 1 Demographics and clinical characteristics of the included patients

Sex	Age (years)	Inflammatory disease	Biological DMARD	Conventional DMARD	Steroids
F	44	Psoriatic arthritis	Golimumab	Leflunomide	5 mg prednisolone
F	35	Psoriatic arthritis	Certolizumab pegol	–	–
F	43	Rheumatoid arthritis	Certolizumab pegol	–	5 mg prednisolone
M	46	MCTD	–	Hydroxychloroquine	–
F	39	Rheumatoid arthritis	Etanercept	Leflunomide	–
F	51	Rheumatoid arthritis	–	Sulfasalazine	–
F	65	Spondyloarthropathy	Infliximab	–	–
M	38	Spondyloarthropathy	Etanercept	–	–
F	45	Sarcoidosis	Infliximab	–	15 mg prednisolone
F	33	Rheumatoid arthritis	Certolizumab pegol	–	–
M	84	Giant cell vasculitis	Tocilizumab	–	5 mg prednisolone
F	47	Psoriasis	Ixekizumab	–	–
M	83	Rheumatoid arthritis	Etanercept	–	2.5 mg prednisolone
M	38	Crohn's disease	Vedolizumab	–	–
F	53	Rheumatoid arthritis	–	Leflunomide	7 mg prednisolone
F	24	Systemic lupus erythematosus	–	Hydroxychloroquine	–
M	42	Psoriasis	Adalimumab	–	–
F	54	Rheumatoid arthritis	Adalimumab	–	–
M	58	Spondyloarthropathy	Secukinumab	–	–
F	51	Psoriasis	Secukinumab	–	–
F	53	Crohn's disease	Infliximab	–	–
M	61	Psoriasis	Ustekinumab	–	–
M	36	Systemic lupus erythematosus	Belimumab	Hydroxychloroquine	–
F	89	Myositis	–	–	2.5 mg prednisolone
F	49	Multiple sclerosis/Crohn's disease	–	Azathioprine	–
F	54	Rheumatoid arthritis	Adalimumab	–	–

DMARDs, disease-modifying antirheumatic drugs; MCTD, mixed connective tissue diseases.

to healthy controls (53.8% vs 43.2% and 42.3% vs 31.6%). A similar pattern was seen for headache (38.5% vs 35.1%). Fever was completely absent in patients with CID while being reported by 13.5% of the healthy cohort. Arthralgia was comparable in both groups.

Some additional side effects were reported in both groups such as nausea and vomiting, thoracic pain and exacerbation of pre-existing asthma (table 2). However, not all controls did report side effects.

Inflammatory disease activity remained stable throughout the study

Activity of inflammatory disease was monitored by DAS28 for patients with inflammatory arthritis and PGA as well as PhGA for all patients with CID.

We did not observe any inflammatory arthritis flares (delta DAS28 >0.6) in the context of either vaccination time points. Delta PGA and PhGA showed a maximal mean change of 0.4 (±1.29) at the time point of the secondary vaccination, whereas the delta for the last time point (7 days after secondary vaccination) was 0.076 (±0.4) compared with baseline. No patient with CID needed to adjust DMARD or glucocorticoid therapy in the 6 weeks of trial duration (figure 2A,B).

DISCUSSION

Due to the ongoing COVID-19 pandemic, the effectiveness and safety of novel mRNA vaccines in immunosuppressed patients is under discussion, but real-world data have been missing. Patients with CID as well as physicians have been confronted with the question as to whether immunosuppressed patients, who were excluded from the phase III vaccine trials, should be vaccinated without prior knowledge of the potential risks of adverse events and changes in efficacy when this new type of vaccine is used in patients with CID. This lack of information has created additional insecurity and hesitation in both physicians and patients.

With the data acquired in this investigation, we are able to demonstrate for the first time in a mixed cohort of patients with CID undergoing a spectrum of immunosuppressive treatments that such conditions, and therapies do not significantly abrogate the anti-SARS-CoV-2 antibody response after vaccination. Hence, in this cohort, no patient with CID was a complete non-responder even though antibody titres were slightly lower in patients with CID compared with controls. Furthermore, all patients had considerable levels of neutralising antibodies 7 days after secondary vaccination. Moreover, the thee patients with CID and three healthy controls with low IgA serum levels displayed substantial neutralisation capacity and IgG levels. Nevertheless, a direct comparison with phase III study data is not possible as different testing systems were used.[22] The only patient with a very low IgG level and absent IgA response was an 85-year-old patient with multiple comorbidities, known to influence vaccine response additionally, receiving anti-interleukin 6 therapy and glucocorticoids. Therefore, age-related immunosenesence may also contribute to the low Ig levels. Nevertheless, this patient also mounted a significant neutralising response after vaccination. Regarding the age difference between patients and controls, the overall antibody levels showed a significant difference between both groups. When comparing the according age groups, however, differences in antibody levels were not found to be significant.

A fraction of patients paused their DMARD medication around the vaccinations. In this cohort, no effect of pausing versus continuing was observed in our cohort. The same holds true for the use of non-steroidal anti-inflammatory drugs. However, none of the patients was in methotrexate therapy, which has been reported to have an impact on vaccination

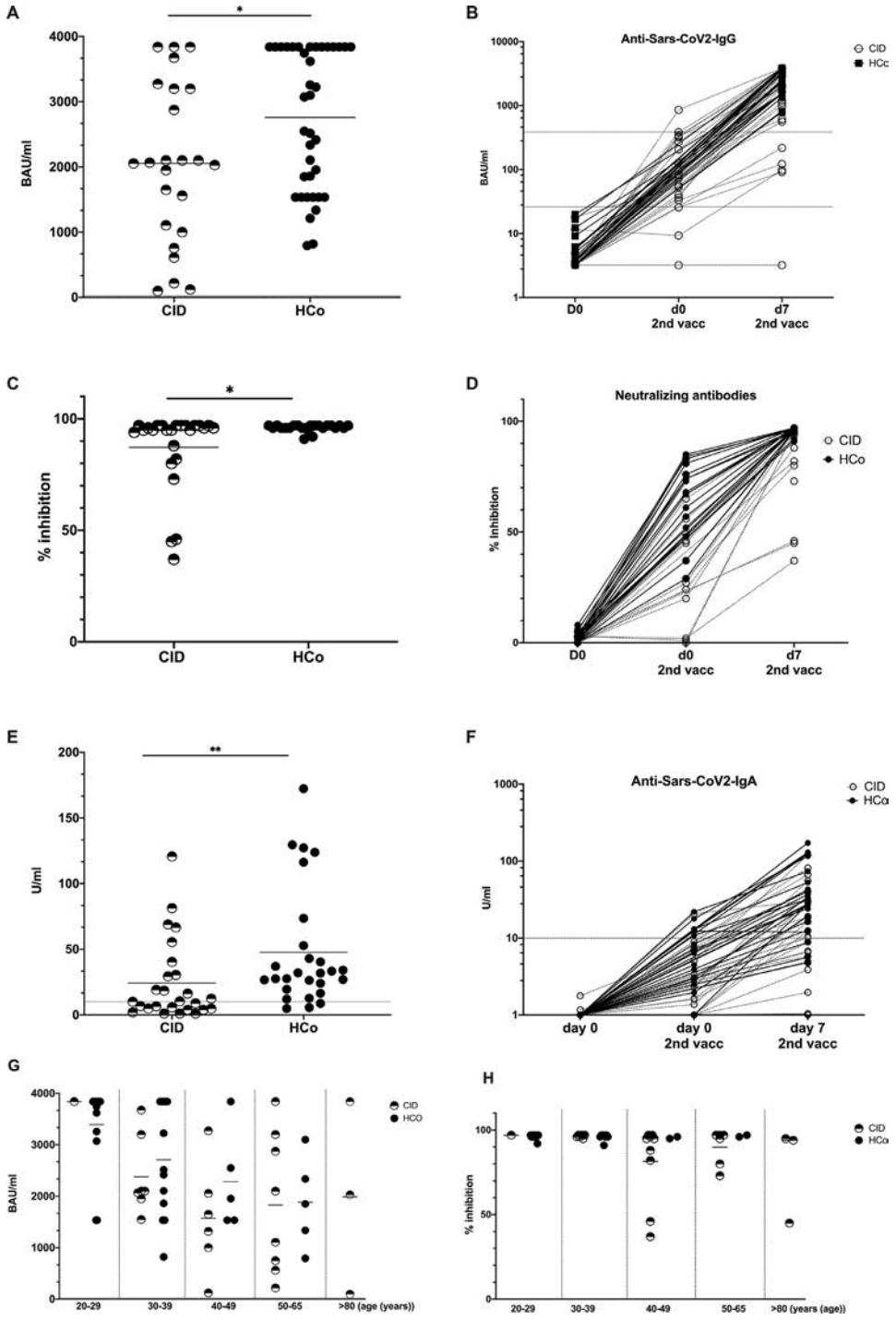

Figure 1 SARS-CoV-2 specific antibodies are detectable in patients and healthy controls. (A) Anti-SARS-CoV-2 IgG antibodies in patients with CID and controls 7 days after secondary immunisation. (B) IgG titres in patients with CID and controls at baseline on the day of the second immunisations and 7 days later. (C) Neutralising activity at 7 days post secondary immunisation. (D) Change in neutralising antibodies from baseline to day 7 after the second immunisation. (E) Anti-SARS-CoV-2 IgA levels 1 week after the second mRNA vaccination in patients and controls. (E) IgA titres at baseline and 7 days after second vaccination. Anti-SARS-CoV2-IgG titres (G) and neutralising capacity (H) in healthy controls and patients by age group 7 days after secondary vaccination. Each symbol represents a single study participant. Bars represent means. Cut-offs for commercial test are displayed as horizontal dashed lines. CID, chronic inflammatory disease; HCo, healthy control.

response. Additionally, no patient on B cell depleting therapy, mycophenolate or cyclophosphamide was included into the study. Especially B cell depleting therapies are known to decrease vaccination response dramatically.

Due to the small cohort, comparison of different therapeutic targets was statistically not feasible. Comparing TNF alpha blockade as the most prevalent therapeutic target in rheumatology as compared with cDMARDs and anti-interleukin 17 blockade showed no significant difference. Obviously, treatment groups were small, and the SD in the TNF blocker group was high. Therefore, generalising from these data might be inappropriate.

Vaccination does not appear to be a major driver of flare ups in patients with CID as none of our cohort showed a significant

Table 2 Side effects after secondary immunisation in healthy controls and patients with CID as documented 7 days after the vaccination

	Healthy donors n=38/42 (%)		Patients n=26/26 (%)	
Symptoms	N	%	N	%
Local pain at injection side	25	65.8	17	65.4
Local reddening	2	5.6	2	7.7
Local swelling	4	11.1	4	15.4
Fatigue	16	43.2	14	53.8
Headache	13	35.1	10	38.5
Fever >38°C	5	13.5	0	0
Fever >40°C	0	0	0	0
Lymph node swelling	4	10.8	3	11.5
Chills	8	21.6	1	3.8
Arthralgia	6	16.2	4	15.4
Myalgia	12	31.6	11	42.3
Other side effects	7	18.4	5	19.2
Need for NSAIDs	10	26.3	9	34.6

NSAIDs, non-steroidal anti-inflammatory drugs.

activation of their inflammatory disease. Mild side effects were only marginally increased, whereas systemic side effects such as fever were reduced in patients with CID compared with healthy controls. These observations may indicate stronger immune reactions in healthy individuals. Such a difference may be due to the younger age of the healthy controls compared with the patients with CID. However, even older controls displayed fever, which was not present in patients. It is also possible that the medication taken by patients with CID is affecting the incidence of systemic side effects.

We are aware that the analysed cohort is small and that our results may be attributable to patient selection. Also, further research is needed to investigate if the differences we observed effect the long-term protection offered by vaccines.

Our data demonstrate for the first time that patients with a selection of immunosuppressive therapies for CID are able to mount an effective immune response after SARS-CoV-2 mRNA vaccination without significant side effects or flares. Thus, we strongly recommend continued vaccination of immunosuppressed patients. However, anti-SARS-CoV-2 antibodies should be monitored in immunosuppressed patients after vaccination, as currently we cannot be certain of antibody titre persistence. The possibility remains that immunosuppressed patients will need a booster (comparable with hepatitis B vaccination) if their antibody titres diminish more rapidly than healthy individuals. Continued monitoring of vulnerable patient groups will be critical in the successful long-term vaccination against SARS-CoV-2.

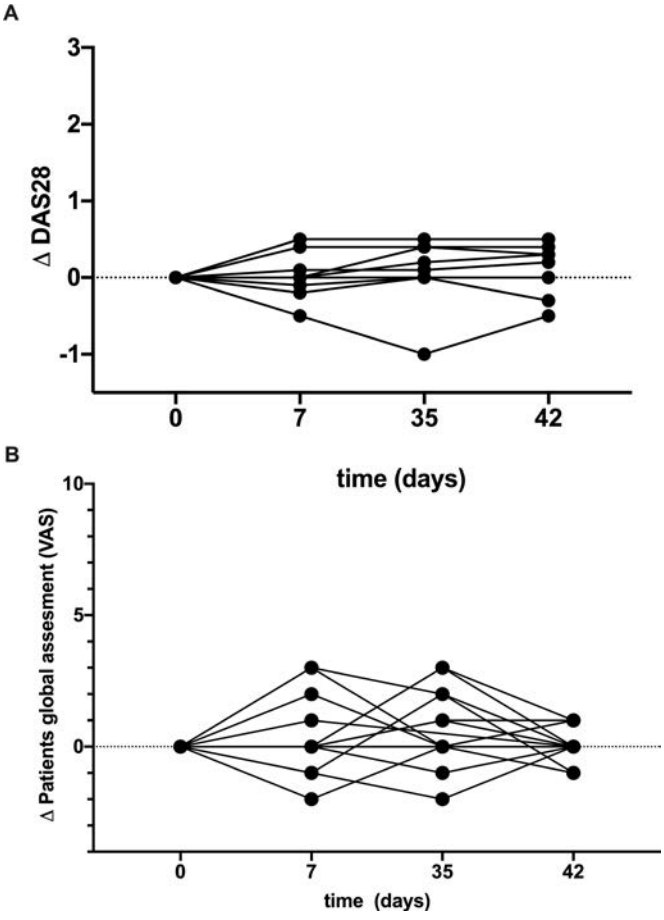

Figure 2 Disease activity does not increase over time after SARS-CoV-2 vaccination. (A) Delta DAS28 for patients with inflammatory arthritis during the 42-day study period. (B) Delta patients global assessment in patients with CID from baseline to day 42. Disease activity was assessed before the first and the second immunisation and 7 days after each vaccination. Each symbol represents one patient. CID, chronic inflammatory disease; DAS28, disease activity score 28.

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Correction notice This article has been corrected sincd it published Online First. Figure 1 has been updated.

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Contributors Study design: UMG, BFH, SS and FT. Sample collection: DKB, FT, MS, SG, AS, RZ, JHS, ACL and AF. Experiments and data analysis: UMG, DKB, LV, HMR, MC, JF, RDHM, CK, and BFH. Tables and figure: BFH, SG and UMG. Data interpretation: BFH and UMG. Writing of the manuscript: BFH, UMG, PH and PM. Critical proof reading of the manuscript: all authors.

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Provenance and peer review Not commissioned; externally peer reviewed.

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CLINICAL SCIENCE

SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases

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ABSTRACT

Objectives To better understand the factors that influence the humoral immune response to vaccination against SARS-CoV-2 in patients with immune-mediated inflammatory diseases (IMIDs).

Methods Patients and controls from a large COVID-19 study, with (1) no previous history of COVID-19, (2) negative baseline anti-SARS-CoV-2 IgG test and (3) SARS-CoV-2 vaccination at least 10 days before serum collection were measured for anti-SARS-CoV-2 IgG. Demographic, disease-specific and vaccination-specific data were recorded.

Results Vaccination responses from 84 patients with IMID and 182 controls were analysed. While all controls developed anti-SARS-CoV-2 IgG, five patients with IMID failed to develop a response (p=0.003). Moreover, 99.5% of controls but only 90.5% of patients with IMID developed neutralising antibody activity (p=0.0008). Overall responses were delayed and reduced in patients (mean (SD): 6.47 (3.14)) compared with controls (9.36 (1.85); p<0.001). Estimated marginal means (95% CI) adjusted for age, sex and time from first vaccination to sampling were 8.48 (8.12–8.85) for controls and 6.90 (6.45–7.35) for IMIDs. Significantly reduced vaccination responses pertained to untreated, conventionally and anticytokine treated patients with IMID.

Conclusions Immune responses against the SARS-CoV-2 are delayed and reduced in patients with IMID. This effect is based on the disease itself rather than concomitant treatment.

Key messages

What is already known about this subject?

► While it is known that SARS-CoV-2 vaccination is effective in the general population, virtually no data on the efficacy and safety of the vaccine in patients with immune-mediated inflammatory diseases exist at the moment. Most importantly, it is not known whether the disease itself or the respective immune-modulatory therapy may affect the immune response to the SARS-CoV-2 vaccine.

What does this study add?

► The study shows that one out of 10 patients with an immune-mediated inflammatory disease fails to develop neutralizing antibodies after SARS-CoV-2 vaccination, while it is only 1 out of 100 in healthy controls.

► Decreased immune response to SARS-CoV-2 vaccination is immanent to the presence of an immune-mediated inflammatory disease but not related to the individual immune-modulatory treatments.

How might this impact on clinical practice or future developments?

► These data suggest that humoral immune responses to SARS-CoV-2 vaccination need to be assessed in patients with immune-mediated inflammatory diseases in order to ascertain protective immunity.

INTRODUCTION

COVID-19 has developed into one of the most impactful pandemics.[1] Within short times, tremendous research efforts have led to the development of effective vaccines.[2 3] Their efficacy and safety in the general population is substantiated by a growing number of studies that demonstrate the development of protective immunity and the appearance of specific antibodies against SARS-CoV-2.[4 5]

The development of protective immunity requires a functional immune system, which can be impaired by diseases or treatments. Patients affected by immune-mediated inflammatory diseases (IMIDs) show aberrant immune responses, increased risk to infections and are exposed by drugs that interfere with immune pathways. Hence, responses of patients with IMID to immunisation against SARS-CoV-2 may be altered. Furthermore, IMIDs are usually associated with comorbidities that increase the risk for severe courses of COVID-19.[6]

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In accordance, the risk for severe courses of COVID-19 has reported to be higher in patients with IMID.[7] For this reason, it seems reasonable to give patients with IMID preferential access to vaccination.[8 9]

At present, however, there is a tremendous paucity of data, that could guide physicians in how individual IMIDs and immune-modulatory treatments associated with these IMIDs would influence the immune response to SARS-CoV-2 vaccination. Patients with IMIDs and those receiving immune-modulatory treatments were excluded from the phase III vaccine trials. One recent small study suggested that vaccination against SARS-CoV-2 works in patients with IMIDs, but leaves it open whether and how the presence of the disease or the use of specific drugs influences the immune responses.[10] We therefore analysed the first vaccination responses in large longitudinal COVID-19 study that follows antibody responses to SARS-CoV-2 in healthy individuals and patients with IMID over time.[11]

METHODS

Participants

Patients with IMID and healthy controls were recruited from a large longitudinal COVID-19 study at the Deutsche Zentrum fuer Immuntherapie that has been initiated in February 2020 and monitors anti-SARS-CoV-2 antibody responses as well as respiratory infections including COVID-19 in healthy controls and patients with IMID.[11] All patients and controls with (1) no previous history of COVID-19, (2) negative anti-SARS-CoV-2 IgG test in December 2020/January 2021 and (3) having received at least one shot of the BNT162b2 mRNA SARS-CoV-2 vaccine (BioNTech/Pfizer) more than 10 days before serum collection were included into this study. Demographic (age, sex, body mass index, comorbidities), disease-specific (type of IMID, type of treatment) and vaccination (date, type of vaccine, adverse reactions) data were recorded.

IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were tested by the recent CE version (April 2020) of the commercial ELISA from Euroimmun (Lübeck, Germany) using the EUROIMMUN Analyzer I platform and according to the manufacturers protocol. All analyses were done in duplicates. Optical density (OD) was determined at 450 nm with reference wavelength at 630 nm. A cut-off of ≥0.8 (OD 450 nm) was considered as positive. To assess neutralisation activity of the antibodies, a CE- In Vitro Diagnostics (CE-IVD)-certified SARS-CoV-2 surrogate virus neutralisation assay (cPASS, Medac,Wedel, Germany) was used. This assay measures the potential of antibodies to inhibit the binding of a labelled SARS-CoV-2 receptor-binding domain (RBD) to coated angiotensin-converting enzyme-2 (ACE2. A cut-off of 30% inhibition was considered as positive, according to the manufacture's instructions.

Statistical analysis

We described participant characteristics using appropriate summary statistics for continuous and categorical data. Antibody levels over time were visually analysed using scatter plot smoothers based on generalised additive models to explore the course of response after the initial vaccine dose. To explore the association of vaccination response with demographic characteristics and disease status, we fitted linear regression models with the OD values from the antibody assay as the dependent variable and participant/treatment groups, age, sex and time after the first vaccine dose as independent variables. Since a non-linear relationship between time and vaccine response is expected, we included days after first vaccination in the model using restricted cubic splines with three knots that were placed based on the inflection points on the scatterplot smoother. This provided a better fit compared with linear or quadratic terms for time.

We reported empirical group means for description. For between-group comparisons, we used estimated marginal means (ie, least square means) from the model. These were weighted for imbalances between covariate categories, averaged over sex and were conditional on overall mean age and mean duration after vaccination in order to account for differences between healthy controls and IMID treatment groups. T tests were used for comparisons. We used Fisher's exact test to compare categorical vaccine response between groups. Two-sided unadjusted p values <0.05 were considered significant. All analyses were carried out using the open-source R software V.4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) running under the GUI RStudio (RStudio corp, Boston, Massachusetts, USA) with the 'rms' and 'emmeans' packages.

RESULTS

Characteristics of patients and controls

From 28 December 2020 until 20 March 2021, 84 patients with IMID (mean age 53.1±17.0 years, 65.5% females) and 182 healthy controls (40.8±12.0 years, 57.1% females) had received at least one shot of the SARS-CoV-2 vaccine (Biontec/Pfizer) at least 10 days ago. The vast majority (96%) of subjects had received two shots of the vaccination. All of these individuals did not have a history of COVID-19 in 2020 and were antibody negative before the vaccination (testing in December 2020). Most patients with IMID had spondyloarthritis (SpA/psoriatic arthritis) (32.1%), followed by rheumatoid arthritis (RA) (29.8%), inflammatory bowel disease (9.5%), psoriasis (9.5%) and systemic IMIDs (table 1). About 42.9% of the patients received biologic (b) or targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs), 23.9% were treated conventional synthetic (cs) DMARDs, while 28.6% received no treatment.

Dynamics of SARS-CoV-2 vaccination responses in patients with IMID and controls

All controls responded to the vaccine, reaching positive (OD >0.8) anti-SARS-CoV-2 IgG antibodies. Positive antibody responses in controls were observed as early as 11 days after the first vaccination. Most patients with IMID also developed positive anti-SARS-CoV-2 IgG antibodies. However, vaccination failed in five patients with IMID (p=0.003; Fisher's exact test). In three of them, lack of immunogenicity was even detectable 11, 27 and 39 days after the second vaccination (one without therapy, one patient with RA treated with baricitinib and one patient with SpA with secukinumab). Patients with IMID showed relatively large OD difference shortly after the second vaccination compared with controls, but this difference converged over time (figure 1A). In a linear model implementing group–time interactions, the adjusted mean difference between controls and patients with IMID at day 28 after the first vaccine administration was 2.21 (95% CI: 1.28 to 3.13, p<0.001) reducing to 0.07 (95% CI: −1.27 to 1.12, p=0.90) at day 70.

Assessment of neutralisation activity of anti-SARS-CoV-2 antibodies, using an assay that measures their potential to block binding of RBD to ACE2 showed that 99.5% (181/182) of controls developed neutralising antibodies, while only 90.5% (76/84) of patients with IMID developed neutralising activity (p=0.0008; Fisher's exact test). Among those failing to develop

Table 1 Demographics and clinical characteristics of patients with IMID and controls

	IMIDs	HC
N	84	182
Demographic characteristics		
Age, years	53.1±17.0	40.8±12.0
Females, N (%)	55 (65.5)	104 (57.1)
BMI	26.8±5.8	24.7±4.1
Current smokers, N (%)	14 (16.7)	31 (17.0)
Comorbidities		
Diabetes	6 (7.1)	2 (1.1)
Hypertension	21 (25.0)	19 (10.4)
History of CV event	1 (1.2)	1 (1.0)
History of thrombotic event	0	0
Type of IMID		
SpA, N (%)	27 (32.1)	0
RA, N (%)	25 (29.8)	0
IBD, N (%)	8 (9.5)	0
Psoriasis, N (%)	8 (9.5)	0
Systemic*, N (%)	16 (19.1)	0
Immune-modulatory therapy		
No treatment, N (%)	24 (28.6)	0
Glucocorticoids, N (%)	10 (11.9)	0
csDMARDs monotherapy, N (%)	20 (23.9)	0
MTX, N (%)	16 (19.1)	0
Hydroxychloroquine, N (%)	3 (3.6)	0
Sulfasalazine, N (%)	1 (1.2)	0
bDMARDs/tsDMARDs, N (%)	36 (42.9)	0
TNF inhibitors, N (%)	11 (13.1)	0
IL-6 inhibitors, N (%)	3 (3.6)	0
IL-23 inhibitors, N (%)	6 (7.1)	0
IL-17 inhibitors, N (%)	7 (8.3)	0
JAK inhibitors, N (%)	6 (7.1)	0
Others†, N (%)	3 (3.6)	0

*Systemic lupus erythematosus, systemic sclerosis, IgG4-related disease, periodic fever syndromes, giant cell arteriitis, granulomatosis with polyangiitis and polymyalgia rheumatic.
†Apremilast, canakinumab and vedolizumab.
bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CV, cardiovascular; HC, healthy controls; IBD, inflammatory bowel disease; IL, interleukin; IMIDs, immune-mediated inflammatory diseases; JAK, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; SpA, spondyloarthritis (including axial spondyloarthritis and psoriatic arthritis); TNF, tumour necrosis factor; tsDMARDs, targeted-synthetic disease-modifying antirheumatic drugs.

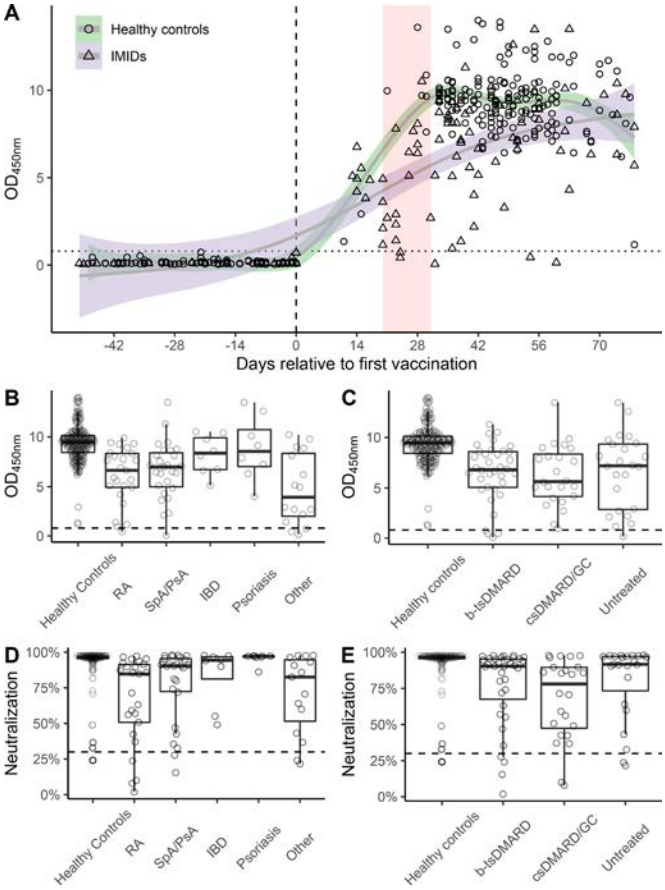

Figure 1 Temporal pattern of vaccination response and antibody levels in different disease and treatment groups. (A) Temporal course of anti-SARS-CoV-2 antibody formation after first and second mRNA vaccine doses, first vaccination is depicted by a dotted vertical line, second vaccination by a red vertical band, smoothed plots show time-conditional mean antibody levels in healthy controls and IMID subgroups. (B) Distribution of antibody levels by type of treatment (B) and diagnosis (C). Dotted horizontal lines represent OD cut-off of ≥0.8 (OD 450 nm). (D, E) Distribution of neutralisation activity of the antibodies based on per cent inhibition of binding of the receptor-binding domain to angiotensin-converting enzyme-2 by type of treatment (D) and diagnosis (E). Dotted horizontal lines represent cut-off of ≥30% inhibition. bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IBD, inflammatory bowel disease; OD, optical density; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; tsDMARDs, targeted-synthetic disease-modifying antirheumatic drugs.

neutralising activity were three Janus kinase inhibitors, two methotrexate, one interleukin-17 inhibitor treated and two untreated patients with IMID .

Comparison of SARS-CoV-2 vaccination responses in patients with IMID and controls

Overall mean (SD) OD values were 6.47 (3.14) in patients with IMID compared with 9.36 (1.85) in controls (adjusted mean difference 1.58, 95% CI: 0.98 to 2.19, p<0.001). Estimated marginal means (95% CI) adjusted for age, sex and time elapsed from first vaccination to sampling date were 8.48 (8.12 to 8.85) for controls and 6.90 (6.45 to 7.35) for IMIDs (table 2). Linear regression model showed that vaccine responses were influenced by the presence of IMID, age, sex and time elapsed from vaccination (online supplemental table 3).

Table 2 Empirical and estimated marginal means by study groups and treatment

Group	Empirical mean (SD)	EMM* (95% CI)
Controls	9.36 (1.85)	8.48 (8.12 to 8.85)
IMIDs all	6.47 (3.14)	6.90 (6.45 to 7.35)
IMIDs b/tsDMARDs	6.49 (2.91)	6.90 (6.22 to 7.58)
csDMARDs	6.26 (3.00)	6.67 (5.84 to 7.50)
Untreated	6.64 (3.70)	7.13 (6.30 to 7.96)

*Adjusted for age, sex, time elapsed from first vaccination date to sampling date.
bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EMM, estimated marginal mean; IMIDs, immune-mediated inflammatory diseases; tsDMARDs, targeted-synthetic disease-modifying antirheumatic drugs.

Effect of IMID group and immune-modulatory treatment on vaccination responses

When analysing immune response to SARS-CoV-2 vaccination in different IMID groups, overall mean ODs were similar across IMIDs and lower than that of controls. We did not detect any significant difference between diseases based on adjusted mean differences (figure 1B). When analysing different treatment regimen (no treatment, csDMARDs, bDMARDs/tsDMARDs), we found that patients with IMID treated with bDMARDs/tsDMARDs did not show a different response compared with patients receiving csDMARDs (6.49 (2.91) vs 6.26 (3.00); mean diff. 95% CI 0.23 (−0.83 to 1.30), p=0.97) or to those without treatment (6.49 (2.91) vs 6.64 (3.70); −0.22 (−1.28 to 0.83), p=0.97) (online supplemental table 2). In contrast, all three IMID treatment groups showed lower OD values than controls (online supplemental table 2; figure 1C). Responses in individual bDMARDs treatments are depicted in online supplemental table 3.

Tolerability of SARS-CoV-2 vaccination in patients with IMID

Side effects of vaccination were assessed in 70 patients with IMID and 164 controls. Side effects were generally more frequent after the second vaccination. Injection side pain was most frequently observed in both groups. Many side effects (injection side reaction, headache, chills, arthralgia) were less frequent in patients and in controls (online supplemental table 4).

DISCUSSION

This study shows that SARS-CoV-2 vaccination essentially works in patients with IMID but responses are delayed and reduced. A minority of patients with IMID did not respond to the vaccine even after second immunisation, suggesting that in some cases the measurement of antibody levels after vaccination might be useful to ascertain development of immunity. In accordance, only 0.5% of the controls failed to develop neutralising antibody activity, while such failures were observed in 9.5% of the patients with IMID. Thus, roughly 1 out of 10 patients with IMID fails to develop neutralising antibodies after SARS-CoV-2 vaccination, while it is only 1 out of 100 in the controls. This findings contrast the data from a small group of 26 patients with IMID suggesting that all patients with IMID respond to the vaccine.[10]

Delayed antibody responses to the SARS-CoV-2 vaccine may suggest an effect of immune-modulatory treatments. However, we could not objectify this hypothesis, as also patients with IMID without treatment had lower antibody responses than controls and furthermore no differences between csDMARDs and b/tsDMARD treated patients were found. Of note this IMID cohort did not comprise rituximab-treated patients, in whom antibody responses are abrogated.[12] Hence, delayed antibody responses seem to be a disease rather than a treatment-related effect. In addition to the presence or absence of IMIDs, sex and age affected SARS-CoV-2 vaccination responses, which is in accordance with published work.[13 14]

In conclusion, our study provides evidence that while vaccination against SARS-CoV-2 is well-tolerated and even associated with lower incidence of side effects in patients with IMID, its efficacy is somewhat delayed and reduced. Nonetheless, the data also show that, in principle, patients with IMID respond to SARS-CoV-2 vaccination, supporting an aggressive vaccination strategy. In addition, cell-mediated responses to vaccination, which were not analysed in this study, may additionally contribute to anti-SARS-CoV-2 immunity in patients with IMID .[15]

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Ethics approval Ethical approval (#157_20 B) to conduct this study was granted by the Institutional Review Board of the University Hospital Erlangen. Written informed consent was obtained from the study participants.

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CLINICAL SCIENCE

Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2

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ABSTRACT

Background The registration trials of messenger RNA (mRNA) vaccines against SARS-CoV-2 did not address patients with inflammatory rheumatic diseases (IRD).

Objective To assess the humoral response after two doses of mRNA vaccine against SARS-CoV-2, in patients with IRD treated with immunomodulating drugs and the impact on IRD activity.

Methods Consecutive patients treated at the rheumatology institute, who received their first SARS-CoV-2 (Pfizer) vaccine, were recruited to the study, at their routine visit. They were reassessed 4–6 weeks after receiving the second dose of vaccine, and blood samples were obtained for serology. IRD activity assessment and the vaccine side effects were documented during both visits. IgG antibodies (Abs) against SARS-CoV-2 were detected using the SARS-CoV-2 IgG II Quant (Abbott) assay.

Results Two hundred and sixty-four patients with stable disease, (mean(SD) age 57.6 (13.18) years, disease duration 11.06 (7.42) years), were recruited. The immunomodulatory therapy was not modified before or after the vaccination. After the second vaccination, 227 patients (86%) mounted IgG Ab against SARS-CoV-2 (mean (SD) 5830.8 (8937) AU/mL) and 37 patients (14%) did not, 22/37 were treated with B cell-depleting agents. The reported side effects of the vaccine were minor. The rheumatic disease remained stable in all patients.

Conclusions The vast majority of patients with IRD developed a significant humoral response following the administration of the second dose of the Pfizer mRNA vaccine against SARS-CoV-2 virus. Only minor side effects were reported and no apparent impact on IRD activity was noted.

Key messages

What is already known about this subject?

- There is very limited data regarding the safety, the humoral immunogenicity and the impact on the rheumatic disease, of two doses of messanger RNA (mRNA) vaccine against SARS-CoV-2, in patients with inflammatory rheumatic diseases (IRD) treated with immunomodulating agents.

What does this study add?

- Our study included a diverse, relatively large size cohort (compared with the data published so far) exposed to widely diverse immunomodulatory treatments including the use of B cell-depleting agents.
- We showed that despite continuing chronic immunosuppression, patients with IRD mounted significant amounts of protective antibodies.
- The humoral response was influenced by the type of the immunomodulatory treatment and not by the type of IRD.
- B cell-depleting agents significantly impair antibody production, particularly in older patients.
- No IRD flare ups were observed following vaccination of patients with IRD.

How might this impact on clinical practice or future developments?

- The two dose Pfizer–BioNTech COVID-19 vaccine is safe in stable patients with IRD.
- The antibody titres are influenced by the type of the immunotherapy.
- So far there is no proof that the antibody titres correlate with improved protection against COVID-19.

INTRODUCTION

The registration trials of messenger RNA (mRNA) vaccines against SARS-CoV-2 did not address patients with inflammatory rheumatic diseases (IRD).[1 2] Concerns were raised whether these patients can mount a protective immune response and whether the vaccination may trigger a flare up of the IRD. Previous studies showed that most protein-based vaccines induce protective antibody titres in patients with IRD.[3] However, the humoral response was found to be blunted in some patients treated with CD20-depleting antibodies (Abs) or immune suppression.[4] Recently, Geisen *et al* reported on the humoral response induced by mRNA vaccines against SARS-CoV-2 and their safety in 26 patients with IRD, but no patients on B cell-depleting therapy were included.[5] Boyarsky

et al reported interim immunogenicity data after one dose of mRNA vaccine in 123 patients with IRD who were recruited via social media.[6]

We wish to report the humoral response after the second dose of mRNA vaccine against SARS-CoV-2, in a well-defined cohort of patients with IRD treated with disease-modifying antirheumatic drugs (DMARDs) under careful rheumatologists' follow-up and the impact of the vaccine on IRD activity.

MATERIALS AND METHODS

Consecutive patients treated at a single tertiary referral rheumatology centre, who received their first SARS-CoV-2 (Pfizer) vaccine, were recruited during their routine visit. The inclusion criteria were established diagnosis of IRD, receival of the first dose of the BNT162b2 mRNA vaccine and agreement to participate in the study. The visit included IRD activity assessment (disease activity score (DAS)28), patient global assessment (PGA), physician global assessment (PhGA) and questioning regarding the vaccine side effects. All patients received the BNT162b2 mRNA vaccine according to Israeli Ministry of Health regulations. The second dose of vaccine was administrated 3 weeks after the first dose. The vaccination was not part of the study. The patients were invited for serology tests and additional IRD assessment 4–6 weeks after the second dose of vaccine. Patients who did not receive the second dose of vaccine were excluded from the study.

A comparison group of patients with IRD who reported, at their routine visit at the rheumatology clinic of COVID-19 disease (diagnosed by positive SARS-CoV-2 PCR) within the previous 2 months, was recruited to the study. The patients were assessed for IRD activity and neutralising Abs within 4–8 weeks after the recovery (symptomatic recovery and negative SARS-CoV-2 PCR).

Neutralising IgG Abs against SARS-CoV-2 virus were detected using the SARS-CoV-2 IgG II Quant (Abbott) assay based on a chemiluminescent microparticle immunoassay on the ARCHITECT ci8200system from Abbott. This assay measures IgG Abs against the spike receptor-binding domain (RBD) of the virus. IgG Abs against the spike (S) RBD of the virus are defined as neutralising Abs since the spike (S) protein contains an RBD that can specifically bind to angiotensin-converting enzyme 2, the receptor on target cells in the host.[7] The test is considered positive above 50 AU/mL. We did not use a neutralising assay.

The study was approved by the local ethical committee (the Ethics Committee of Rambam Health Care—417-20). Informed consent was obtained from all study participants prior to the initiation of any study procedure.

Statistical analysis: we used SPSS software (IBM SPSS Statistics for Windows, V.27, IBM, Armonk, New York, 2020). All statistical tests were two sided, statistical significance was defined as p value below 0.05. Categorical variables were summarised as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q–Q plots and reported as median and IQR. Association between continuous variables was evaluated using Spearman correlation. Association between categorical variables was evaluated using χ^2 test or Fisher exact test. Continuous variables were compared using Kruskal-Wallis test or Mann-Whitney test. Multivariate logistic regression was used to compare patients with humoral response versus patients without response, while controlling for potential confounders.

Table 1 Clinical characteristics and immunomodulatory therapy of vaccinated and COVID-19 recovered patients

	Vaccinated (n=264)	COVID-19 recovered (n=26)
Diagnosis, n (%) inflammatory arthritis	**152 (58)**	**16(58)**
Rheumatoid arthritis	96 (37)	11 (42)
Juvenile arthritis	4 (2)	
Psoriatic arthritis	30 (12)	1 (4)
Spondyloarthropathy	21 (8)	3 (12)
Sarcoidosis	1 (0.4)	1 (4)
Connective tissue diseases	**87 (34)**	**9 (35)**
Systemic sclerosis	50 (19)	5 (19)
Systemic lupus erythematosus	25 (10)	2 (0.8)
Myositis	9 (3)	1 (4)
Sjogren	2 (0.7)	
MCTD**	1 (0.4)	1 (4)
Vasculitis	**19 (7)**	**1 (4)**
Granulomatosis with polyangiitis	4 (2)	
Eosinophilic granulomatosis with polyangiitis	3 (1)	
Takayasu vasculitis	7 (3)	1 (4)
Behcet's disease	4 (2)	
Polyarteritis nodosa	1 (0.4)	
Others††	6 (2)	
Therapy, n (%)		
None	22 (8.3)	3 (11)
csDMARDs	160 (60.6)	15 (58)
Methotrexate	78 (29.5)	5 (19)
Mycophenolate mofetil	26 (9.8)	7 (27)
Salazopyrine	7 (0.3)	1 (4)
Hydroxychloroquine	43 (16)	5 (19)
Leflunomide	13 (5)	0
Azathioprine	14 (5)	1 (4)
Purimethol	2 (0.7)	0
Cyclosporine	1 (0.3)	0
Colchicine	6 (0.2)	0
Nintedanib	3 (0.1)	1 (4)
Biological/targeted DMARDs	178 (67.4)	19 (73)
B-cell depleting (anti-CD-20)	48 (18.2)	5 (19)
Belimumab	11 (4.2)	3 (11)
Anti-TNF§	63 (23.9)	8 (31)
Anti-interleukins¶	40 (15.2)	2 (8)
Abatacept	8 (3)	1 (4)
Anti-JAK** agents	9 (3.4)	0
Combined therapy‡‡	95 (36)	11 (42)
Corticosteroids	92 (34.8)	13 (50)

*Mixed connective tissue disease.
†IGG4-related disease, idiopathic recurrent pericarditis, familial mediterranean fever, polymyalgia rheumatica, adult Still's disease.
‡csDMARDs+b/tsDMARDs; conventional synthetic disease-modifying antirheumatic drugs+biological/targeted synthetic DMARDs.
§Anti-TNF (infliximab, adalimumab, golimumab, certolizumab, etanercept).
¶Anti-interleukins (tocilizumab, sarilumab, secukinumab, ixekizumab, ustekinumab, risankizumab, mepolizumab, anakinra).
**Anti-JAK agents (tofacitinib, baricitinib, upadacitinib).
DMARDs, disease-modifying antirheumatic drugs; IGG4, immunoglobulin G4; JAK, janus kinase; MCTD, mixed connective tissue disease.

RESULTS

We recruited 264 consecutive patients ((76% women) mean (SD) age 57.6 (13.18) years, disease duration 11.06 (7.42) years), who received their first SARS-CoV-2 (Pfizer) vaccine and 26 COVID-19 recovered patients (73% women), (mean (SD) age 47.3 (16.73) years, disease duration 6.53 (4.76) years).

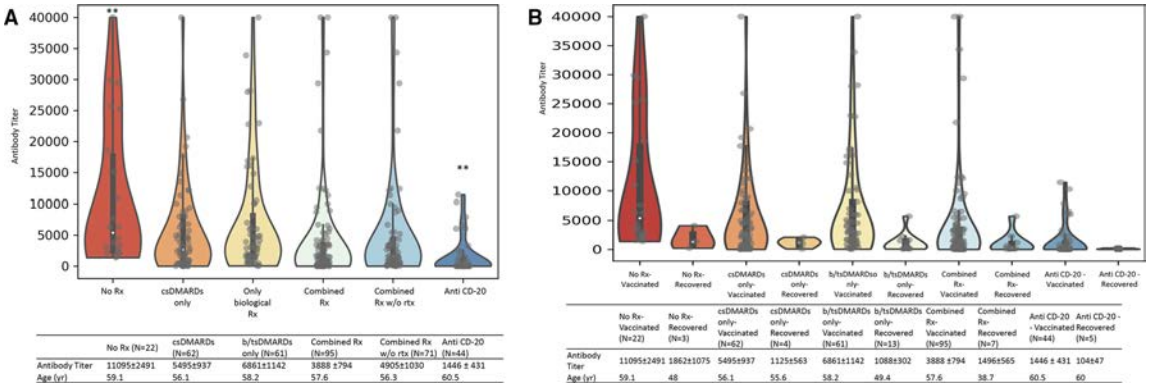

Figure 1 (A) Antibody titres for the different treatments presented as violin plots with included boxplots. The violin illustrates the kernel probability density of antibody titres, and the boxplot indicates the median and quartiles with whiskers up to 1.5 times the IQR. (B) Violin plots of antibody titres for the different treatments in vaccinated and COVID-19 recovered patients. Mean antibody titres±SE per treatment group. **p-value<0.01; Rx- treatment. csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; b/tsDMARDs, biological/targeted synthetic DMARDs; rtx, rituximab; combined Rx, csDMARDs+b/tsDMARDs; combined Rx w/o rtx, combined treatment without rituximab.

The IRD diagnoses of the vaccinated patients are described in table 1. The treatment regimens included conventional synthetic (cs)DMARDs only, biological/targeted synthetic (b/ts)DMARDs only or combinations of the two (23%, 23%, 336%, respectively). Corticosteroids were used by 3% (mean dose (range) 5.6 mg (2.5–20 mg) prednisone). None of the patients discontinued immunomodulatory therapy before or after the vaccination. All the patients had stable disease (DAS28 (C-reactive protein (CRP)) mean (SD) 2.9 (1.7), PGA 3.4 (1.5), PhGA 2.6 (1.8).

After the second vaccination, 227 patients (86%) mounted a significant humoral response of neutralising IgG Ab against SARS-CoV-2 virus (mean (SD) 6764.27 (9291.61) AU/mL, median 3058 AU/mL, range 58–40000) and 37 patients (14%) did not: 24 out of 47 rituximab-treated patients (1.5–12 months before), 3 out of 8 abatacept-treated patients, 4 out of 21 patients treated with mycophenolate mofetil (MMF) only, 2 out of 11 belimumab-treated patients (one patient also received MMF), 1 out of 5 anti-IL17-treated patients, 1 patient treated with prednisone 20 mg, 1 patient treated with chemotherapy for a lung neoplasm and the only patient treated with obinutuzumab (figure 1). The demographic and clinical data of the patients who did not mount a significant humoral response are shown in the online supplemental table 3. We performed univariate analysis and multivariate logistic regression analysis which included age, disease duration, type of rheumatic disease, type of treatment (methotrexate (MTX), MMF, all csDMARDS, all b/tsDMARDs, anti-tumour necrotising factor (anti-TNF), anti-interleukins, antiCD20, belimumab, abatacept, combination csDMARDs +b/tsDMARDs, prednisone). The type of the immunomodulatory treatment influenced the humoral response and not the IRD diagnosis (table 2A, figure 2). In multivariate logistic regression analysis, only IRD duration, treatment with anti-CD20, abatacept or MMF were associated with the humoral response (table 2B).

Treatment with csDMARDs, MTX, anti-CD20, anti-interleukins and older age was associated with lower levels of neutralising IgG Ab against SARS-CoV-2 (online supplemental table 4). Only

10 out of 78 MTX-treated patients did not mount a significant humoral response (seven patients received concomitant treatment with rituximab, one with abatacept and another with 20 mg prednisone). When we excluded the patients who received MTX and concomitant rituximab treatment, this difference was not significant anymore.

Fifty-two per cent of anti-CD20-treated patients did not develop a significant humoral response. Comparing the

Table 2 Humoral response—univariate and multivariate analyses

(A) Univariate analyses			
Humoral response	**Positive**	**Negative**	**P value**
Age mean(SD)	56.9 (13.3)	62.05 (11.6)	0.024
Gender —female	157	27	0.64
Disease duration mean (SD)	10.7(7.3)	13.2(7.3)	0.032
Type of rheumatic disease			
IJD	135	17	0.277
CTD	70	17	
Vasculitis	17	2	
Other	5	1	
Therapy, n			
None	22	0	0.052
csDMARDs	136	24	0.567
Methotrexate	68	10	0.717
Mycophenolate mofetil	17	9	0.004
Biological/targeted DMARDs	148	30	0.056
B-cell depleting (Anti-CD-20)	24	24	0.0001
Belimumab	9	2	0.656
Anti-TNF anti-interleukins abatacept	63 39 5	0 1 3	0.02 0.023 0.086
Anti-JAK agents	9	0	0.618
Combined therapy (without rituximab)	65	5	0.043
Corticosteroids	76	16	0.248
(B) Multivariate logistic regression analysis			
Variables	**P value**	**OR**	**95% CI lower to upper**
Age	0.084	0.965	0.927 to 1.005
Disease duration	0.043	0.948	0.900 to 0.998
MMF	0.0001	0.064	0.017 to 0.239
Anti-CD20	0.0001	0.033	0.012 to 0.092
Abatacept	0.003	0.07	0.012 to 0.399

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CTD, connective tissue diseases; IJD, inflammatory joint diseases; JAK, janus kinase; MMF, mycophenolate mofetil.

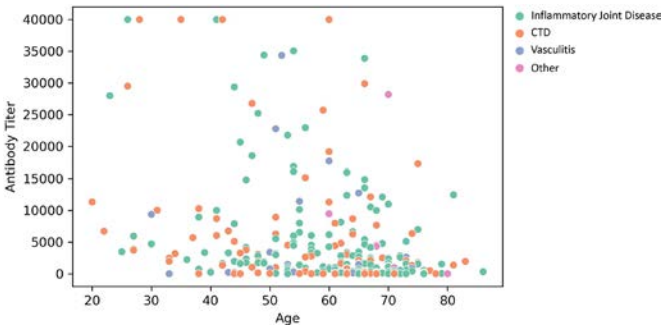

Figure 2 Serology per age, classification by disease Scatter plots of antibody titre level by age. Spearman rank correlation coefficient corresponds to −0.24. Colours represent different disease groups: inflammatory joint disease, connective tissue disease, vasculitis and other diseases. CTD, connective tissue diseases.

anti-CD20 group with humoral response with the one without, it did not reveal any statistically significant difference regarding type of IRD, concomitant treatment, the levels of immunoglobulins prior to rituximab treatment, the number of rituximab courses (mean (SD) 5 (3.19), median five courses vs 5.75 (3.2), 5, p=0.43) or the timing of the last rituximab course related to the vaccination (mean (SD) 9.2 (6.3), median 9 months vs 6.04 (5.5), 5 months, p=0.086). The only significant difference between the groups was the age of the patients (mean (SD) age 64.1 (10.9), median, 66.5 years in the group without humoral response, vs 56.4 (11.1), 55 years in the group with humoral response, p=0.021).

Interestingly, a granulomatosis with polyangiitis (GPA) rituximab-treated patient, who was hospitalised two times for severe COVID-19 disease and reactivation (2 months after rituximab treatment) and who did not have neutralising Abs on recovery, developed a significant humoral response after being vaccinated 4 months after his recovery (11 434 AU/mL—the patient was included in the vaccinated group).

Among the 26 patients with IRD who recovered from COVID-19: 18 patients (70%) received csDMARDs, 10 (38%) received combined treatment with csDMARDs and b/tsDMARDs, 8 (31%) received bDMARDs monotherapy and 13 patients (50%) corticosteroids (mean dose (range) 10.5 mg (2.5–20 mg) prednisone) (table 1). Only two patients, from the recovered COVID-19 group, did not have neutralising Abs: one RA rituximab-treated patient and one systemic sclerosis (SSc) patient treated with MMF and rituximab. Both patients were also on 10 mg prednisone chronic therapy. They both received rituximab treatment 2 months prior to COVID-19 disease; they had a mild viral disease. Only one patient with RA treated with high-dose steroids and immunoglobulins for pyoderma gangrenosum needed hospitalisation for severe COVID-19 disease and received oxygen support, remdesivir and antibiotics for secondary bacterial pneumonia. All the others had very mild COVID-19 disease or were asymptomatic. They did not receive any treatment for COVID-19 19 and the immunomodulatory treatment for the IRD was not discontinued.

The IgG Ab titres were significantly higher in the vaccinated patients compared with the recovered COVID-19 patients with IRD (mean (median) mean (SD) 6764.27 (9291.61) AU/mL, median 3058 AU/mL vs mean (SD) 2044.8 (4944.8), median 480 AU/mL, p<0.05 (figure 1).

The reported side effects of the vaccine were minor (local pain, redness or swelling at injection site—58%, fatigue—30%, muscle sore—12%, headache—20%, low grade fever—3%). One patient with Familial Mediterranean fever, interstitial lung disease and positive rheumatoid factor reported new-onset arthritis 2 weeks after the first dose of vaccine. No flare-up of the underlying IRD occurred within 2 months after vaccination in any other patient (DAS28 (CRP) before and after vaccination mean (SD) 2.9 (1.7) vs 2.8 (1.9), PGA 3.4 (1.5) vs 3.5 (1.6), PhGA 2.6 (1.8) vs 2.5 (1.8)) .

DISCUSSION

The Pfizer mRNA vaccine against SARS-CoV-2 virus appears to be safe in our patients, only minor side effects were reported and no apparent impact on IRD activity was noted. The vast majority of patients with IRD developed a significant humoral response following the administration of the second dose of the vaccine, even though the immunomodulating treatment was not modified, either before or after the vaccination. The type of immunotherapy and the IRD duration influenced the humoral response. There was no statistically significant association between the type of the IRD or the patient's age and the ability to develop a significant humoral response, although older patients had lower levels of IgG Abs. Previous studies reported a 100% and 97.9% humoral response in the healthy control group they used in their study.[8 9] The age groups mean were 44 and 55 years for each study, so that it is very close to the age group of our cohort. Another study compared the humoral response in two age groups (<60 and >80 years) after the first and second Pfizer mRNA vaccine against SARS-CoV-2 virus and found lower IgG neutralising Abs in the elderly group (68.7%).[10] Our cohort included only four patients older than 80 years.

Untreated and DMARDs-treated patients mounted Ab titres that were about one log higher than the patients treated with biologics and MMF. The IgG Ab titres were significantly higher in the vaccinated patients compared with the recovered COVID-19 patients with IRD. It is worth to emphasise that our cohort of recovered COVID-19 patients with IRD included mostly patients with very mild viral disease. The humoral response in patients with severe COVID-19 might be higher than the response in patients with mild disease. In a recently published study, Haberman *et al* found a diminished humoral response in MTX-treated patients.[11] In our cohort, MTX did not have a negative impact on the ability to mount a significant humoral response, although the neutralising Ab levels were lower compared with those in patients without MTX (mean (SD) 4757 (8501) vs 6281 (9097) AU/mL). Worth to emphasise that 9 out of 10 MTX-treated patients with negative humoral response, in our cohort, were on concomitant treatment with rituximab, abatacept or high-dose prednisone. When we excluded these patients from the analysis, the difference was not statistically significant anymore. We do believe that the impairment of the humoral response might be attributed to the concomitant treatment (rituximab, abatacept, steroids) and not to the MTX. All the patients treated with anti-TNF agents, anti-interleukin six agents, anti-janus kinase (JAK) agents and most of the patients on belimumab treatment developed significant neutralising Ab levels. Our results are concordant with previous studies.[5 6] Three out of eight abatacept-treated patients did not develop a significant humoral response. Due to the small number of abatacept-treated patients in our study, we cannot draw any conclusions regarding the impact of the drug on the humoral response, although the results are quite intriguing. Notably, 67% of the nonresponders were treated with B cell-depleting agents. Except for younger age, all other parameters including disease duration, type of IRD, concomitant immunomodulatory treatment,

immunoglobulins levels, the number of previous rituximab treatment courses and the timing of last rituximab treatment were not significantly different between patients with positive humoral response to vaccine versus those with negative response. We do not have results of CD19 counts in these patients. We attribute the impaired response to vaccination in rituximab-treated patients to rituximab itself and not to the premedication with methylprednisolone because the median time between the treatment and vaccination was over a month, and the corticosteroid effect should wither within this time period (the longest interval between therapy and vaccination in a patient who did not develop Abs is 1 year, which is consistent with the long-term immunological effect).

The results regarding MMF are consistent with observed outcome of SARS-CoV-2 mRNA vaccination in the solid organ transplant population.[12]

The strength of our study is the inclusion of a diverse, relatively large size cohort (compared with the data published so far) exposed to widely diverse immunomodulatory treatments including the use of B cell-depleting agents. The cohort comprised patients with inflammatory joint diseases, vasculitis and connective tissue diseases, including a relatively large number of systemic sclerosis patients (our centre is a tertiary referral centre for systemic sclerosis). Moreover, the assessment of the IRD activity and the evaluation of the adverse events were performed by the treating rheumatologists of the recruited patients, who were all acquainted with the patient's disease course.

We acknowledge that so far there are no data demonstrating a correlation between neutralising Ab levels and vaccine efficacy, therefore, caution is advised when instructing the patients how to conduct following the vaccine. Though of interest, the evaluation of the cellular immune response to vaccination was beyond the scope of our study. Future studies are awaited to define the best marker of protection against COVID-19. We plan to continue to follow these patients to assess whether the Ab titres correlate with clinical outcomes. Our main aim was to assess whether IRD patients, on immunomodulatory treatment, can mount a positive serologic response to mRNA vaccine against SARS CoV2 virus, therefore, we did not include a healthy control group. We complied with the current policy of vaccination that does not require Ab assessment before vaccination, previous infection was ruled out by history alone.

Our results can provide reassurance to patients with IRD treated with immunomodulatory agents and their physicians, regarding the immunogenicity and short-term safety of mRNA vaccine against SARS-CoV-2 virus. Considering the satisfactory humoral response despite the immunomodulatory treatments versus the increased risk for severe COVID-19 disease and the unknown vaccine efficacy and safety in patients with active IRD, we advise not to withhold immunomodulatory treatment around the vaccination. Further studies should assess whether lower Ab titres are associated with diminished protection against COVID-19-severe disease and whether the timing of anti-CD20 agents' administration influences the neutralising Ab titre.

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Contributors Study design: YB-M, AB-G. Sample collection: YB-M, DM, SG, KT, YT, KD, AB-G. Experiments and data analysis: YB-M, MK, MB, AB-G. Tables and figure: YB-M, MB. Data interpretation: YB-M, MK. Writing of the manuscript: YB-M, AB-G. Critical proofreading of the manuscript: all authors.

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Provenance and peer review Not commissioned; externally peer reviewed.

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CLINICAL SCIENCE

Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression

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ABSTRACT

Objective There is an urgent need to assess the impact of immunosuppressive therapies on the immunogenicity and efficacy of SARS-CoV-2 vaccination.

Methods Serological and T-cell ELISpot assays were used to assess the response to first-dose and second-dose SARS-CoV-2 vaccine (with either BNT162b2 mRNA or ChAdOx1 nCoV-19 vaccines) in 140 participants receiving immunosuppression for autoimmune rheumatic and glomerular diseases.

Results Following first-dose vaccine, 28.6% (34/119) of infection-naïve participants seroconverted and 26.0% (13/50) had detectable T-cell responses to SARS-CoV-2. Immune responses were augmented by second-dose vaccine, increasing seroconversion and T-cell response rates to 59.3% (54/91) and 82.6% (38/46), respectively. B-cell depletion at the time of vaccination was associated with failure to seroconvert, and tacrolimus therapy was associated with diminished T-cell responses. Reassuringly, only 8.7% of infection-naïve patients had neither antibody nor T-cell responses detected following second-dose vaccine. In patients with evidence of prior SARS-CoV-2 infection (19/140), all mounted high-titre antibody responses after first-dose vaccine, regardless of immunosuppressive therapy.

Conclusion SARS-CoV-2 vaccines are immunogenic in patients receiving immunosuppression, when assessed by a combination of serology and cell-based assays, although the response is impaired compared with healthy individuals. B-cell depletion following rituximab impairs serological responses, but T-cell responses are preserved in this group. We suggest that repeat vaccine doses for serological non-responders should be investigated as means to induce more robust immunological response.

Key messages

What is already known about this subject?

- There are very few data relating to the effect of immunosuppression on immune responses to SARS-CoV-2 vaccination, as patients receiving immunomodulatory therapies were excluded from all vaccine trials.

What does this study add?

- When assessed by both serological and T cell-based assays, most patients (89.3%) develop immune responses following two doses of vaccine, despite immunosuppressive therapies.
- B-cell depletion following rituximab treatment was significantly associated with failure to seroconvert, although most of these patients developed T-cell responses to SARS-CoV-2.
- Tacrolimus use was associated with impaired T-cell responses.

How might this impact on clinical practice or future developments?

- Assessment of both serological and T-cell responses may be necessary to fully define responses to vaccination in immunosuppressed populations.
- Administration of additional vaccine ('booster') doses may be a potential strategy for serological non-responders.

INTRODUCTION

There is an urgent need to understand the impact of immunosuppressive therapies on the efficacy of vaccines to SARS-CoV-2.[1 2] Patients with autoimmune diseases have been considered clinically vulnerable to SARS-CoV-2 infection since the onset of the COVID-19 pandemic,[3] and population-based and registry-based studies suggest that they experience significant rates of hospitalisation, severe disease and death during its global spread.[4–6]

Several vaccine candidates have been shown to prevent severe disease in the general population,[7–10] although all clinical trials to date excluded patients receiving immunosuppression, who are at risk of diminished vaccine responses. The degree to which the immune response is altered may vary with the specific immunomodulatory regimen and the vaccine used. Published data, for example, indicate impaired humoral responses to influenza and pneumococcal vaccination, especially in those undergoing treatment with rituximab.[11–14] However, existing data derived from experience with other vaccine types may not translate to the novel vaccines deployed for COVID-19.

Here, we describe the serological and T-cell responses to first-dose and second-dose vaccines (with either BNT162b2 mRNA or ChAdOx1 nCoV-19 replication-deficient adenoviral vector vaccines) in a cohort of patients with autoimmune glomerular and rheumatic diseases treated with rituximab or other non-biological

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immunosuppressive therapies, in order to describe the impact of these treatments on vaccine response in this patient population.

METHODS

Study participants

Baseline samples were collected from 161 patients with immune-mediated glomerulonephritis and vasculitis who received their first-dose of SARS-CoV-2 vaccination (BNT162b2 mRNA or ChAdOx1 nCoV-19) between 17 January 2o21 and 9 March 2021. For assessment of immunological responses after the first-dose vaccine, 140 patients provided a first follow-up sample at a median of day 28 (IQR 28–30 days) after first-dose administration; 53 of these also provided paired samples for assessment of SARS-CoV-2 T-cell responses. To date, 103 patients in the study have received second-dose vaccine at a median of 30 days (IQR 28–42) after first dose and have provided a subsequent sample for serological analysis at a median of 21 days (IQR 19–28 days) after second-dose administration; 49 also provided paired samples for analysis of T-cell responses.

A group of healthy volunteer (HV) healthcare workers (HCWs) were used as a comparator group for the study (n=70). In this group, assessment of first-dose response was undertaken at a median of 21 days (IQR 19–25 days) after first-dose administration and at a median of 27 days (IQR 21.5–28.0 days) after second-dose administration. This group received second-dose vaccine at a median of 66 days after first-dose (IQR 61–69 days). To control for some of the differences between the cohorts of immunosuppressed (IS) patients (IS group) and the HV group, matching for age and vaccine type was performed.

Separate cohorts of HCWs were used to identify a threshold for positivity on the ELISpot assay in participants who were infection-naïve and unvaccinated (n=30).[15]

Serological testing

Serum was tested for antibodies to nucleocapsid protein (anti-NP) using the Abbott Architect SARS-CoV-2 IgG two-step chemiluminescent immunoassay (CMIA) according to the manufacturer's instructions. This is a non-quantitative assay and samples were interpreted as positive or negative with a threshold index value of 1.4. Spike (S) protein antibodies (anti-S IgG) were detected using the Abbott Architect SARS-CoV-2 IgG Quant II CMIA. Anti-S antibody titres are quantitative with a threshold value for positivity of 7.1 binding antibody units (BAU)/mL.

T-cell ELISpot

SARS-CoV-2-specific T-cell responses were detected using the T-SPOT Discovery SARS-CoV-2 (Oxford Immunotec) according to the manufacturer's instructions. In brief, peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples with the addition of T-Cell Select (Oxford Immunotec) where indicated. A total of 250 000 PBMCs were plated into individual wells of a T-SPOT Discovery SARS-CoV-2 plate. The assay measures immune responses to five different SARS-CoV-2 structural peptide pools: S1 protein, S2 protein, NP protein, M protein (membrane), a mixed panel and positive (phytohaem-agglutinin) and negative controls. Cells were incubated and interferon-γ secreting T cells were detected. Spot-forming units (SFUs) were detected using an automated plate reader (Auto-immun Diagnostika). Infection-naïve, unvaccinated participants were used to identify a threshold for a positive response using mean+3 SD SFU/10^6 PBMC for S peptide pools. This resulted in a cut-off for positivity of 40 SFU/10^6 PBMC for S protein responses.[15]

Statistical analysis

Statistical analysis was conducted using Prism V.9.0 (GraphPad Software, San Diego, California, USA). Unless otherwise stated, all data are reported as median with IQR. Where appropriate, Mann-Whitney U and Kruskal-Wallis tests were used to assess the difference between 2 or >2 groups, with Dunn's post hoc test to compare individual groups. For paired analysis, Wilcoxon test was used. Multivariate analysis was carried out using multiple logistic regression using variables which were found to be significant on univariate analysis.

Patient involvement

The initial study proposal was supported and funded by the West London Kidney Patient Association. Patients were not directly involved in the experimental design or in performing the study.

RESULTS

Sample collection and baseline data

A total of 140 IS patients provided samples at baseline and at 28-40 days after first vaccine dose; 103 patients provided a further sample 18–29 days after second-dose vaccine (administered at a median of 32 and 30 days after first dose for ChAdOx1 and BNT162b2, respectively). Clinical characteristics and immunosuppressive treatments are summarised in online supplemental table S1. One hundred and fourteen patients (81.4%) previously received rituximab, of whom 56.1% (64/114) were treated within the last 6 months, and 60.5% (69/114) were B-cell deplete (circulating CD19 <10 cells/µL) at the time of vaccination. All 69 patients who were B-cell deplete had received treatment with rituximab, 69.6% (48/69) within the last 6 months. Nineteen patients (13.6%) had evidence of previous SARS-CoV-2 infection on baseline testing—in keeping with the low prevalence of disease previously described in our cohort[16]—and these were analysed separately from those who were infection-naive. Two further patients developed anti-NP IgG after vaccination, indicating SARS-CoV-2 infection at or since vaccination and were excluded from analysis.

Immunological response to first-dose vaccine in infection-naïve patients

One hundred and nineteen infection-naïve patients were included in the analysis of response to first-dose vaccine. At 28–40 days, 28.6% (34/119) had detectable anti-S IgG (figure 1A; median 0.61 BAU/mL (IQR 0.03–9.8)). By univariate analysis, ChAdOx1 vaccine, prior cyclophosphamide treatment, prior rituximab treatment,and current B-cell depletion were all associated with a decreased likelihood of seroconversion (figure 1B,C). In the group of patients who had received rituximab, treatment within the last 6 months was associated with decreased rates of seroconversion (table 1), and the median anti-S titre was significantly lower in this group (0.12 and 1.1 BAU/mL in those treated <6 and >6 months, respectively, p=0.01). By multivariate analysis, B-cell depletion at the time of vaccination was associated with non-seroconversion (figure 1B; OR 0.3, p=0.03).

The rate and magnitude of serological responses in the IS group were significantly lower than those in an HV group (online supplemental table S2) at a similar time point after first-dose vaccine (figure 1D; 97.1% (68/70) seroconversion in the HV group, median anti-S titre 90 BAU/mL (IQR 40.7–199.8), p<0.0001 compared with IS cohort). In the IS cohort, we did not identify any correlation between serological

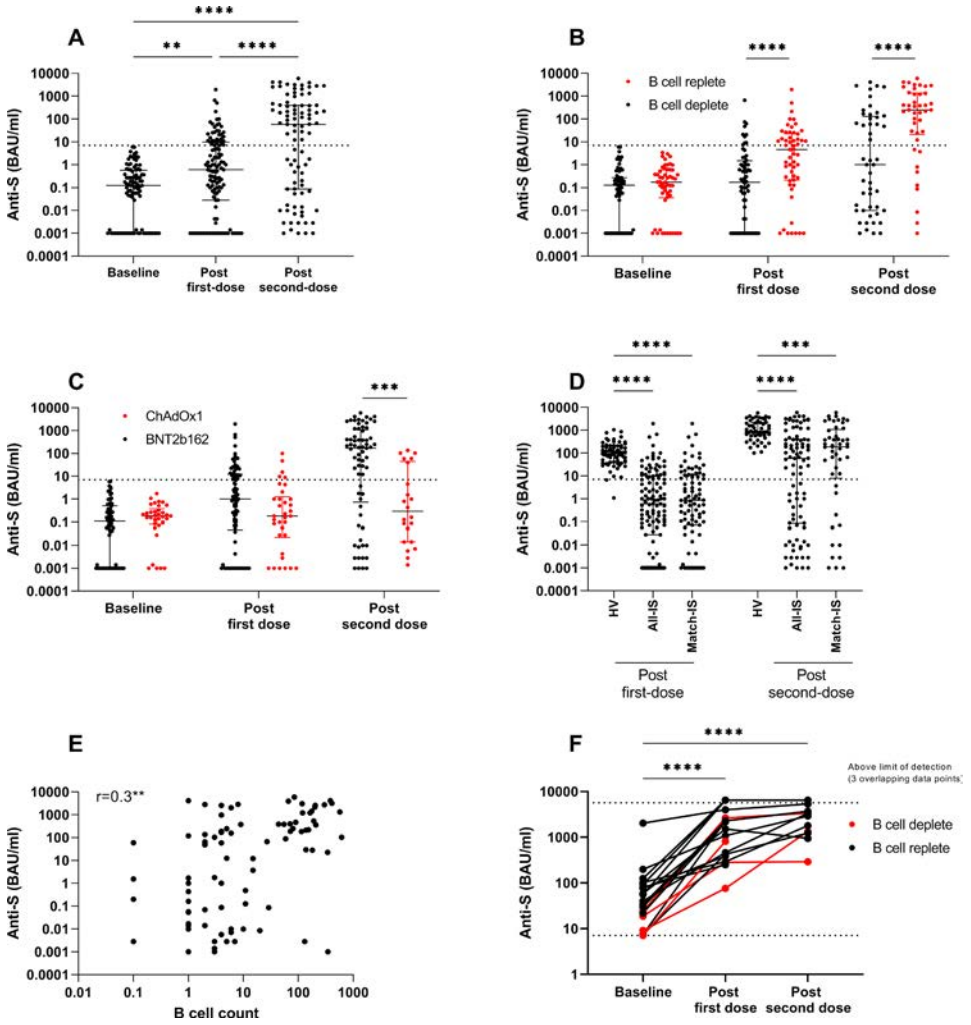

Figure 1 Humoral responses to SARS-CoV-2 vaccination in IS patients. (A) Anti-S titre at baseline, following first-dose and second-dose vaccine in patients who were infection-naïve. (B) Anti-S titre by B-cell status at the time of vaccination in infection-naïve patients at baseline, 28–40 days following first-dose vaccine and 18–29 days after second-dose vaccine. (C) Anti-S titre by vaccine type at the time of vaccination in infection-naïve patients at baseline, 28–40 days following first-dose vaccine and 18–29 days after second-dose vaccine. (D) Anti-S titre following first-dose and second-dose vaccinations in healthy volunteers (HVs), IS patients and a matched cohort of IS patients. (E) Correlation of anti-S titre after second-dose vaccination and B-cell count at the time of vaccination in IS patients. (F) Anti-S titre in patients with previous natural infection at baseline, following first-dose and second-dose vaccines. Dotted line indicates 7.1 BAU/mL, the threshold for detectable anti-S antibodies. For visualisation of data on a log scale, values=0 are represented by 0.001, which is below the lower limit of the assay (0.00142). HV, healthy volunteer; IS, immunosuppressed; S, spike. **p<0.01, ***p<0.001, ****p<0.0001.

response to first-dose vaccine and age, although we and others have reported this in healthy individuals.[15 17] The group of HVs included in this study is significantly younger than the IS group (online supplemental table S2; median age 41.4 and 53.7 years for HV and IS groups, respectively; p<0.0001). However, when an age-matched cohort of IS patients (median age 46.2 years) is used for comparison, serological responses were not significantly different from the whole IS cohort and remained lower than those in HV (figure 1D; median 0.85 BAU/mL (IQR 0.07–10.9), p<0.0001 compared with HV). This suggests that the overall younger age of our HV cohort does not fully account for the significant difference in serological response.

T-cell responses were assessed in 50/119 infection-naïve patients following first-dose vaccine. Only 26.0% (13/50) had detectable T-cell responses (>40 SFU/10^6 PBMC) (figure 2A and table 2). Patients receiving tacrolimus were less likely to have T-cell responses above the threshold for positivity: 0% (0/13) and 29.7% (11/37) of patients in T-cell responder and non-responder groups, respectively, were receiving tacrolimus (p=0.05) (figure 2B; median 6 and 16 SFU/10^6 PBMC in those receiving tacrolimus vs those who were not, p=0.003). Patients receiving ChAdOx1 were more likely to mount T-cell responses following first-dose vaccine: 69.2% (9/13) and 35.1% (13/37) of T-cell responders and non-responders, respectively, received ChAdOx1 vaccine (p=0.05) (figure 2C; median SFU/10^6 PBMC 8 and 29 for BNT162b2 and ChAdOx1, p=0.0007). Similar to serological responses after first-dose vaccine, T-cell responses were poorer in the IS group compared with HV (figure 2D; 61.1% (41/67) of HV had detectable responses, median 15 and 52 SFU/10^6 PBMC for IS and HV, respectively; p<0.0001).

In patients for whom both serological and T-cell assessments were available, 64.0% (32/50) did not have a demonstrable response to first-dose vaccine by either measure (online supplemental table S3).

Table 1 Patient characteristics by serological status in those with no evidence of previous natural infection

			First dose (n=119)				Second dose (n=91)		
			Non-seroconversion	Seroconversion			Non-seroconversion	Seroconversion	
Characteristics		n	n=85 (71.4%)	n=34 (28.6%)	P value	n	n=37 (40.7%)	n=54 (59.3%)	P value
Gender	Male	62	44 (71.0)	18 (29.0)		49	20 (40.8)	29 (59.2)	
	Female	57	41 (71.9)	16 (28.1)		42	17 (40.5)	25 (59.5)	
Age	Years (IQR)		52.0 (39.9–63.9)	56.2 (36.1–60.7)			60.5 (43.8–69.5)	51.8 (37.3–60.2)	0.05
Ethnicity	White	62	44 (71.0)	18 (29.0)		50	22 (44.0)	28 (56.0)	
	Black	10	7 (70.0)	3 (30.0)		7	1 (14.8)	6 (85.2)	
	South Asian	34	24 (70.6))	10 (19.6)		27	12 (44.4)	15 (55.6)	
	Mixed-race	7	6 (85.7)	1 (14.3)		3	1 (33.3)	2 (66.7)	
	Other	6	4 (66.7)	2 (33.3)		4	1 (25.0)	3 (75.0)	
Diagnosis	AAV and anti-GBM disease	45	35 (77.8)	10 (22.2)		34	17 (50.0)	17 (50.0)	
	Podocytopathy*	28	18 (64.3)	10 (35.7)		25	12 (48.0)	13 (52.0)	
	Membranous GN	23	15 (65.2)	8 (34.8)		21	6 (28.6)	15 (71.4)	
	SLE	19	14 (73.7)	5 (26.3)		8	1 (12.5)	7 (87.5)	
	Other†	4	3 (75.0)	1 (25.0)		3	1 (33.3)	2 (66.7)	
Comorbidities	Diabetes	19	17 (89.5)	2 (10.5)		16	9 (56.3)	7 (43.7)	
	Asthma/COPD	25	17 (68.0)	8 (32.0)		14	4 (28.6)	10 (71.4)	
	Previous malignancy	6	4 (66.7)	2 (33.3)		4	3 (75.0)	1 (25.0)	
Immunotherapy	Previous rituximab	99	77 (77.8)	22 (22.2)	0.002	75	35 (46.7)	40 (53.3)	0.01
	Last 6 months	56	49 (87.5)	7 (12.5)	0.016	44	26 (59.1)	18 (40.9)	0.0007
	Tacrolimus	23	17 (73.9)	6 (26.0)		21	7 (33.3)	14 (67.7)	
	Azathioprine	13	6 (46.1)	7 (53.9)		8	3 (37.5)	5 (62.5)	
	MMF	7	5 (71.4)	2 (29.6)		13	6 (46.2)	7 (53.8)	
	Methotrexate	3	2 (66.7)	1 (33.3)		2	0	2 (100)	
	Prednisolone	52	40 (76.9)	12 (23.1)		36	14 (38.9)	22 (61.1)	
	≥10 mg	19	13 (68.4)	6 (31.6)		11	5 (45.5)	6 54.5)	
	Belimumab	4	3 (75.0)	1 (25.0)		1	0	1 (100)	
	No current IS	4	1 (25.0)	3 (75.0)		4	1 (25.0)	3 (75.0)	
	Previous CYP	58	47 (81.0)	11 (19.0)	0.03	41	18 (43.9)	23 66.1)	
Vaccine	AZ/ChAdOx1	34	29 (85.3)	5 (14.7)	0.04	22	16 (72.3)	6 (37.7)	0.0009
	Pfizer/ BNT162b2	85	56 (65.9)	29 (34.1)		69	21 (30.4)	48 (69.6)	
Clinical parameter	B-cell depletion	64	54 (63.5)	10 (29.4)	0.001	49	28 (57.1)	21 (42.9)	0.0006
	Hypogammaglobulinaemia	25	19 (76.0)	6 (34.0)		22	12 (54.5)	10 (45.5)	

Comparison between groups by χ^2 test.
*Podocytopathy included minimal change disease and focal segmental glomerulosclerosis.
†Other diagnoses included C3 glomerulopathy and IgG4-related disease.
AAV, ANCA-associated vasculitis; COPD, chronic obstructive pulmonary disease; CYP, cyclophosphamide; GBM, glomerular basement membrane; IS, immunosuppressed; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus.

Immunological response to second-dose vaccine in infection-naïve patients

Ninety-one patients were included in the analysis of response to second-dose vaccine. At 18–29 days after second-dose vaccine, the proportion of patients with detectable anti-S IgG increased to 59.4% (54/91, figure 1A). In contrast, all HV individuals had detectable anti-S IgG after second-dose vaccine. The median anti-S titre after second-dose vaccine was significantly lower in IS patients than in HV, whether analysed as the whole cohort, or as an age-matched and vaccine-matched subgroup (figure 1D; median 58.7 (IQR 0.8–437.2), median 189.3 (IQR 7.9–1090) and median 877 (IQR 575–2203) BAU/mL for IS total cohort, IS matched grou and HV, respectively; p<0.0001).

Within the IS group, in those who had already seroconverted following first-dose vaccine, anti-S titres increased significantly in all patients. In those who were seronegative after first dose, a further 42.4% (28/66) now had detectable anti-S IgG. In keeping with our findings after first-dose vaccine, ChAdOx1 vaccine, prior rituximab treatment and current B-cell depletion were associated with a decreased likelihood of seroconversion, as was increasing age (figure 1B,C, and table 1). There was moderate correlation between serological response to second-dose vaccine and peripheral B-cell count at the time of vaccination (figure 1E). In the group of patients treated with rituximab, administration within the last 6 months was significantly associated with failure to seroconvert; 40.9% (18/44) vs 71.0% (22/31) seroconversion in those treated <6 months and >6 months previously, respectively (p=0.02). By multivariate analysis, B-cell depletion at the time of vaccination (OR 0.32, p=0.04) was significantly associated with non-seroconversion.

T-cell responses were assessed in 46/91 patients following second-dose vaccine and were detected in 82.6% (38/46, figure 2A). There were no differences in the rate or magnitude of T-cell response between those who seroconverted (81.2% (18/22), median SFU/10^6 PBMC 123) and those who did not (83.3% (20/24), median SFU/10^6 PBMC 148) (figure 2E and table 2). The number of patients without detectable T-cell responses following second-dose was small (n=8), and age

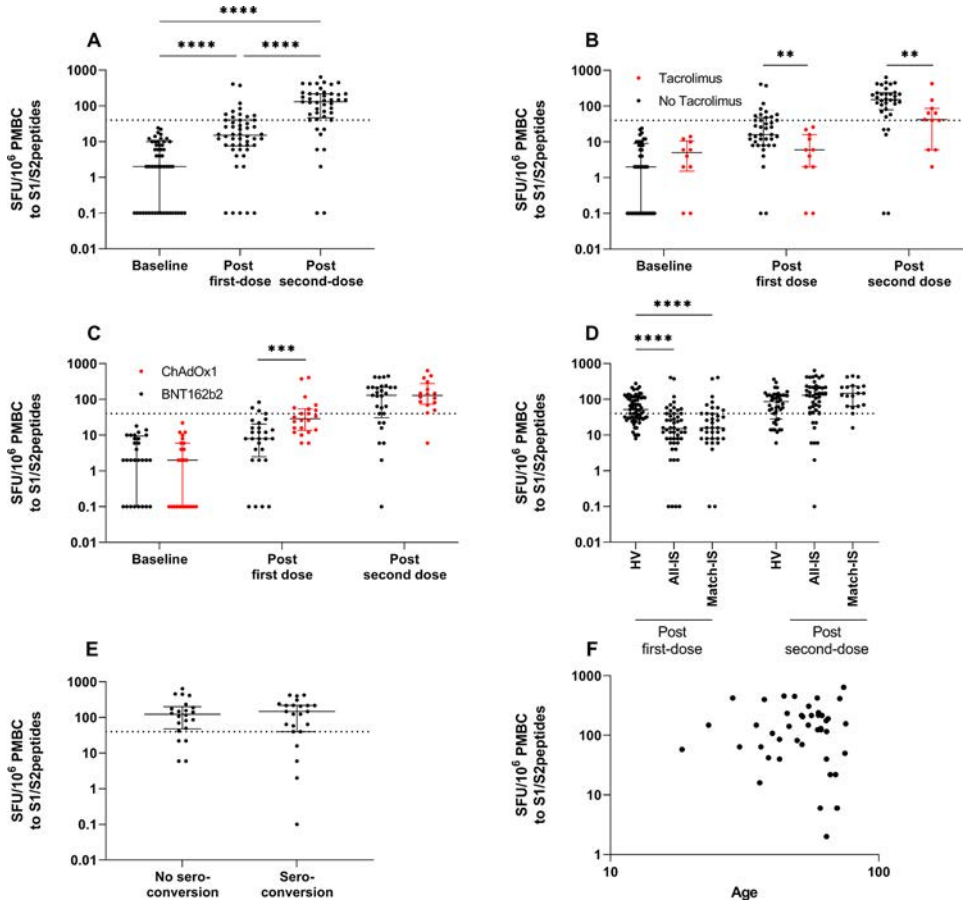

Figure 2 Cellular responses to SARS-CoV-2 vaccination in IS patients. (A) T-cell responses to spike protein peptides of SARS-CoV-2 in infection-naïve patients at baseline, 28–40 days following first-dose vaccine and 18–29 days after second-dose vaccine. (B) T-cell responses in those receiving tacrolimus therapy versus those who were not in infection-naïve participants at baseline, after first-dose vaccine and after second-dose vaccine. (C) T-cell responses by vaccine type in infection-naïve participants at baseline, after first-dose vaccine and after second-dose vaccine. (D) T-cell responses following first-dose and second-dose vaccinations in healthy volunteers (HVs), IS patients and a matched cohort of IS patients. (E) T-cell responses following second-dose vaccine in those who did and did not also seroconvert. (F) Correlation of T-cell responses after second-dose vaccination and age at time of vaccination. Dotted line indicates mean plus 3 SDs for spike peptide pool reactivity calculated from infection-naïve, non-vaccinated individuals (40 SFU/10^6 PBMC). For visualisation of data on a log scale, values=0 are represented by 0.1. HV, healthy volunteer; IS, immunosuppressed; PMBC, peripheral blood mononuclear cell; SFU, spot-forming unit.

was the only parameter significantly associated with absence of T-cell response to vaccination, although there was no correlation between age and magnitude of response (figure 2F and table 2; median age 51.9 and 61.5 years for those with T-cell responses above and below threshold, respectively; p=0.05). Although there was no significant difference in the proportion of patients with T-cell responses above threshold, the magnitude of response was significantly lower in patients treated with tacrolimus (figure 2B; median 53 and 152 SFU/10^6 PBMC for those treated with tacrolimus and not, p=0.01).

In infection-naïve patients for whom both serological and T-cell assessments were available, 47.8% (22/46) had negative serological responses after second-dose vaccine. Of these patients, 81.8% (18/22) had detectable T-cell responses. In patients who were B-cell deplete, an assessment of both serological and T-cell assessments were available in 30 patients, 60.0% (18/30) of whom had negative serological responses. In this B-cell deplete group with no serological response to vaccine, 83.3% (15/18) had detectable T-cell responses.

Comparing the HV and IS group, there was no significant difference in the proportion with T-cell responses to second-dose vaccine (figure 1D, 74.4% (32/43) of HV had T-cell responses above threshold) or in the magnitude of response (median 130 and 86 SFU/10^6 PBMC for IS and HV, respectively; p=not significant (ns)). Since second-dose vaccine samples in HV were limited to individuals who received BNT162b2; an analysis of age-matched and vaccine-matched IS patients was performed, and there were no significant differences in response (median 140 and 86 SFU/10^6 PBMC for matched IS and HV, respectively, p=ns; the numerical differences in T-cell number between these groups were not statistically significant and may reflect a degree of T cell enrichment in PMBC preparations from B-cell deplete IS patients).

In infection-naïve patients for whom both serological and T-cell assessments were available, the response rate (by one or both immunological parameters) increased significantly following each dose (36.0% (18/50) and 91.3% (42/46), respectively; p<0.0001). The four patients with no immunological response after second-dose were significantly older than those with a response by either measure; all four had received rituximab previously, although one was no longer B-cell deplete (online supplemental table S3).

Table 2 Patient characteristics by T-cell responses in those with no evidence of previous natural infection

		First dose (n=50)				Second dose (n=46)			
			No T-cell response	T-cell response	P		No T-cell response	T-cell response	
Characteristics		n	n=37 (74.0%)	n=13 (26.0%)	value	n	n=8 (17.4%)	n=38 (82.6%)	P value
Gender	Male	31	24 (77.4)	7 (22.5)		27	3 (11.1)	24 (88.9)	
	Female	19	13 (68.4)	6 (31.6)		19	5 (26.3)	14 (73.7)	
Age	Years (IQR)		54.9 (42.7–63.9)	49.4 (39.8–62.8)			65.1 (61.4–70.0)	51.9 (42.1–75.3)	0.02
Ethnicity	White	28	20 (71.4)	8 (28.6)		24	4 (16.7)	20 (83.3)	
	Black	1	1 (100)	0		2	0	2 (100)	
	South Asian	19	15 (78.9)	4 (21.1)		18	4 (22.2)	14 (77.8)	
	Mixed-race	2	1 (50.0)	1 (50.0)		1	0	1 (100)	
	Other	0	0	0		1	0	1 (100)	
Diagnosis	AAV and anti-GBM disease	24	14 (58.3)	10 (41.7)		19	4 (21.1)	15 (78.9)	
	Podocytopathy*	15	13 (86.7)	2 (13.3)		15	2 (13.3)	13 (86.7)	
	Membranous GN	10	9 (90.0)	1 (10.0)		9	2 (22.2)	7 (77.8)	
	SLE	0	0	0		2	0	2 (100)	
	Other†	1	1 (100)	0		1	0	1 (100)	
Comorbidities	Diabetes	10	7 (70.0)	3 (30.0)		8	3 (37.5)	5 (62.5)	
	Asthma/COPD	10	7 (70.0)	3 (30.0)		11	2 (18.2)	9 (81.8)	
	Previous malignancy	0	0	0		0	0	0	
Immunotherapy	Rituximab	44	31 (70.5)	13 (29.5)		41	7 (17.1)	34 (82.9)	
	Last 6 months	32	21 (65.6)	11 (34.4)		28	4 (14.3)	24 (85.7)	
	Tacrolimus	11	11 (100)	0	0.04	12	3 (25.0)	9 (75.0)	
	Azathioprine	4	2 (50.0)	2 (50.0)		3	0	3 (100)	
	MMF	5	3 (60.0)	2 (40.0)		4	1 (25.0)	3 (75.0)	
	Methotrexate	0	0	0		1	1 (100)	0	
	Prednisolone	17	14 (82.3)	3 (17.6)		14	2 (14.3)	12 (85.7)	
	≥10 mg	5	4 (80.0)	1 (20.0)		3	1 (33.3)	2 (66.7)	
	Belimumab	0	0	0		0	0	0	
	No IS	1	1 (100)	0		1	0	1 (100)	
	Previous CYP	25	15 (60.0)	10 (40.0)		20	3 (15.0)	17 (85.0)	
Vaccine	AZ/ChAdOx1	22	13 (59.1)	9 (40.9)	0.05	17	1 (5.9)	16 (94.1)	
	Pfizer/ BNT162b2	28	24 (85.7)	4 (14.3)		29	7 (24.1)	22 (75.9)	
Clinical parameter	B-cell depletion	33	22 (66.7)	11 (33.3)		30	5 (16.7)	25 (83.3)	
	Hypogammaglobulinaemia	13	10 (76.9)	3 (13.1)		9	3 (33.3)	6 (66.7)	

*Podocytopathy included minimal change disease and focal segmental glomerulosclerosis.
†Other diagnoses included C3 glomerulopathy and IgG4-related disease. Comparison between groups by χ^2 test.
AAV, ANCA-associated vasculitis; COPD, chronic obstructive pulmonary disease; CYP, cyclophosphamide; GBM, glomerular basement membrane; GN, glomerulonephritis; IS, immunosuppression; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus.

Immunological response to vaccination in patients with prior natural infection

In keeping with our previous report in healthy individuals,[15] the 19 participants with evidence of prior SARS-CoV-2 infection mounted robust serological responses to first-dose vaccination, including those who had previously received rituximab (n=13/19) or who were B-cell deplete (n=4/19, figure 1F). In 12 patients, serology was available following second-dose vaccine. Anti-S titre increased further following second-dose vaccine ('third' S protein challenge) in 8/12, remained above the limit of detection in 2/12, and declined or plateaued in only 2/12 (figure 1F). Due to the number of patients with responses above the threshold of detection of the assay, it was not possible to compare median anti-S titres following first-dose and second-dose vaccine in this group. T-cell responses were available for three patients in this cohort; all mounted robust cellular immunity to both first-dose and second-dose vaccines (60–616 and 300–580 SFU/10^6 PBMC after first and second doses, respectively).

DISCUSSION

The immune response to first-dose BNT162b2 mRNA or ChAdOx1 nCoV-19 vaccine was poor in patients receiving immunosuppression, with only 28.6% of patients having detectable humoral or T-cell responses. These rates compare poorly to a cohort of non-IS HVs. Reassuringly, immune responses were augmented by second-dose vaccine, increasing the seroconversion and T-cell response rates to 59.4% and 82.6%, respectively. Only 8.7% of patients had neither antibody nor T-cell responses following second-dose vaccine. These findings indicate that both vaccines are immunogenic in patients receiving immunosuppression, but that protocolised two-dose vaccination schedules are required. The augmented response to second-dose vaccine (and 'third' challenge in patients with prior natural infection) suggests that repeat boost strategies could be considered in this patient group, to induce more robust immune responses in the future.

B-cell depletion (following prior rituximab treatment) at the time of vaccination was the strongest predictor of failure to seroconvert, in keeping with data on impaired humoral responses to other

vaccines in patients treated with rituximab. These studies found that time since rituximab treatment was a determinant of serological response,[13 14] consistent with our finding of lower response rates in those who were currently B-cell deplete versus those who had repopulated peripheral B cells. Current guidelines differ regarding the timing of SARS-CoV-2 vaccination after rituximab.[18–20] While our data suggest that better serological responses may be achieved by delaying vaccination until B-cell reconstitution has occurred, it may not be ethical to do so when community transmission rates are high (or to defer rituximab treatment when needed for disease control). We therefore suggest that additional courses of vaccination should be made available to these patients between or after completed rituximab cycles.

While current vaccine efforts have focused on the induction of neutralising antibodies to SARS-CoV-2, T-cell immunity may also provide protection from infection. Experimental data suggest that CD8 + T-cell responses in particular may have a protective role in the presence of waning or subprotective antibody titres.[21] In addition, patients with agammaglobulinaemia have been described to recover from COVID-19 in the absence of a serological response, suggesting T-cell responses may be sufficient to mount protection or aid recovery from disease.[22–24] It is reassuring that vaccine-induced T-cell responses were detected in most of our study cohort, including those who were B-cell deplete at the time of vaccination, and those who failed to seroconvert. Tacrolimus use was associated with impaired T-cell response, and further studies are needed to investigate the impact of calcineurin inhibitors and other T cell-directed therapies on vaccine response in more detail.

The immune correlates of protection from disease, however, are not clearly defined. Published trials have not reported antibody measurements of participants who contracted COVID-19 following vaccination, and in vitro assessments of antibody neutralising activity have not been correlated with clinical outcomes. Robust CD8 and CD4 T-cell responses to BNT162b2/ChAdOx1 were reported in early-phase clinical studies,[25 26] although all participants also mounted neutralising antibody responses. Thus, further work is needed to determine whether the serological or T-cell response observed in our cohort will confer protection from clinical disease and whether the longevity of the immune response in this group is comparable to that in healthy individuals.

A limitation of our study is that only a small proportion of patients were treated with conventional synthetic disease-modifying antirheumatic drugs such as methotrexate or MMF, and some conditions such as systemic lupus erythematosus are under-represented. While we observed possible differences between vaccine types (with stronger serological responses in patients receiving BNT2b162 and better T-cell responses in those receiving ChAdOx1), our study is underpowered to determine if vaccine choice should be influenced by underlying disease or immunosuppressive treatment. Further studies in larger cohorts will be required to understand the impact of these factors and whether there are preferred vaccine types in these high-risk patient groups. In addition, the HV group in our study is not ideally matched to the IS cohort; individuals are younger, and an assessment of second-dose response was only available in participants receiving BNT162b2. The HV group also received second-dose vaccination after a longer time period than the IS cohort (67 and 30 days, respectively). We have undertaken limited matching based on age and vaccine type, but sufficiently detailed data for the HV cohort is not available to provide a more accurate comparator group.

Despite these limitations, our data confirm the immunogenicity of SARS-CoV-2 vaccination in an IS cohort, finding that B-cell depletion following rituximab impairs serological responses, but T-cell responses are preserved in this group. Reassuringly, our data confirm an immunological response in most patients, when assessed by a combination of serological and cell-based assays. Our findings support SARS-CoV-2 vaccination in this patient group; however, since the overall quality of response was impaired compared with healthy individuals, we suggest that repeat vaccine doses may be necessary to optimise the immunological response and to induce more robust serological responses in particular, for these vulnerable patients.

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CLINICAL SCIENCE

Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study

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ABSTRACT

Introduction Vaccination represents a cornerstone in mastering the COVID-19 pandemic. Data on immunogenicity and safety of messenger RNA (mRNA) vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) are limited.

Methods A multicentre observational study evaluated the immunogenicity and safety of the two-dose regimen BNT162b2 mRNA vaccine in adult patients with AIIRD (n=686) compared with the general population (n=121). Serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were measured 2–6 weeks after the second vaccine dose. Seropositivity was defined as IgG ≥15 binding antibody units (BAU)/mL. Vaccination efficacy, safety, and disease activity were assessed within 6 weeks after the second vaccine dose.

Results Following vaccination, the seropositivity rate and S1/S2 IgG levels were significantly lower among patients with AIIRD versus controls (86% (n=590) vs 100%, p<0.0001 and 132.9±91.7 vs 218.6±82.06 BAU/mL, p<0.0001, respectively). Risk factors for reduced immunogenicity included older age and treatment with glucocorticoids, rituximab, mycophenolate mofetil (MMF), and abatacept. Rituximab was the main cause of a seronegative response (39% seropositivity). There were no postvaccination symptomatic cases of COVID-19 among patients with AIIRD and one mild case in the control group. Major adverse events in patients with AIIRD included death (n=2) several weeks after the second vaccine dose, non-disseminated herpes zoster (n=6), uveitis (n=2), and pericarditis (n=1). Postvaccination disease activity remained stable in the majority of patients.

Conclusion mRNA BNTb262 vaccine was immunogenic in the majority of patients with AIIRD, with an acceptable safety profile. Treatment with glucocorticoids, rituximab, MMF, and abatacept was associated with a significantly reduced BNT162b2-induced immunogenicity.

Key messages

What is already known about this subject?

- Data on efficacy and safety of the SARS-CoV-2 BNT162b2 messenger RNA (mRNA) vaccine in patients with autoimmune inflammatory rheumatic diseases (AIIRD) are limited.

What does this study add?

- This is the largest observational prospective study conducted to confirm immunogenicity of the BNT162b2 mRNA vaccine in the majority of patients with AIIRD compared with controls.
- Immunogenicity was severely impaired by rituximab; moderately impaired by glucocorticoids, abatacept, and mycophenolate mofetil; and mildly impaired by methotrexate.
- The vaccine was generally safe in terms of adverse events.
- Postvaccination disease activity remained stable in the majority of patients with AIIRD.

How might this impact on clinical practice or future developments?

- Most disease-modifying antirheumatic drugs, including methotrexate, anticytokine biologics and Janus kinase inhibitors, can be continued with relation to the administration of the BNT162b2 mRNA vaccine.
- Postponing treatment with rituximab, when feasible, should be considered to improve immunogenicity. Holding treatment with mycophenolate mofetil and abatacept, especially when combined with methotrexate, may be considered on an individual basis.

INTRODUCTION

The prevention of COVID-19 pandemic has become of paramount importance. BNT162b2, a messenger RNA (mRNA)-based vaccine, has demonstrated a high efficacy rate with an acceptable safety profile.[1 2] A mass BNT162b2 vaccination campaign has been launched in Israel, with high uptake of vaccination in about 55.5% of the country's population. Patients with autoimmune inflammatory rheumatic diseases

Table 1 Demographic characteristics of patients with AIIRD and controls

	Age, median (range)	Female n (%)	Disease duration, years*	Influenza vaccine n (%)†
Controls, n=121	50 (18–90)†*	78 (65)	NA	89 (82.4)
AIIRD diagnosis, n				
All patients with AIIRD, n=686	59 (19–88)	475 (69.3)	10 (0–68)	542 (79.4)
RA, n=263	64 (20–88)	215 (81.75)	10 (0–50)	213 (82.88)
PsA, n=165	55 (20–86)	78 (47.56)	8 (0–68)	120 (74.07)
AxSpA, n=68	49.5 (21–83)	36 (52.94)	10 (1–51)	54 (80.6)
SLE, n=101	46 (22–80)	89 (88.12)	14 (0–44)	76 (77.55)
IIM, n=19	64 (34–76)	14 (73.68)	2 (1–21)	19 (100)
Vasculitis, n=70				
LVV, n=21	70 (26–85)	17 (80.95)	2.5 (0–12)	20 (95.24)
AAV, n=26	60.5 (26–85)	14 (53.85)	4 (0.75–28)	22 (84.62)
Other vasculitis, n=23	56 (19–77)	12 (52.17)	6 (0.5–35)	18 (78.26)

*Data on disease duration were available for 683 patients with AIIRD (they were missing for two patients with PsA and one patient with SLE).
†Data on influenza vaccination were available for 781 participants: 673 AIIRD and 108 controls.
‡p<0.0001.
AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AIIRD, autoimmune inflammatory rheumatic diseases; AxSpA, axial spondyloarthritis; IIM, idiopathic inflammatory myositis; LVV, large vessel vasculitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

(AIIRD) have been prioritised for urgent vaccination to mitigate COVID-19 risk, consistent with the American College of Rheumatology (ACR) guidelines,[3] despite a paucity of data on the efficacy and safety of mRNA COVID-19 vaccines in this population. Recently, some encouraging data on mRNA vaccination in immunosuppressed patients have emerged based on two small studies with a limited follow-up.[4–6] Therefore, we conducted a large prospective observational multicentre study to evaluate immunogenicity, efficacy, and safety of the BNT162b2 mRNA vaccine in patients with AIIRD compared with control subjects without rheumatic diseases or immunosuppressive therapies.

METHODS

This prospective observational exploratory multicentre study was conducted at the Rheumatology Departments of Tel Aviv Sourasky, Carmel, and Hadassah Medical Center, Israel, between December 2020 and March 2021.

End points of the study

The primary end point was immunogenicity of the BNT162b2 mRNA vaccine in adult patients with AIIRD compared with controls measured 2–6 weeks after the second vaccine dose.

Secondary end points included

1. Effect of immunosuppressive treatments on vaccine's immunogenicity.
2. Efficacy of vaccination, defined as prevention of COVID-19 disease, confirmed by a PCR testing.
3. Safety of vaccination in patients with AIIRD compared with controls.
4. Effect of vaccination on clinical disease activity in patients with AIIRD.

Study population

Consecutive adult patients (aged ≥18 years) were recruited into the study according to the following inclusion criteria: rheumatoid arthritis (RA)/ACR/European League Against Rheumatism (EULAR) 2010 classification criteria[7]; psoriatic arthritis (PsA)/Classification Criteria for PsA[8]; axial spondyloarthritis (axSpA)/Assessment of SpondyloArthritis International Society classification criteria[9]; systemic lupus erythematosus (SLE)/1997 ACR[10] or 2012 Systemic Lupus Erythematosus International Collaborating Clinics criteria[11]; systemic vasculitis: large vessel vasculitis (LVV), antineutrophil cytoplasmic antibody-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA/Chapel Hill Consensus Conference definitions[12]; central nervous system (CNS) vasculitis, including primary CNS vasculitis, neuro-Behcet and Susac syndrome; and idiopathic inflammatory myositis (IIM)/EULAR/ACR classification criteria.[13]

Table 2 Treatments used in patients with AIIRD

	Immunosuppressive treatments, n (%)								
AIIRD diagnosis, n	**GC**	**MTX**	**TNFi**	**IL6i**	**Anti-CD20**	**ABA**	**JAKi**	**IL17i**	**MMF**
All AIIRD, n=686	130 (18.95)	176 (25.66)	172 (25.07)	37 (5.39)	87 (12.68)	16 (2.33)	49 (6.9)	48 (7)	28 (4.08)
RA, n=263	55 (20.91)	116 (44.11)	47 (17.87)	29 (11.03)	43 (16.35)	15 (5.7)	46 (16.9)	0	0
PsA, n=165	3 (1.82)	36 (21.82)	74 (44.85)	0	0	1 (0.61)	2 (1.2)	40 (24.24)	0
AxSpA, n=68	1 (1.47)	9 (13.24)	48 (70.59)	0	1 (1.47)*	0	0	8 (11.76)	2 (2.94)
SLE, n=101	22 (21.78)	8 (7.92)	0	0	7 (6.93)	0	0	0	17 (16.83)
IIM, n=19	15 (78.95)	2 (10.53)	0	0	13 (68.42)	0	0	0	6 (31.58)
LVV, n=21	11 (52.38)	2 (9.52)	1 (4.76)	8 (38.1)	0	0	0	0	0
AAV, n=26	12 (46.15)	2 (7.69)	0	0	18 (69.23)	0	0	0	0
Other vasculitis, n=23	11 (47.83)	1 (4.35)	2 (8.7)	0	5 (21.74)	0	0	0	3 (13.04)

*This patient had multiple sclerosis and was treated with ocrelizumab.
AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ABA, abatacept; AIIRD, autoimmune inflammatory rheumatic diseases; anti-CD20, CD-20 inhibitors; AxSpA, axial spondyloarthritis; GC, glucocorticoids; IIM, idiopathic inflammatory myositis; IL6i, interleukin 6 inhibitors; IL17i, interleukin 17 inhibitors; JAKi, Janus kinase inhibitors; LVV, large vessel vasculitis; MMF, mycophenolate mofetil; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNFi, tumour necrosis factor inhibitors.

Table 3 Immunogenicity of the BNT162b2 messenger RNA vaccine in patients with AIIRD and controls

Study participants, n	Seropositivity rate, n (% of total)	Serum anti-S1/S2 IgG titre, mean±SD, BAU/mL
Controls, n=121	121 (100)	218.6±82.06
Patients with AIIRD, n=686	590 (86.0)*	132.9±91.7*
RA, n=263	216 (82.1)	108.7±84.7
PsA, n=165	160 (96.9)	162.0±71.7
AxSpA, n=68	67 (98.5)	173.1±90.1
SLE, n=101	93 (92.1)	161.9±105.2
IIM, n=19	7 (36.8)	42.9±62.6
LVV, n=21	20 (95.2)	143.3±84.6
AAV, n=26	8 (30.8)	40.3±73.2
Other vasculitis, n=23	19 (86.6)	122.7±87.9

*p<0.0001.
AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AIIRD, autoimmune inflammatory rheumatic diseases; AxSpA, axial spondyloarthritis; BAU, binding antibody units; IIM, idiopathic inflammatory myositis; LVV, large vessel vasculitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Patients were instructed to continue all medications during the vaccination period, except for rituximab treatment that was delayed after the vaccination in certain cases on a physician's discretion.

The control group included a sample of the general population, consisting mainly of healthcare personnel. Exclusion criteria for all groups were pregnancy, history of past vaccination allergy, and previous COVID-19 infection and for controls—history of AIIRD and immunosuppressive treatment.

Vaccination procedure

All study participants were administered the two-dose regimen BNT162b2 mRNA vaccine (Pfizer-BioNTech), 30 µg per dose, by intramuscular injection in the deltoid muscle 3 weeks apart, as indicated by the national guidelines.

Immunogenicity of the vaccine

The vaccine immunogenicity was evaluated by measuring the serum IgG neutralising antibody levels against SARS-CoV-2 trimeric spike S1/S2 glycoproteins, using the LIAISON (DiaSorin) quantitative assay, performed 2–6 weeks after the second vaccine dose. This Food and Drug Administration-authorised assay has a clinical sensitivity and specificity above 98%.[14] A value above 15 binding antibody units (BAU) was considered as positive, according to the manufacturer's instruction.

Efficacy of the vaccine

The participants were questioned whether they contracted COVID-19 infection, confirmed by PCR, following each vaccine dose. In addition, up to the data cut-off, the patient files were reviewed for evidence of COVID-19 infection.

Safety of the vaccine

The participants were contacted by phone within 2 weeks after the first vaccine dose and within 2–6 weeks after the second vaccine dose to complete a questionnaire regarding adverse events.

Clinical assessment of AIIRD

Medical history and the use of medications were recorded. Data regarding disease activity before vaccination were retrieved from patients' medical records, within up to 3 months before vaccination. Postvaccination disease activity was assessed by an in-person clinical examination within 2–6 weeks after the second vaccine dose. The following disease activity indices were included: Clinical Disease Activity Index, Simplified Disease Activity Index, DAS-28-CRP for RA, Disease Activity in Psoriatic Arthritis, Leeds Enthesitis and Dactylitis Index, Psoriasis Area Severity Index for PsA, Bath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity Score for axSpA, Systemic Lupus Disease Activity Index for SLE, and patients' and physician's global assessment, using a visual analogue scale of 0–10 mm, for vasculitis and inflammatory myositis.

Patient and public involvement

The research question and outcome measures of this study were developed in collaboration with the representatives of patients with AIIRD based on a shared priority to investigate the efficacy and safety of the novel mRNA BNT162b2 vaccine. Patients with AIIRD under the care of the medical centres conducting the trial were actively informed regarding the study and offered to participate. In view of the ongoing COVID-19 pandemic and related

Table 4 Immunogenicity of the BNT162b2 messenger RNA vaccine according to the use of immunosuppressive treatments in comparison with controls

Immunosuppressive treatments, n	Seropositivity rate, n (%)	P value
GC, n=130	86 (66)	**<0.0001**
GC monotherapy, n=13	10 (77)	**<0.0001**
MTX, n=176	148 (84)	**<0.0001**
MTX monotherapy, n=41	38 (92)	**0.02**
HCQ, n=133	120 (90)	**0.001**
HCQ monotherapy, n=50	49 (98)	0.65
LEF, n=28	25 (89)	**0.004**
LEF monotherapy, n=11	11 (100)	NA
TNFi, n=172	167 (97)	0.15
TNFi monotherapy, n=121	119 (98)	0.48
TNFi +MTX, n=29	27 (93)	**0.04**
IL6i, n=37	37 (100)	NA
IL6i monotherapy, n=19	19 (100)	NA
IL6i+MTX, n=7	7 (100)	NA
Anti-CD20, n=87	36 (41)	**<0.0001**
Anti-CD20 monotherapy, n=28	11 (39)	**<0.0001**
Rituximab+MTX, n=14	5 (36)	**<0.0001**
IL17i, n=48	47 (98)	0.63
IL17i monotherapy, n=37	37 (100)	NA
IL17i+MTX, n=7	6 (85)	0.05
Abatacept, n=16	10 (62)	**<0.0001**
Abatacept monotherapy, n=7	5 (71)	**<0.0001**
Abatacept+MTX, n=5	2 (40)	**<0.0001**
JAKi monotherapy, n=21	19 (90)	**0.02**
JAK+MTX, n=24	22 (92)	**0.03**
Belimumab, n=9	7 (77)	**0.0001**
MMF, n=28	18 (64)	**<0.0001**

anti-CD20, CD20 inhibitors; GC, glucocorticoids; HCQ, hydroxychloroquine; IL6i, interleukin 6 inhibitors; IL17i, interleukin 17 inhibitors; JAKi, Janus kinase inhibitors; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; TNFi, tumour necrosis factor inhibitors.

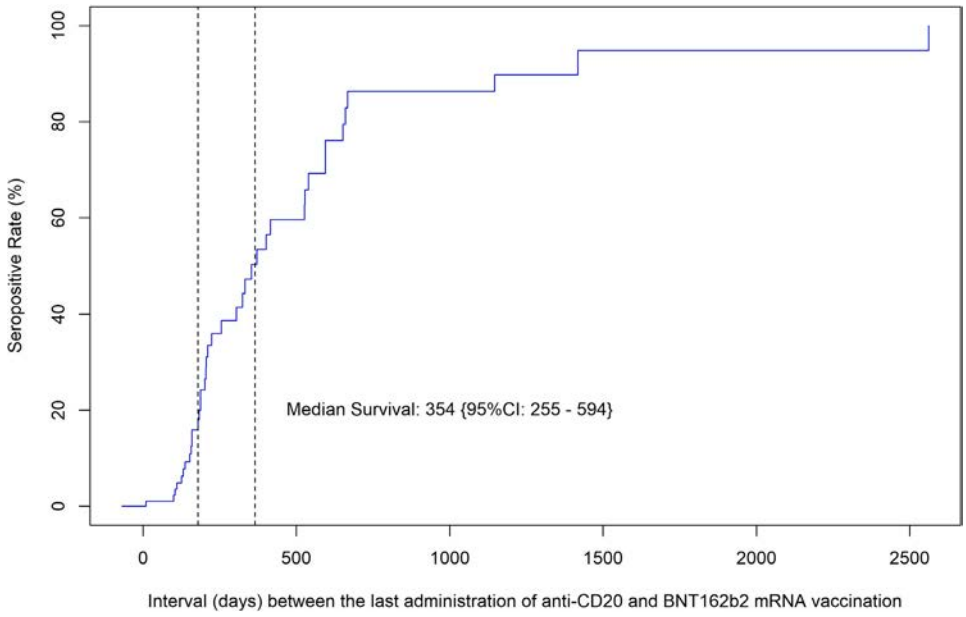

Figure 1 Cumulative seropositive rate according to the interval (days) between the last course of rituximab administration and BNT1622b vaccination. mRNA, messenger RNA.

stringent restrictions, patients were not involved in the conduct of the study. The main study results will be disseminated to the participants, and we will seek patient and public involvement in the development of an appropriate method of dissemination.

Statistical analysis

Differences between continues variables were tested for significance using the independent-samples t-test. Differences between categorical variables were tested for significance using the χ^2 test or Fisher's exact test (as appropriate). Multivariate models (linear and logistic) were adjusted for age, diagnosis, treatment with methotrexate and anti-CD20. All tests applied were two-tailed. The widths of the intervals have not been adjusted for multiplicity, and the inferences drawn from inferences may not be reproducible. Missing data were assumed as missing at random. No imputations were done. The data were analysed using R V.4.0.5 (R Development Core Team, Vienna, Austria).

RESULTS

Study population

A total of 710 patients with AIIRD and 124 controls vaccinated with the two-dose regimen BNT162b2 mRNA vaccine were enrolled in the study. The final analysis included 686 patients with AIIRD and 121 controls due to missing serology tests (table 1; online supplemental figure S1). RA was the most common disease (n=263), followed by PsA (n=165), SLE (n=101), systemic vasculitis (n=70), axSpA (n=68) and IIM (n=19). Patients with AIIRD included a subgroup of elderly patients aged ≥65 years (32.8%, n=225) and were significantly older than controls, mean age±SD 56.76±14.88 vs 50.76±14.68, respectively; p<0.0001.

A total of 95.2% (n=653) of patients with AIIRD were treated with immunomodulatory medications (table 2). Glucocorticoids (GC) were used in 18.95% (n=130), at a mean prednisone dose of 6.7±6.25 mg/day. Conventional synthetic disease-modifying antirheumatic drug (csDMARD) monotherapy was used in 23.18% (n=159). Biologic DMARDs were used as a monotherapy or in combination with csDMARDs in 38.19% (n=262) and 13.56% (n=93), respectively. Janus kinase inhibitors (JAKi) were used as a monotherapy or in combination with csDMARDs in 3.06% (n=21) and 3.79% (n=26), respectively. Eighty-seven (12.68%) patients were treated with CD20-depleting (anti-CD20) therapies, of whom 86 received rituximab at a mean dose of 1656.1±623.6 mg. The mean interval between the last dose of rituximab and BNT162b2 vaccination was 51±83 days. One patient received ocrelizumab. During the study period, changes in immunomodulatory drugs after the first vaccine dose were reported in 3% (n=20) of patients and after the second vaccine dose in 4.04% (n=27).

Immunogenicity of the BNT162b2 vaccine

The seropositivity rate was 86% (n=590) in patients with AIIRD compared with 100% in controls (p<0.0001). The level of the S1/S2 antibodies was significantly reduced in patients with AIIRD compared with controls (mean±SD, 132.9±91.7 vs 218.6±82.06; p<0.0001). In patients with PsA, axSpA, SLE and LVV, the seropositive rate was above 90%. In patients with RA, the seropositive rate was 82.1%, whereas the lowest seropositive rate (<40%) was observed in patients with AAV and IIM (table 3).

Effect of immunosuppressive treatments on the immunogenicity of the BNT162b2 vaccine

More than 97% of patients treated with anticytokine therapies, including tumour necrosis factor inhibitors (TNFi), interleukin 17 inhibitors (IL-17i) and interleukin 6 inhibitors (IL-6i), had an appropriate immunogenic response when used as monotherapy (table 4). Anti-CD20 significantly impaired vaccine's immunogenicity, with the lowest seropositivity rate of 39%. The time interval between the prevaccination administration of rituximab and the BNT162b2 vaccination had a significant impact on the vaccine's immunogenicity, as shown in figure 1. The seropositivity rate in patients vaccinated within 6 months after rituximab treatment was below 20% but increased to about 50% in patients vaccinated 1 year after rituximab treatment. Similarly, the use of

Table 5 Unadjusted and adjusted logistic regression models examining the factors associated with seropositivity

	Seropositivity rate, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P value
Age >65 years, n=246	195 (79.27)	0.33 (0.22 to 0.52)	0.43 (0.25 to 0.75)	**0.002**
AIIRD diagnosis				
PsA, n=165	160 (96.97)	Reference	Reference	
RA, n=263	216 (82.13)	0.14 (0.06 to 0.37)	0.31 (0.11 to 0.82)	**0.02**
AxSpA, n=68	67 (98.53)	2.09 (0.24 to 18.26)	2.01 (0.23 to 17.72)	0.52
SLE, n=101	93 (92.08)	0.36 (0.12 to 1.14)	0.35 (0.11 to 1.16)	0.08
IIM, n=19	7 (36.84)	0.02 (0.01 to 0.07)	0.06 (0.02 to 0.27)	**<0.001**
LVV, n=21	20 (95.24)	0.63 (0.07 to 5.63)	0.82 (0.09 to 7.54)	0.86
AAV, n=26	8 (30.77)	0.01 (0.004 to 0.05)	0.04 (0.01 to 0.17)	**<0.001**
Other vasculitis, n=23	19 (82.61)	0.15 (0.04 to 0.6)	0.26 (0.06 to 1.22)	0.09
AIIRD treatments				
Anti-CD20, n=87	36 (41.38)	0.05 (0.03 to 0.08)	0.13 (0.07 to 0.24)	**<0.001**
Anti-CD20 monotherapy, n=28	11 (39.29)	0.07 (0.03 to 0.16)	0.92 (0.33 to 2.57)	0.87
Anti-CD20 +MTX, n=14	5 (35.71)	0.07 (0.02 to 0.21)	0.94 (0.23 to 3.89)	0.93
MTX, n=176	148 (84.09)	0.64 (0.4 to 1.03)	0.58 (0.31 to 1.07)	0.08
MTX monotherapy, n=41	38 (92.68)	1.75 (0.53 to 5.79)	1.84 (0.5 to 6.74)	0.36
GC, n=130	86 (66.15%)	0.16 (0.1 to 0.29)	0.48 (0.26 to 0.87)	**0.02**
TNFi, n=172	167 (97.09)	5.6 (2.24 to 14.0)	1.89 (0.68 to 5.24)	0.22
TNFi monotherapy, n=121	119 (98.35)	9.46 (2.3 to 38.87)	2.58 (0.56 to 11.94)	0.22
TNFi +MTX, n=29	27 (93.1)	1.86 (0.44 to 7.94)	1.46 (0.31 to 6.91)	0.63
IL6i, n=37	37 (100)	NA	NA	NA
IL6i monotherapy, n=19	19 (100)	NA	NA	NA
IL6i+MTX, n=7	7 (100)	NA	NA	NA
IL17i, n=48	47 (97.92)	6.73 (0.92 to 49.32)	1.42 (0.16 to 12.83)	0.75
IL17 monotherapy, n=37	37 (100)	NA	NA	NA
IL17 +MTX, n=7	6 (85.71)	0.81 (0.1 to 6.8)	0.25 (0.02 to 2.7)	0.25
Abatacept, n=16	10 (62.5)	0.21 (0.08 to 0.6)	0.14 (0.04 to 0.43)	**<0.001**
Abatacept monotherapy, n=7	5 (71.43)	0.33 (0.06 to 1.74)	0.2 (0.033 to 1.16)	0.073
Abatacept+MTX, n=5	2 (40)	0.09 (0.01 to 0.53)	0.07 (0.01 to 0.48)	**0.007**
JAKi monotherapy, n=21	19 (90.48)	1.29 (0.3 to 5.63)	0.72 (0.15 to 3.48)	0.68
JAKi+MTX, n=24	22 (91.67)	1.5 (0.35 to 6.48)	1.78 (0.38 to 8.35)	0.46
MMF, n=28	18 (64.29)	0.22 (0.1 to 0.5)	0.1 (0.03 to 0.34)	**0.0013**
MMF monotherapy, n=5	3 (60)	0.2 (0.03 to 1.21)	0.11 (0.02 to 0.83)	**0.03**

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AIIRD, autoimmune inflammatory rheumatic diseases; anti-CD20, CD20 inhibitors; AxSpA, axial spondyloarthritis; GC, glucocorticoids; IIM, idiopathic inflammatory myositis; IL6i, interleukin 6 inhibitors; IL17i, interleukin 17 inhibitors; JAKi, Janus kinase inhibitors; LVV, large vessel vasculitis; MMF, mycophenolate mofetil; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNFi, tumour necrosis factor inhibitors.

GC, MMF, and abatacept was significantly associated with a lack of humoral response. Seropositivity rate in patients treated with MTX monotherapy and in combination with other treatments was significantly reduced (92% and 84%, respectively), although at a lesser magnitude than with anti-CD20, MMF, and abatacept treatments. The combination of TNFi with MTX reduced the rate of seropositivity to 93% (p=0.04).

In the univariate logistic regression model (table 5), age >65 years,diagnosis of RA, IIM, and AAV and treatment with GC, MMF, and anti-CD20, and abatacept were associated with a lack of humoral response to vaccination. Multivariate regression analysis (using PsA, the largest subgroup with the highest seropositivity, as a reference) accounting for age, AIIRD diagnosis, and treatment with MTX and anti-CD20 confirmed these associations (table 5). The impact of GC, MMF, anti-CD20 and abatacept on immunogenicity was independent from the concomitant use of other DMARDs (data not shown).

Efficacy of the BNT162b2 vaccine

There were no COVID-19 symptomatic disease among AIIRD patients during the study follow-up, whereas one subject in the control group was diagnosed with mild COVID-19 after the second vaccine dose.

Safety of the BNT162b2 vaccine

The prevalence of mild adverse events was similar in patients with AIIRD and controls. There were no serious or major adverse events in the control group. Two patients with AIIRD died after the second vaccine dose. The first patient had a history of AAV, in remission and without any immunosuppressive therapy for 3 years before the vaccination, apart from a low-dose prednisone. Three weeks after the second vaccine dose, she developed fulminant haemorrhagic cutaneous vasculitis with subsequent fatal sepsis. The second patient suffered from PsA which was in remission under treatment with secukinumab and had multiple comorbidities, including diabetes mellitus and ischaemic heart disease. He

Table 6 Adverse events of the BNT162b2 vaccine in patients with AIIRD and controls

	After the first vaccine dose		After the second vaccine dose	
Adverse event	**Controls n=121**	**AIIRD n=673**	**Controls n=121**	**AIIRD n=670**
Local reactions, n (%)				
Pain	69 (57.02)	377 (56.02)	51 (42.5)	314 (46.87)
Erythema	4 (3.31)	12 (1.78)	6 (5)	10 (1.49)*
Swelling	6 (4.69)	18 (2.68)	6 (5)	15 (2.24)
Pruritus	3 (2.48)	8 (1.19)	2 (1.67)	4 (0.6)
Tingling	7 (5.79)	3 (0.45)**	1 (0.83)	0
Systemic reactions, n (%)				
Fever ≥38.0°C	1 (0.83)	8 (1.19)	6 (4.96)	35 (5.24)
Nausea	0	7 (1.04)	2 (1.67)	14 (2.09)
Vomiting	1 (0.83)	3 (0.45)	0	1 (0.15)
Rhinorrhea	3 (2.48)	0 *	0	1 (0.15)
Cough	1 (0.83)	2 (0.3)	0	1 (0.15)
Myalgia	5 (4.13)	25 (3.71)	21 (17.36)	63 (9.4)*
Arthralgia	1 (0.83)	23 (3.42)	6 (4.96)	49 (7.32)
Chills	2 (1.65)	13 (1.93)	21 (17.36)	60 (8.96)*
Malaise	1 (0.83)	13 (1.93)	21 (17.36)	53 (7.91)*
Headache	7 (5.97)	47 (6.98)	18 (14.88)	85 (12.69)
Allergic reaction	0	0	0	1 (0.15)
Lethargy	6 (4.96)	36 (5.35)	10 (8.26)	90 (13.49)
Worsening of rheumatological symptoms	NA	17 (2.53)	NA	12 (1.79)
Other symptoms, n	Dizziness 2	Throat pain 5	Weakness 3	Weakness 28
	Numbness 1	Arm numbness 5	Dizziness 1	Dizziness 11
	Throat pain 1	Dizziness 4	Numbness 3	Throat pain 6
	Chest pain 1	Weakness 4	Facial pain 1	Excessive sweating 3
		Rash 2	Chest pain 2	Pericarditis 1
		Flu-like 2		Chest pain 1
		Diarrhoea 2		Local lymphadenopathy 2
		Pruritus 2		Vaginal bleeding 2
		Palpitations 2		Lack of appetite 2
		Uveitis 1		Diarrhoea 2
		Herpes Labialis 1		High blood pressure 2
		Other 3		Herpes zoster 6
				Uveitis 2
				Other 7
Death	0	0	0	2 (0.3)

*p≤0.05; **p≤0.0001.
AIIRD, autoimmune inflammatory rheumatic diseases.

died from a myocardial infarction 2 months after the second vaccine dose. Adverse events of special interest in patients with AIIRD included uveitis (n=2), herpes labialis (n=1), pericarditis (n=1), and non-disseminated herpes zoster (HZ)[15] in five patients after the first vaccine dose and in one patient after the second vaccine dose. One case included HZ ophtalmicus, without corneal involvement (table 6).

BNT162b2 vaccine effect on disease activity in patients with AIIRD

In patients with RA, PsA, axSpA and SLE, the postvaccination indices of disease activity remained stable (figure 2).

DISCUSSION

The current approach to COVID-19 vaccination of patients with AIIRD is mainly based on data extrapolated from studies on other vaccines. Herein, we report the results of the first large multicentre prospective study conducted during the COVID-19 pandemic demonstrating that BNT162b2 mRNA vaccine was immunogenic in the majority of patients with AIIRD compared with controls, with a seropositivity rate of 86% vs 100%, respectively. S1/S2 IgG levels were significantly lower among patients with AIIRD compared with controls. These findings confirm the results reported by Geisen *et al*, where considerable immunogenicity was induced by anti-SARS-CoV-2 mRNA vaccines in a small group of patients with chronic inflammatory diseases.[4] The mean level of the anti-spike S1/S2 IgG neutralising antibodies measured 2–6 weeks after the second vaccine dose was significantly lower in patients with AIIRD compared with controls in all age groups, consistent with the response to a single dose of mRNA vaccines in patients with rheumatic disease reported by Boyarsky *et al*,[5] raising concerns about the long-term protection of the vaccine in patients with AIIRD.

Our study provided detailed information regarding the impact of various immunosuppressive treatments on vaccine-induced immunogenicity. GC are essential for many patients with AIIRD. The seropositivity rate of patients with AIIRD treated with GC was only 66%. The data are scarce regarding the pure effect of GC on vaccination response in patients with AIIRD, as GC are commonly used in combination with other immunosuppressants

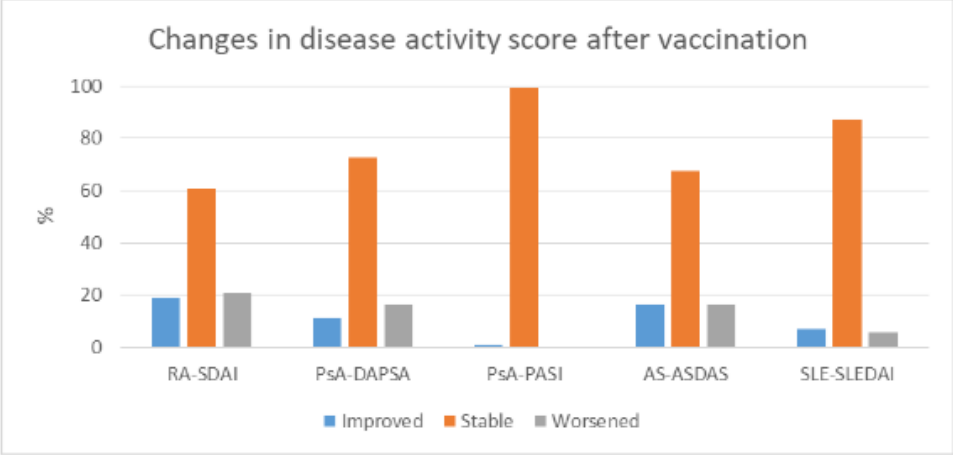

Figure 2 Disease activity scores before and after completing two doses of BNT162b2 vaccine. Data on prevaccination and postvaccination disease activity measures were available for 165 patients with RA-SDAI, 182 patients with RA-CDAI, 164 patients with RA-DAS-28-CRP, 121 patients with PsA-CDAI, 117 patients with PsA-DAPSA, 131 patients with PsA-PASI, 43 patients with AxSpA-ASDAS, 47 patients with AxSpA-BASDAI and 85 patients with SLE-SLEDAI. ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CDAI, Clinical Disease Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Disease Activity Index for SLE.

and their doses tend to vary over the disease course. A dose of ≥10 mg/day was associated with a reduced vaccine-induced humoral response to pneumococcal vaccine in patients with various inflammatory diseases.[16] The mean GC dose in our study population was relatively low (6.2 mg/day), precluding analysis on the dose-dependent effect of GC on vaccination response. MTX represents a cornerstone medication in a spectrum of rheumatic diseases. MTX may reduce humoral response to influenza and pneumococcal vaccines in patients with RA .[17–20] Temporary discontinuation of MTX for 2 weeks after vaccination improved the immunogenicity of influenza vaccination in patients with RA.[21 22] In our study, the use of MTX as monotherapy or in combination with other treatments was mainly associated with a slightly reduced seropositivity and lower levels of the S1/S2 IgG antibodies compared with controls, suggesting no need for treatment modification with MTX in most cases of anti-COVID-19 vaccination. Holding of MTX may be considered if combined with abatacept or rituximab, in view of a prevalent negative serological response under these regimens. Importantly, anticytokine biologics including TNFi, IL17i and IL6i did not interfere with the production of BNTb262-induced antibodies. This observation is in line with the studies demonstrating a considerable immunogenicity induced by influenza and pneumococcal vaccines in patients with treated with TNFi,[20 23–26] IL-6i[27–29] and IL-17i.[30 31] JAKi, representing a smaller fraction of treatments in our study, demonstrated a minor non-significantly negative effect on the production of BNTb262-induced antibodies. Limited data regarding other vaccines have shown that patients with RA treated with tofacitinib achieved a considerable response to influenza vaccine but an impaired response to a pneumococcal vaccine, especially when combined with MTX.[32] Holding of tofacitinib for 1 week prevaccination and postvaccination had little impact on the immunogenicity of either vaccine.[32] A considerable pneumococcal humoral response was achieved in patients with RA treated with baricitinib.[33]

Treatment with anti-CD20 therapies, mainly represented by rituximab in this study, significantly reduced vaccine-induced humoral response, with seropositivity of 41.3% when administered as monotherapy and 36% when administered in combination with MTX. The interval between the administration of rituximab and vaccination had a critical role in predicting the response to the vaccine. Our findings are in line with the previously published data regarding the negative impact of anti-CD20 therapy on the humoral response to various vaccines, although seroprotection could be still achieved after vaccination in rituximab-treated[20 26 34–36] and ocrelizumab-treated[37] patients. The degree of B-cell recovery at the time of vaccination correlated with the extent of the humoral response to vaccination, as reported for influenza vaccine in patients with RA treated with rituximab.[38] In a retrospective analysis of 30 patients with rheumatic diseases treated with rituximab, only 10 patients (33.3%) developed a serological response to anti-SARS-CoV-2 vaccination.[39] B-cell depletion was associated with a lack of serological response, based on data available for 11 patients.[39] Unfortunately, these data were not available for patients treated with anti-CD20 therapies in our study. As protection from SARS-CoV-2 relies on both humoral and T-cell-mediated immunity,[40 41] patients with a deficient humoral response may be still protected by the latter. Treatment with abatacept reduced vaccine-induced humoral response, with a seropositive rate of 71% as monotherapy, reduced to 40% when combined with MTX. Previous data regarding the impact of abatacept on other vaccination-related immunity are conflicting.[29 42] Treatment with MMF reduced humoral response to a seropositivity rate of 64% in 28 patients. Consistently, solid organ transplant recipients treated with regimens including MMF were at risk of a negative humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine.[43 44]

From the standpoint of particular AIIRD at risk of low immunogenic response to vaccine, RA, AAV and IIM were associated with a low humoral response to the vaccine. This finding seems to be at least partially explained by the underlying treatment.

Regarding the safety of vaccination, our study provides a reassurance for a good safety profile of the vaccine, with most adverse events being transient and mild, consistent with two other studies.[4 6] No causal link between the two deaths of the patients with AIIRD and vaccination could be established. Other rare adverse events in patients with AIIRD were limited

in number and did not seem to cause long-term complications. Occurrence of HZ in six patients with AIIRD merits a special attention as reported by our group.[15] In this study, the affected patients were women within the age range of 36–61 years (mean, 49±11 years) with a mild or stable rheumatic disease. Two patients were treated with JAKi and one with rituximab and MMF, indicating a baseline increased risk for HZ, whereas three others had a low level of immunosuppression, calling for a potential causal link between the events.[15] As the occurrence of HZ was not specifically captured in the mRNA vaccine clinical trials, no data are available on the postvaccination HZ prevalence in the general population. Case reports on HZ following the BNT162b2 mRNA vaccination in subjects without immunosuppressive treatment[45 46] and in one patient with AAV in remission[47] were recently published. Further epidemiological studies and surveillance programmes are needed to investigate the prevalence of HZ in vaccinated subjects.

There was no evidence of significant disease flares across different AIIRD. Yet, this should be interpreted with a certain caution due to an exploratory analysis of disease activity assessment performed within a variable prevaccination and postvaccination time frame.

The limitations of our study include a non-randomised design, a lack of matching between patients and controls by age, and the absence of long-term follow-up data. Neither data on B-cell repopulation at the time of vaccination for patients under anti-CD20 therapy nor data on cellular immunity were available.

In summary, the data presented in this study have important implications for the management of anti-COVID-19 vaccination in patients with a wide spectrum of AIIRD. Most immunosuppressive treatments, including csDMARDs, anticytokine biologics and JAKi, can be safely continued without significantly attenuating vaccine-induced immunogenicity. The results of our study do not support withholding MTX and JAKi in relation to COVID-19 vaccination as recommended by the ACR.[3]

Treatment with GC, rituximab, abatacept in combination with MTX, and MMF was associated with significantly decreased vaccine-induced immunogenicity. Therefore, timing of vaccination has a critical role in these cases. Postponing administration of rituximab and abatacept, especially when combined with methotrexate, when clinically feasible, seems to be reasonable to improve vaccine-induced immunogenicity. Yet, the absence of a humoral response does not preclude T-cell-mediated vaccine-induced immunity, and if shown effective, may serve as a rationale for anti-COVID-19 vaccination of these patients. Importantly, this study provides evidence of overall good tolerance of the BNT162b2 mRNA vaccine in adult patients with AIIRD. Further studies are needed to assess the durability of the humoral vaccination response, T-cell-mediated immunity in patients with a poor humoral response and long-term efficacy and safety of vaccination in patients with AIIRD.

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Contributors The study was designed, directed and coordinated by OE, the principle investigator. VF, TE, DZ and HP, the sub-investigators, were in charge of the study conducted at all stages. All the MD co-authors recruited participants into the study and evaluated predisease and postdisease activity measures in patients. GS and OS performed the serology tests. SP and SN served as main study coordinators and questioned the study participants regarding the adverse events of vaccination. OE, VF and TE had full access to the study's data and wrote the article, which was critically reviewed by DP, DZ and HP.

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Patient consent for publication Not required.

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TRANSLATIONAL SCIENCE

Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease

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ABSTRACT

Objective To investigate the humoral and cellular immune response to messenger RNA (mRNA) COVID-19 vaccines in patients with immune-mediated inflammatory diseases (IMIDs) on immunomodulatory treatment.

Methods Established patients at New York University Langone Health with IMID (n=51) receiving the BNT162b2 mRNA vaccination were assessed at baseline and after second immunisation. Healthy subjects served as controls (n=26). IgG antibody responses to the spike protein were analysed for humoral response. Cellular immune response to SARS-CoV-2 was further analysed using high-parameter spectral flow cytometry. A second independent, validation cohort of controls (n=182) and patients with IMID (n=31) from Erlangen, Germany, were also analysed for humoral immune response.

Results Although healthy subjects (n=208) and patients with IMID on biologic treatments (mostly on tumour necrosis factor blockers, n=37) demonstrate robust antibody responses (over 90%), those patients with IMID on background methotrexate (n=45) achieve an adequate response in only 62.2% of cases. Similarly, patients with IMID on methotrexate do not demonstrate an increase in CD8+ T-cell activation after vaccination.

Conclusions In two independent cohorts of patients with IMID, methotrexate, a widely used immunomodulator for the treatment of several IMIDs, adversely affected humoral and cellular immune response to COVID-19 mRNA vaccines. Although precise cut-offs for immunogenicity that correlate with vaccine efficacy are yet to be established, our findings suggest that different strategies may need to be explored in patients with IMID taking methotrexate to increase the chances of immunisation efficacy against SARS-CoV-2 as has been demonstrated for augmenting immunogenicity to other viral vaccines.

Key messages

What is already known about this subject?

- The impact of COVID-19 has been felt across the globe, and new hope has arisen with the approval of messenger RNA (mRNA) vaccines against SARS-CoV-2. Studies have shown immunogenicity and efficacy rates of over 90% in the immunocompetent adult population. However, there is a lack of knowledge surrounding the response of patients with immune-mediated inflammatory diseases (IMIDs) who may also be on immunomodulatory medications.
- Patients with IMID have been shown to have attenuated immune responses to seasonal influenza vaccination.

What does this study add?

- This study looks at the humoral and cellular immune response to two doses of BNT162b2 mRNA COVID-19 vaccine in participants with IMID (on immunomodulators) compared with healthy controls.
- Individuals with IMID on methotrexate demonstrate up to a 62% reduced rate of adequate immunogenicity to BNT162b2 mRNA vaccination. Those on anticytokine or non-methotrexate oral medications demonstrate similar levels of immunogenicity as healthy controls (greater than 90%).
- Similarly, vaccination did not induce an activated CD8+ T-cell response in participants on background methotrexate, unlike healthy controls and patients with IMID not receiving methotrexate.

INTRODUCTION

Patients with immune-mediated inflammatory diseases (IMIDs) have an inherently heightened susceptibility to infection and may thus be considered high risk for developing *COVID-19*. Importantly, however, the strength of response to viral vaccines (ie, influenza and hepatitis B) and their long-lasting protective effects in patients with IMID taking conventional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, or biologic DMARDs, such as tumour necrosis factor inhibitors (TNFis), may not be as robust

Key messages

How might this impact on clinical practice or future developments?

- These results suggest that patients on methotrexate may need alternate vaccination strategies such as additional doses of vaccine, dose modification of methotrexate or even a temporary discontinuation of this drug. Further studies will be required to explore the effect of these approaches on mRNA vaccine immunogenicity.

as it is in the general population following immunisation.[1–5] Data regarding messenger RNA (mRNA) COVID-19 vaccines' safety, immunogenicity and efficacy are rapidly emerging for the immunocompetent adult population,[6] where more than 90% of subjects achieve a satisfactory humoral response. However, the ability of patients with IMID to adequately respond to these vaccines and the differences in humoral and cellular immune response to SARS-CoV-2 vaccination are not known, leaving a significant gap in knowledge that prevents optimal management of this patient population.

Given the experience with seasonal influenza vaccine immunogenicity,[2 7] we hypothesised that patients with IMID treated chronically with certain conventional synthetic DMARDs (ie, methotrexate) would have an attenuated response to mRNA COVID-19 vaccines compared with patients with IMID receiving anticytokine treatment or non-IMID participants. To achieve this, we obtained preimmunisation and postimmunisation peripheral blood monocyte cells (PBMCs) and sera from IMID participants (n=82) in two independent cohorts (SAGA (Serologic Testing and Genomic Analysis of Autoimmune, Immune-Mediated and Rheumatic Patients with COVID-19) cohort in New York City, USA, and Erlangen, Germany) and analysed SARS-CoV-2 spike-specific antibody titres compared with non-IMID controls (n=208). Cellular immune responses were further investigated using high-dimensional spectral flow cytometry in the New York City cohort.

METHODS

Participants

Established patients with IMID (n=51) receiving methotrexate, anticytokine biologics or both participating in the SAGA study at New York University Langone Health in New York City,[8] who were receiving BNT162b2 mRNA vaccination were assessed at baseline and after the second dose during the period from 23 December 2020 through 31 March 2021. Healthy subjects served as controls (n=26). IgG antibody responses to the S protein were analysed for humoral immune response. A second independent validation cohort of controls (n=182) and patients with IMID (n=31) on either TNFi or methotrexate monotherapy from Erlangen, Germany, was also analysed for humoral response. Cellular immune responses to the vaccine were also studied for the New York SAGA participants using high-parameter spectral flow cytometry.

Humoral and cellular immune response to BNT162b2 mRNA vaccine

Humoral immune response was assessed by testing IgG antibodies against the spike protein of SARS-CoV-2.[9] In the New York City cohort, direct ELISA was used to quantify antibody titres on serum as previously described.[10] Titre of 5000 units or greater was used as the cut-off to determine an adequate response to vaccination. IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were tested in Erlangen participants using the commercial ELISA from Euroimmun (Lübeck, Germany) on the EUROIMMUN Analyzer I platform and according to the manufacturer's protocol.[11] Adequate response was defined as greater than 5.7 nm OD. Immune cell phenotyping before and after immunisation in New York participants was performed by 35-colour spectral flow cytometry on PBMCs. Further details on methodology and analysis can be found in the online supplemental appendix.

Statistical analysis

Patient characteristics were summarised using means, medians, SD, ranges and percentages as appropriate. χ^2 tests of independence and Fisher's exact tests were used for categorical data. Mann-Whitney U and Kruskal-Wallis tests were used for unpaired continuous data, and Wilcoxon signed-rank tests were used for paired continuous data. A p value of less than 0.05 was considered significant. All analyses were done using R V.3.6.0 software (R Foundation for Statistical Computing) and GraphPad Prism V.9 (GraphPad Software).

Patient and public involvement

This study was designed in response to frequent questions asked by patients with IMID but did not contain any direct public involvement.

RESULTS

The New York City cohort comprised 26 healthy individuals, 25 individuals with IMID receiving methotrexate monotherapy or in combination with other immunomodulatory medications, and 26 individuals with IMID on anticytokine therapy and/or other oral immunomodulators (table 1). Healthy individuals and those with IMID not on methotrexate were similar in age (49.2±11.9 years and 49.1±14.9 years, respectively), whereas patients with IMID receiving methotrexate were generally older (63.2±11.9 years). IMID diagnoses were predominantly psoriasis/psoriatic arthritis and rheumatoid arthritis. The Erlangen cohort consisted of 182 healthy subjects, 11 subjects with IMID receiving TNFi monotherapy and 20 subjects with IMID on methotrexate monotherapy (online supplemental table 1). Individuals on methotrexate monotherapy were on average older than healthy individuals and those with IMID not on methotrexate (54.5±19.2 vs 40.8±12.0 and 45.0±15.5, respectively).

Decreased antibody response to mRNA COVID-19 vaccine in patients with IMID on methotrexate

Immunogenicity was characterised by testing IgG antibodies against the spike protein of SARS-CoV-2. In the New York City cohort, of the healthy participants, 25 (96.1%) of 26 demonstrated adequate humoral immune response. Patients with IMID not on methotrexate achieved a similar rate of high antibody titres (24/26, 92.3%), whereas those on methotrexate had a lower rate of adequate humoral response (18/25, 72.0%) (figure 1A; table 1). This remains true even after the exclusion of patients who had evidence of previous COVID-19 infection (p=0.045). Median titres were 104 354 (range, 141–601 185), 113 608 (25–737 310) and 46 901 (25–694 528) for participants who were healthy, for those with IMID not on methotrexate and for those with IMID on methotrexate, respectively. Similarly, in the Erlangen validation cohort, 179 (98.3%) of 182 healthy controls, 10 (90.9%) of 11 patients with IMID receiving no methotrexate and 10 (50.0%) of 20 receiving methotrexate

Table 1 Baseline characteristics and spike-specific SARS-CoV-2 antibody titres in the New York City cohort

Characteristic	Healthy (n=26)	IMID No MTX (n=26)	IMID Yes MTX (n=25)	P value
Age, mean (range, SD)	49.2 (28–74, 11.9)	49.1 (29–79, 14.9)	63.2 (22–77, 11.9)	<0.001
Female, n (%)	16 (61.5)	18 (69.2)	18 (66.7)	0.352
Race, n (%)				0.220
White	16 (61.5)	20 (76.9)	17 (63.0)	
Black	1 (3.8)	2 (7.7)	3 (11.1)	
Asian	9 (34.6)	3 (11.5)	3 (11.1)	
Other	0 (0.0)	1 (3.8)	2 (7.4)	
Hispanic ethnicity, n (%)	1 (3.8)	3 (11.5)	5 (18.5)	0.200
Primary IMID, n (%)				0.107
Psoriasis and/or psoriatic arthritis	--	15 (57.7)	9 (36.0)	
Rheumatoid arthritis	--	10 (38.5)	12 (48.0)	
Other*	--	1 (3.8)	4 (16.0)	
Long-term medication, n (%)				
Methotrexate	--	0 (0.0)	25 (100.0)	--
Tumour necrosis factor inhibitor	--	11 (42.3)	9 (36.0)	0.776
Other anticytokines/Janus kinase inhibitors†	--	9 (34.6)	1 (4.0)	0.011
Other oral immunomodulators‡	--	7 (26.9)	6 (24.0)	1.00
Methotrexate dose, mean (SD)	--	--	15.7 (5.0)	
COVID-19 infection before vaccination, n (%)	4 (15.4)	5 (19.2)	2 (8.0)	0.509
Days from first vaccination dose, mean (range, SD)	29.0 (23–44, 4.6)	32.5 (25–45, 5.0)	34.6 (21–73, 9.9)	0.002
Number receiving second vaccination dose, n (%)	26 (100.0)	26 (100.0)	25 (100.0)	1.00
Adequate humoral response§¶, n (%)	25 (96.1)	24 (92.3)	18 (72.0)	0.023
Spike-specific SARS-CoV-2 antibody titres¶				0.294
Titre median (range)	104 354 (141–601 185)	113 608 (25–737 310)	46 901 (25–694 528)	

*Vasculitis, dermatomyositis, adult-onset Still's disease, sarcoidosis and polymyalgia rheumatica.
†For IMID No MTX: IL-17i (3), IL-23i (2), abatacept (1), rituximab (1), JAKi (2). For IMID Yes MTX: IL-17 (1).
‡For IMID No MTX: leflunomide (2), oral steroid (1), sulfasalazine (2), apremilast (1), hydroxychloroquine (1). For IMID Yes MTX: oral steroid (2), sulfasalazine (2), hydroxychloroquine (2).
§Adequate humoral response defined as greater than 5000 units.
¶All values 1 week after second vaccination.
IMID, immune-mediated inflammatory disease; MTX, methotrexate.

achieved adequate immunogenicity (figure 1B). Median ODs for this cohort were 9.4 (range, 1.2–14), 7.8 (2.3–11.3) and 5.9 (0.95–13.5) for participants who were healthy, for those with IMID not on methotrexate and for those with IMID on methotrexate, respectively. Furthermore, when looking at the two cohorts in conjunction (n=290), 204 (98.1%) of 208 healthy controls, 34 (91.9%) of 37 patients with IMID receiving no methotrexate and 28 (62.2%) of 45 receiving methotrexate achieved adequate immunogenicity (p<0.001) (online supplemental figure S1).

Because of the imbalance in age between groups, we further analysed immunogenicity based on a cut-off age of 55. In both

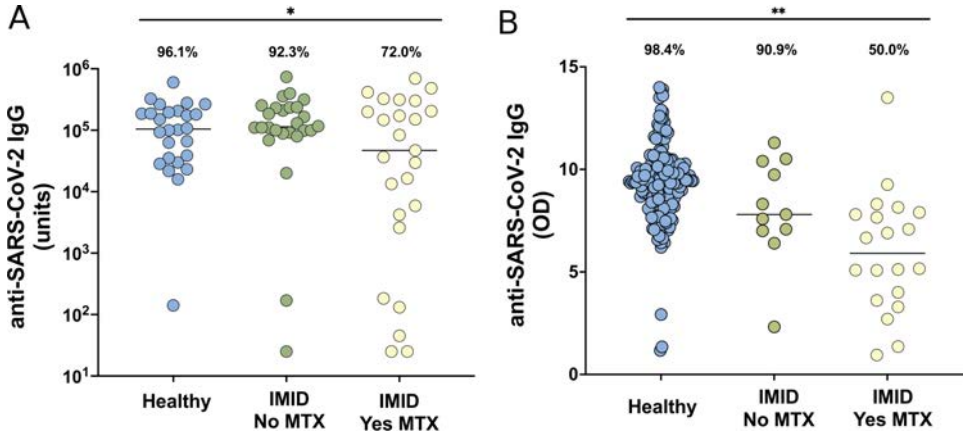

Figure 1 Anti-SARS-CoV-2 IgG levels in cohorts from New York City (A) and Erlangen (B) in healthy participants without IMID (blue), patients with IMID not receiving MTX (green) and patients with IMID treated with MTX (yellow). Solid lines represent mean titre of each group. For the New York City cohort (A), adequate response is defined as greater than 5000 units, and for the Erlangen cohort (B), adequate response is defined as greater than 5.7 (OD, 450 nm), 2 SDs of the mean of controls. Percentages and group comparisons using χ^2 test of independence reflect proportion of those achieving an adequate response within each group. * indicates p value less than .05 and ** indicates p value less than .001. IMID, immune-mediated inflammatory disease; MTX, methotrexate.

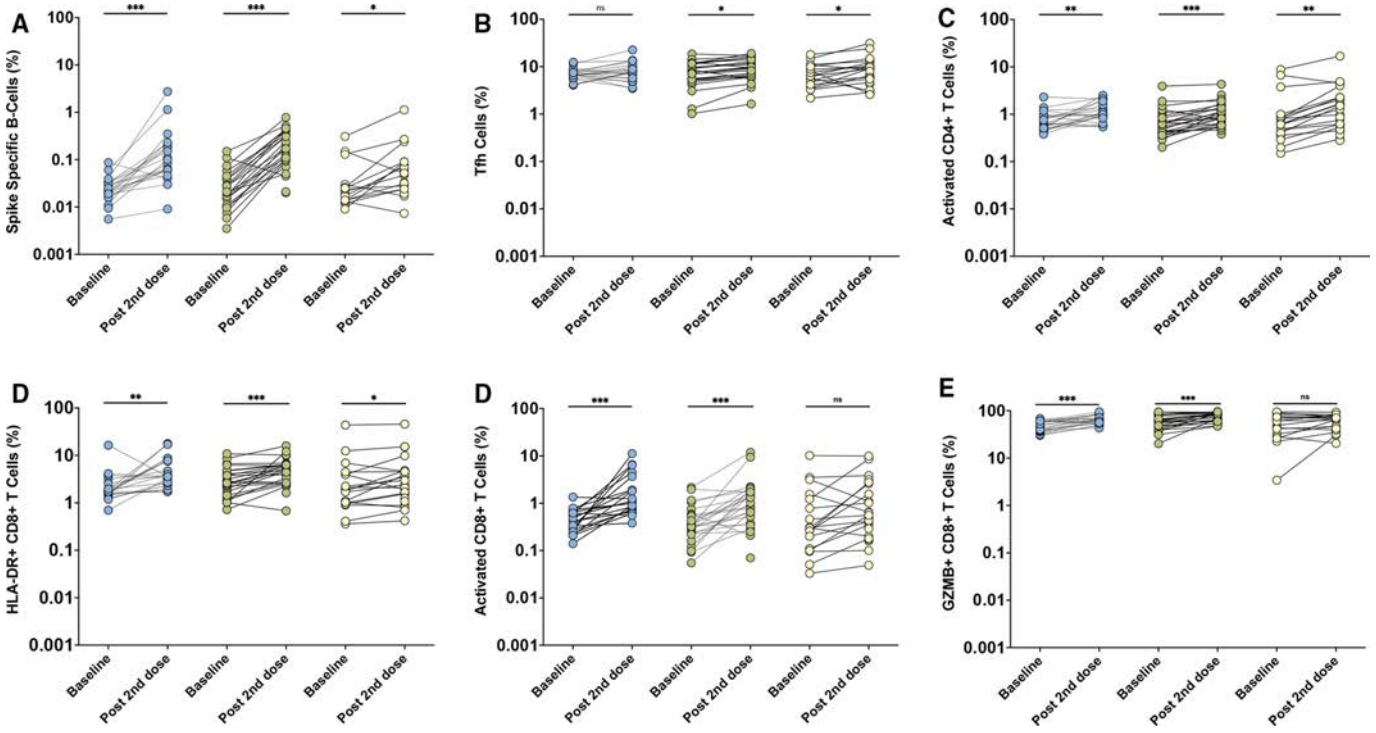

Figure 2 Immune cell populations from the New York City cohort by high spectral flow in healthy controls (blue, n=20), patients with immune-mediated inflammatory disease (IMID) not on methotrexate (MTX; green, n=24) and patients with IMID on MTX (yellow, n=18), at baseline and after the second dose of BNT162b2 mRNA vaccine. Prevaccination and postvaccination comparisons were performed using Wilcoxon signed-rank tests. Y-axes presented as a logarithmic scale. NS indicates no statistical significance. * indicates p value less than .05. ** indicates p value less than .01. *** indicates p value less than .0001. Tfh, T follicular helper.

age groups, the response rate for those on methotrexate remained significantly lower ($p<0.001$) (online supplemental figure S2). As an added sensitivity analysis, we used a stricter definition of inadequate antibody response (ie, less than 1000 units for New York City cohort and less than 5 OD for the Erlangen cohort). With the use of these more conservative cut-off levels, patients with IMID on background methotrexate continued to show significantly decreased antibody response ($p<0.001$) (online supplemental figure S3).

Lack of CD8+ T-cell activation in patients with IMID on methotrexate following mRNA COVID-19 vaccine

In the New York City cohort, 20 healthy controls, 24 patients with IMID not receiving methotrexate and 18 patients with IMID who were receiving methotrexate underwent immune cell phenotyping before and after vaccination. The proportions of spike-specific B cells, circulating T follicular helper (cTfh; CD4+ ICOS+ CD38+ subset) cells, activated CD4+ T cells and HLA-DR+ CD8+ T cells increased significantly in all groups after immunisation (figure 2A–D). Activated CD8+ T cells, defined as CD8+ T cells expressing Ki67 and CD38, and the granzyme B-producing (GZMB) subset of these activated CD8+ T cells were induced in healthy adults and participants with IMID not on methotrexate, but not induced in patients receiving methotrexate (figure 2E,F).

DISCUSSION

In two geographically independent cohorts of patients with IMID, we found that methotrexate, a widely used immunomodulator for the treatment of several IMIDs, adversely affected humoral and cellular immunogenicity to COVID-19 mRNA vaccines.

For humoral immunity, the BNT162b2 mRNA vaccines did not induce adequately elevated SARS-CoV-2 spike-specific IgG antibody titres in up to a third of the patients on methotrexate, compared with patients with IMID on other DMARDs, who demonstrated a response as robust as that of healthy controls. This finding was analogous to the previously described effects of methotrexate on influenza vaccine immunogenicity.[5 12–14] While a recent report has shown no differences in immunogenicity for patients with IMID, none of the included participants were on methotrexate.[15] A second study in patients with self-reported rheumatic and musculoskeletal diseases recruited via social media showed that 10 of 13 participants on background methotrexate had detectable antibody levels after only one dose of SARS-CoV-2 mRNA vaccine,[16] although this was both underpowered and used a semiquantitative ELISA measuring antibodies against SARS-CoV-2 receptor-binding domain. Therefore, the findings from our work looking at antibody responses in patients with IMID after full vaccination regimen are of potentially high clinical relevance because it was recently shown that a temporary discontinuation of methotrexate for 2 weeks significantly improved influenza vaccine immunogenicity in patients with rheumatoid arthritis.[2]

Importantly, the use of high-dimensional spectral flow cytometry allowed for the interrogation of specific cellular immune responses before and after immunisation. Spike-specific B cells, activated CD4+ T cells and cTfh cells were induced similarly in all groups after mRNA vaccination. In contrast, activated CD8+ T-cell responses were notably attenuated in the methotrexate cohort. Moreover, the poor induction of activated CD8+ T cells expressing granzyme B may indicate reduced cytotoxic functionality of these cells. Indeed, CD8+ T-cell responses were identified to be a correlate of protection in non-human primate studies

of SARS-CoV-2 infection.[17] Thus, reduced induction of cytotoxic CD8+ T-cell responses, combined with inconsistent induction of antibody responses, may further impair the effectiveness of COVID-19 vaccines and render patients with IMID on methotrexate more at risk of inadequate vaccine response. However, this finding requires a cautious interpretation as it is quite possible that the use of methotrexate may delay (rather than prevent) adequate cellular mediated immunity against SARS-CoV-2. While spike-specific T-cell immunity has been detected as early as 10 days following one dose of mRNA COVID-19 vaccines in healthy individuals,[18] mRNA-1273-specific CD4+ and CD8+ T-cell responses were most robustly elicited 2 weeks after the second dose.[19] Therefore, more detailed and comprehensive studies that include long-term characterisation of the dynamics of cellular responses to these vaccines will be required to understand the clinical implications of these findings.

Although our analysis was limited in sample size, followed participants with biosampling for a relatively short period of time without standardised disease activity status metrics and was restricted to one type of mRNA immunisation, our findings were validated in an independent cohort and revealed that methotrexate, which is widely used for many indications, adversely affected the humoral and cellular immunogenicity to COVID-19 mRNA vaccination. Furthermore, because of the inclusion of patients with prior COVID-19 infection, it is possible that results could be biased in favour of those not on methotrexate. However, when excluding all patients with prior infection, the results remained similar. We also acknowledge that there may have been participants with asymptomatic COVID-19 infection that we have not captured.

While immunosenescence may reduce the level of antibody responses to immunisations,[20] recent studies on COVID-19 mRNA vaccines have not shown differences in clinical outcomes for the older population.[6] In our study, patients with IMID on methotrexate were generally older, which may potentially explain some differences in immunogenicity. However, even when looking at participants younger than 55 years, decreased rates of humoral response were still significant. Further validation in even larger cohorts that address efficacy will be required to understand the interaction between age and methotrexate in the context of COVID-19 vaccination.

Importantly, it is not yet clear what level of immunogenicity is representative of vaccine efficacy (and this includes the arbitrary cut-offs chosen for our measurements). We recognise that the definition of adequate cellular and humoral immune response may need to be refined in the future when correlation with efficacy becomes available. However, even after applying more conservative cut-offs, the hampering effects of methotrexate on immunogenicity are still evident.

Taken together, our results suggest that the optimal protection of patients with IMID against COVID-19 will require further studies to determine whether additional doses of vaccine, dose modification of methotrexate or even temporary discontinuation of this drug can boost immune response as has been demonstrated for other viral vaccines in this patient population.[7]

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Contributors RHH and JUS designed the New York study, designed the data collection tools, analysed and cleaned the data, and drafted and revised the paper. RH, MS and MM designed the New York study, designed and performed the cellular analysis, and revised the paper. SA designed the New York Study and revised the paper. RBB designed the New York study, acquired data and revised the draft. DS, RA, KT, MN and GS designed the Erlangen study, designed the data collection tools, analysed and cleaned the data, and revised the paper. SA aided in original design, statistical analysis and revised the paper. MT, SK, RA and AC analysed data and revised the draft. RC, PR, GS, NA, PR, PI, JS, BG and SMR helped accrue data and revised the draft.

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Competing interests JUS declares that he has served as a consultant for Janssen, Novartis, Pfizer, Sanofi, UCB and Abbvie and has received funding for investigator-initiated studies from Novartis, Sanofi and Janssen. GS has served as a consultant for Abbvie, BMS, Eli Lilly, Gilead, GSK Novartis, Janssen and Roche and has received funding for investigator-initiated studies from BMS, Eli Lilly, GSK, Novartis and UCB. MM declares grants from Eli Lilly, Pfizer and Sanofi and personal fees from Meissa Vaccines. PI has received consulting fees from GSK. RHH has received consulting from Janssen. SA reports grant support from Johnson and Johnson. GS declares consulting fees from AbbVie.

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CLINICAL SCIENCE

SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity

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ABSTRACT

Objectives Evidence suggests that B cell-depleting therapy with rituximab (RTX) affects humoral immune response after vaccination. It remains unclear whether RTX-treated patients can develop a humoral and T-cell-mediated immune response against SARS-CoV-2 after immunisation.

Methods Patients under RTX treatment (n=74) were vaccinated twice with either mRNA-1273 or BNT162b2. Antibodies were quantified using the Elecsys Anti-SARS-CoV-2 S immunoassay against the receptor-binding domain (RBD) of the spike protein and neutralisation tests. SARS-CoV-2-specific T-cell responses were quantified by IFN-γ enzyme-linked immunosorbent spot assays. Prepandemic healthy individuals (n=5), as well as healthy individuals (n=10) vaccinated with BNT162b2, served as controls.

Results All healthy controls developed antibodies against the SARS-CoV-2 RBD of the spike protein, but only 39% of the patients under RTX treatment seroconverted. Antibodies against SARS-CoV-2 RBD significantly correlated with neutralising antibodies (τ=0.74, p<0.001). Patients without detectable $CD19^+$ peripheral B cells (n=36) did not develop specific antibodies, except for one patient. Circulating B cells correlated with the levels of antibodies (τ=0.4, p<0.001). However, even patients with a low number of B cells (<1%) mounted detectable SARS-CoV-2-specific antibody responses. SARS-CoV-2-specific T cells were detected in 58% of the patients, independent of a humoral immune response.

Conclusions The data suggest that vaccination can induce SARS-CoV-2-specific antibodies in RTX-treated patients, once peripheral B cells at least partially repopulate. Moreover, SARS-CoV-2-specific T cells that evolved in more than half of the vaccinated patients may exert protective effects independent of humoral immune responses.

Key messages

What is already known about this subject?

- B cell-depleting therapy with rituximab (RTX) can lead to severe or prolonged disease courses after SARS-CoV-2 infection.
- B cell-depleting therapy with RTX affects humoral immune responses after vaccination. It is still unclear whether patients without measurable peripheral B cells after RTX treatment can develop antibodies against SARS-CoV-2 after vaccination and whether T-cell-mediated immune response is affected.

What does this study add?

- This study describes that patients who received RTX treatment and have no measurable peripheral B cells do not develop antibodies after SARS-CoV-2 vaccination. Patients with repopulated B cells can mount antibody responses after COVID-19 vaccination.
- T-cell-mediated immune response after COVID-19 vaccination was detected in the majority of patients after RTX treatment irrespective of the presence or absence of B cells and a humoral immune response.

How might this impact on clinical practice or future developments?

- RTX treatment should not preclude COVID-19 vaccination, since a robust T-cell response can be mounted even in the absence of circulating B cells.
- Delaying RTX treatment may be justified in patients with stable disease until peripheral B cells repopulate to allow development of a humoral response to vaccination.

INTRODUCTION

SARS-CoV-2 causes COVID-19 often resulting in a severe acute respiratory distress syndrome. Different vaccines have been developed as a critical factor to manage this global public health emergency. A major concern is the immunogenicity of vaccination during immunomodulatory therapies.[1–8] Among the immunosuppressive therapies, rituximab (RTX), a monoclonal antibody targeting CD20, represents an important treatment for various inflammatory diseases.[9] An increased risk of more severe disease courses and persistent viraemia have been reported in RTX-treated patients on SARS-CoV-2 infection.[10–13] RTX treatment in particular might

affect the COVID-19 disease course and the immunogenicity of SARS-CoV-2 vaccination, as reported previously.[1–7 14] Studying a small cohort of RTX-treated patients, we have recently provided some initial evidence that T-cell-mediated immune response is maintained even in the absence of a humoral anti-SARS-CoV-2 response. However, it remains unclear whether, or to which extent, repopulation of peripheral B cells is needed for antibody development in RTX-treated patients.[15]

To determine if or for how long it might be useful to withhold COVID-19 vaccination in RTX-treated patients, we assessed the cellular and humoral immune response and related it to numbers of peripheral B cells.

METHODS

Patients

Patients under RTX treatment at our outpatient clinic were enrolled. All patients were vaccinated twice with an mRNA vaccine (either BioNTech/Pfizer BNT162b2 or Moderna mRNA-1273). Serum samples obtained after second vaccination were stored at the Biobank of the Medical University of Vienna, a centralised facility for the preparation and storage of biomaterial with certified quality management (International Organization for Standardization (ISO) 9001:2015).[16] Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation and stored in liquid nitrogen until further use. Antibodies against the receptor-binding domain (RBD) were determined after the second vaccination.

Samples from healthy blood donors without exposure to SARS-CoV-2 were collected before the SARS-CoV-2 pandemic (June–November 2019) and served as prepandemic healthy controls. Sex-matched and age-matched individuals who were vaccinated twice with BNT162b2 served as healthy vaccination controls. Ethical approval for this study was granted by the ethics committee of the Medical University of Vienna, Austria (1291/2021; 559/2005; 1073/2021). Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Quantification of $CD19^+$ peripheral B cells

Immunological phenotyping was performed by flow cytometry (FACSCanto II, San Jose, California, USA) using the whole blood first stain and then lyse and wash method (Becton Dickinson). Lymphocyte subsets were characterised with a combination of the following monoclonal antibodies (all provided by Becton Dickinson): fluorescein isothiocyanate (FITC)-labelled anti-CD3, phycoerythrin (PE)-labelled anti-$CD16^+56^+$, peridinin-chlorophyll-protein (PerCP)-cy5.5-labelled anti-CD4, PE-Cy7-labelled anti-CD19, allophycocyanin (APC)-Cy7-labelled anti-CD8, V450-labelled anti-human leukocyte antigen (HLA)-DR, V500-labelled anti-CD45 and APC-labelled anti-CD14. Between 20 000 and 500 000 events were acquired to recover a significant B cell population of at least 50 cells. Results were expressed as proportion of $CD19^+$ B cells among total lymphocytes.

Humoral immune responses

Anti-SARS-CoV-2 antibody testing

The Elecsys Anti-SARS-CoV-2 S immunoassay was used for the quantitative determination of antibodies to the RBD of the viral spike (S) protein.[17 18] The quantitation range is between 0.4 and 2500.0 U/mL. Tests were performed on a Cobas e801 analyser (Roche Diagnostics, Rotkreuz, Switzerland) at the department of laboratory medicine, Medical University of Vienna (certified acc. to ISO 9001:2015 and accredited acc. to ISO 15189:2012).

SARS-CoV-2 neutralisation test (NT)

The NT was performed as described previously.[19] Twofold serial dilutions of heat-inactivated serum samples were incubated with 50–100 tissue culture infectious dose 50% (TCID50) SARS-CoV-2 for 1 hour at 37°C before the mixture was added to Vero E6 (ATCC CRL-1586) cell monolayers. Incubation was continued for 3 days. NT titres were expressed as the reciprocal of the serum dilution required for protection against virus-induced cytopathic effects. NT titres ≥10 were considered positive.

T-cell responses

Peptides

For T-cell stimulation, PepMix SARS-CoV-2 peptide pools were purchased from JPT (Berlin, Germany). The pools cover the entire sequences of the SARS-CoV-2 S protein and comprise 15-mer peptides overlapping by 11 amino acids (aa). The S peptides are split into two subpools S1 (aa 1–643) and S2 (aa 633–1273). Peptides were dissolved in dimethyl sulfoxide and diluted in AIM-V medium for use in enzyme-linked immunosorbent spot (ELISpot) assays.

T-cell IFN-γ ELISpot assay

For ex vivo ELISpot assays, PBMCs were thawed. A total of $1–2\times10^5$ cells per well were incubated with SARS-CoV-2 peptides (2 µg/mL; duplicates), AIM-V medium (negative control; 3–4 wells) or phytohemagglutinin (PHA) (L4144, Sigma; 0,5 µg/mL; positive control) in 96-well plates coated with 1.5 µg anti-IFN-γ (1-D1K, Mabtech) for 24 hours. After washing, spots were developed with 0.1 µg biotin-conjugated anti-IFN-γ (7-B6-1, Mabtech), streptavidin-coupled alkaline phosphatase (Mabtech, 1:1000) and 5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium (Sigma). Spots were counted using a Bio-Sys Bioreader 5000 Pro-S/BR177 and Bioreader software generation 10. Data were calculated as spot-forming cells (SFCs) per 10^6 PBMCs after subtraction of the spots from the negative control (mean spot number from three to four unstimulated wells).

Statistical analysis

According to the distribution, continuous variables are presented as mean with SD or median with IQR. Unpaired groups were compared depending on the distribution by either t-test and one-way analysis of variance or using non-parametrical tests such as the Kruskal-Wallis test. Categorical variables were analysed using Fisher's exact test. Associations between continuous variables were assessed via Kendall rank correlation coefficient (τ). Univariate and a multivariable logistic regression analysis was implemented to assess association of relevant variables with seroconversion. The investigators selected the variables included based on the expected relevance (age, concomitant medication and the number of peripheral B cells). GraphPad Prism (V.9.1.0) was used for the graphical presentation of the data. 'R' V.4.0.3 was used for the entire statistical analysis. The following packages were used: 'ggplot2', 'ggbeeswarm' and 'sjPlot' for creating plots and 'tableone' to create baseline tables.

RESULTS

Patient characteristics and sample collection

Seventy-four patients (mean age 61.7±13.3 years, 77% women) with immune-mediated inflammatory diseases (IMID) under B

Table 1 Patient characteristics at baseline

n	74
Age (mean (SD))	61.7 (13.3)
Gender: woman (%)	57 (77.0)
Diagnosis, n (%)	
IgG4-related disease	2 (2.7)
Connective tissue diseases	22 (29.7)
Rheumatoid arthritis	33 (44.6)
Vasculitis	17 (23.0)
Peripheral B cells, absolute (median (IQR))	2.00 (0.00, 32.50)
Detectable B cells, n (%)	38 (51.4)
IgG (median (IQR)) (mg/dL)	820 (646, 1052)
IgM (median (IQR)) (mg/dL)	47 (26, 69)
Months between RTX and vaccination (mean (SD))	6.9 (6.0)
Days between vaccine and laboratory assessment (mean (SD))	21.9 (16.6)
Concomitant medication, n (%)	
Any csDMARD	42 (56.8)
Methotrexate	24 (32.4)
Mycophenolate mofetil	8 (10.8)
Hydroxychloroquine	7 (9.5)
Azathioprine	5 (6.8)
Leflunomide	4 (5.4)
Sulfasalazine	1 (1.4)
Immunoglobulin therapy	3 (4.1)
Prednisone	22 (29.7)
Vaccine, n (%)	
mRNA-1273	13 (17.6)
BNT162b2	61 (82.4)

csDMARD, conventional synthetic disease-modifying antirheumatic drug; RTX, rituximab.

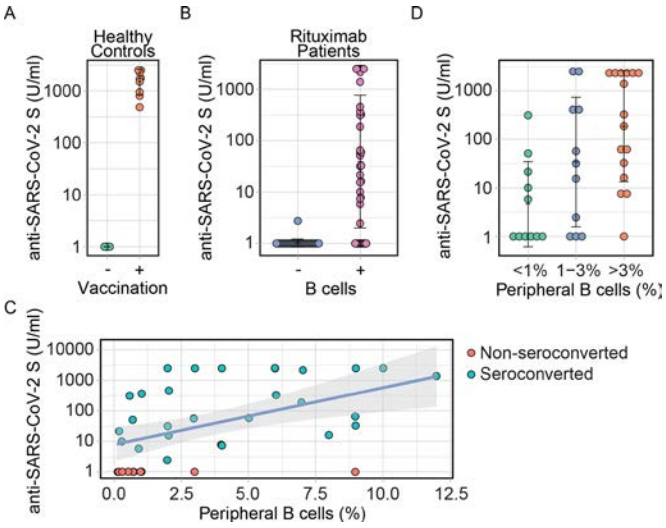

Figure 1 Humoral immune response to SARS-CoV-2 vaccination in rituximab (RTX)-treated patients. Antibodies to the receptor-binding domain (RBD) of the viral spike (S) protein were determined using an anti-SARS-CoV-2 immunoassay. (A.) Antibody levels were determined in prepandemic healthy controls (n=5) and in vaccinated healthy controls (n=10). (B.) Antibody levels were determined in RTX-treated patients (n=74) without (-) and with (+) detectable $CD19^+$ peripheral B cells. (C.) Scatter plot of antibody levels to the RBD of the S protein and the percentage of $CD19^+$ peripheral B cells with linear regression line including a 95% CI. (D.) Antibody levels grouped in patients according to the percentage of $CD19^+$ peripheral B cells. Mean±SD deviation is shown.

cell-depleting therapy with RTX received two vaccinations with either BNT162b2 (Pfizer/BioNTech) (n=61, 82%) or mRNA-1273 (Moderna) (n=13, 18%). Blood was collected at a mean of 21.9 days (range: 7–49 days) after the second vaccination to determine cellular and humoral immune response. None of the patients had a clinical history of, or developed a, SARS-CoV-2 infection during the observation period. Most patients with IMID had rheumatoid arthritis (45%), followed by connective tissue diseases (30%), vasculitides (23%) and IgG4-related disease (3%) (table 1). The mean time between the last RTX treatment and the first COVID-19 vaccination was 6.9 (±6.0) months. Forty-three percent of the patients received RTX monotherapy, while 57% received comedication with conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) (n=24), mycophenolate mofetil (MMF) (n=8), hydroxychloroquine (n=7) and leflunomide (n=4); 30% of the patients received a therapy with low-dose prednisone (mean: 5.5±3.6 mg). Fity-one percent of the patients had detectable B cells.

Humoral immune responses to COVID-19 vaccination

Antibodies against the SARS-CoV-2 RBD of the S protein were analysed after the second dose of BNT162b2 or mRNA-1273 vaccine. Healthy individuals who received two vaccinations with BNT162b2 (n=10) and unvaccinated prepandemic healthy individuals (n=5) served as controls. None of the prepandemic healthy controls but all healthy vaccinated controls had detectable antibodies (figure 1A).

In 29 of the 74 RTX-treated patients (39%), seroconversion was seen (online supplemental table 1). Among patients in whom peripheral B cells were not detectable (n=36), anti-RBD antibodies were also not detectable, with one exception (figure 1B). In patients with detectable peripheral B cells (n=38), seroconversion rate was 74%; levels of peripheral B cells correlated significantly with antibody levels (τ=0.4, p<0.001) (figure 1C). Comparison of antibody levels in patients with different proportions of peripheral B cells revealed that 45% of patients with more than 0% but less than 1% peripheral B cells (n=11) were able to mount an antibody response, suggesting that the mere presence of peripheral B cells allows seroconversion irrespective of the B cell count (figure 1D).

Comparative univariate analysis of seroconverted and non-seroconverted patients revealed a statistical significance for time since last RTX administration and first vaccination (p=0.001), but not for comedication, type of vaccine or diagnosis (online supplemental table 1). Accordingly, time since the last RTX treatment was significantly correlated with B cell levels (τ=0.43, p<0.001) and antibody levels (τ=0.37, p<0.001) (online supplemental figure 1A,B). Multivariable logistic regression analysis showed that the percentage of peripheral B cells contributed significantly to seroconversion (OR 2.4, 95% CI 1.63 to 4.15) when adjusted for age, csDMARDs and prednisone (figure 2). The calculated McFadden's R^2 of 0.41 indicates a good model fit. Time since the last RTX treatment did not show an additional effect on seroconversion nor did it improve model fit (likelihood-ratio test, p=0.777) (online supplemental figure 1C).

Forty-two patients (57%) received comedication with csDMARDs (table 1). Among them, 24 (32%) were treated with MTX and eight (11%) with MMF; 22 (30%) received

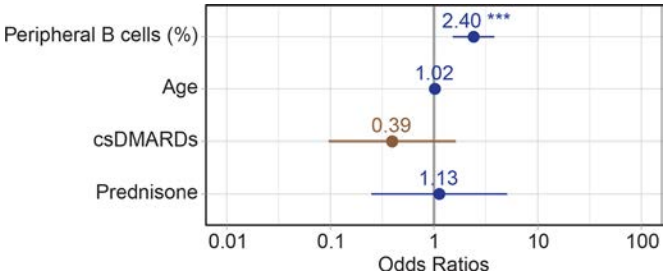

Figure 2 ORs of logistic regression assessing seroconversion in vaccinated rituximab-treated patients. csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

prednisone. No difference was observed in the levels of antibodies against the SARS-CoV-2 RBD of the S protein in the presence or absence of comedication with csDMARDs (online supplemental figure 1D). Although the OR might suggest a negative impact of comedication with csDMARDs on seroconversion, it does not reach statistical significance nor does the omission of csDMARDs alter the model fit (likelihood-ratio test, p=0.184) (figure 2). Of note, 58.3% of the MTX-treated and 75% of the MMF-treated patients did not seroconvert.

Neutralising activity against SARS-CoV-2

Neutralising antibodies against SARS-CoV-2 were measured in 36 RTX-treated patients after the second vaccination. Patients who did not have detectable antibodies against the SARS-CoV-2 RBD as determined in the immunoassay also did not have neutralising antibodies (online supplemental figure 2A). Accordingly, RBD-specific antibody levels (U/mL) significantly correlated with neutralising activity (τ=0.74, p<0.001) (online supplemental figure 2B). Except for one patient, who also developed anti-RBD antibodies, no neutralising antibodies could be detected in patients without peripheral B cells (online supplemental figure 2C). Neutralising antibody levels correlated significantly with levels of peripheral B cells (τ=0.54, p<0.001) (online supplemental figure 2D). Overall, these data suggest that seroconversion reflects functionally protective antibody responses.

T-cell-mediated immune responses to COVID-19 vaccination

To investigate whether the patients mounted a SARS-CoV-2-specific T-cell response, we analysed PBMCs from 45 patients after the second COVID-19 vaccination. All healthy vaccinated controls had detectable SARS-CoV-2-specific T-cell responses, and the prepandemic controls had low or no background responses (figure 3A,B). Interestingly, 26 out of 45 patients (58%) had detectable cellular responses to the S peptide pools (S1/S2). Among them, 12/26 (46%) did have detectable RBD-specific antibodies as compared with 14/26 (54%) who did not seroconvert after the second vaccination. Nineteen of the 45 patients (42%) did not have a T-cell-mediated immune response to COVID-19 vaccination. Among them, 6/19 (32%) had antibodies after vaccination in the absence of a detectable T-cell response. Thirteen out of nineteen (68%) were negative in the RBD immunoassay. Thus, overall, 13 out of 45 patients (29%) developed neither a T-cell response nor antibodies against SARS-CoV-2 (online supplemental table 3). Comparative analysis of seroconverted and non-seroconverted patients without a T-cell response revealed a statistical significance for time since last RTX administration and first vaccination (p=0.006) and for peripheral B cells (p=0.003), but not for age, comedication, type of vaccine or diagnosis (online supplemental table 4). No

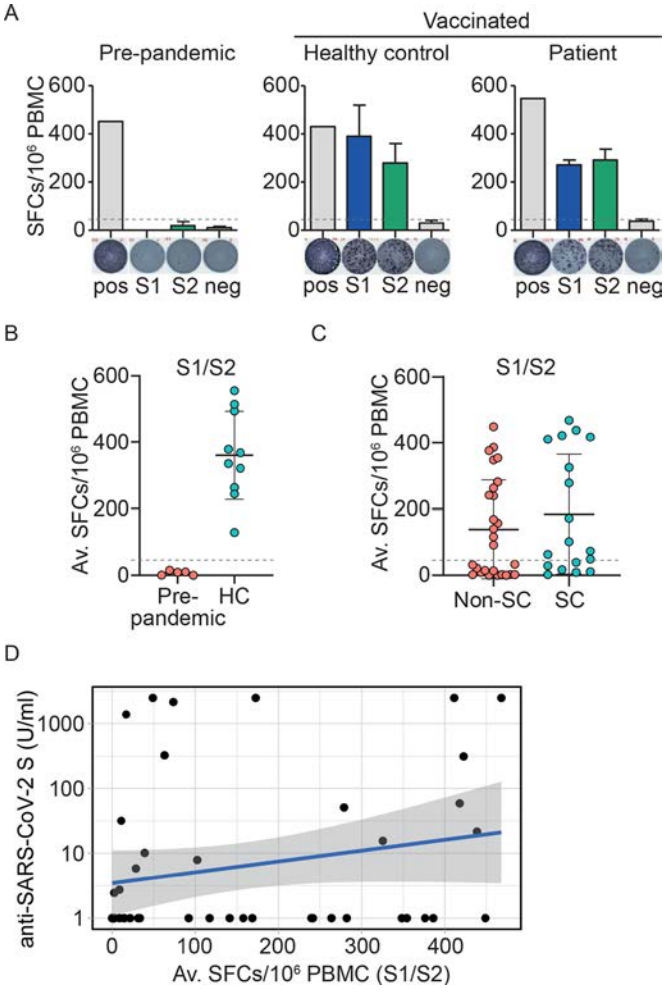

Figure 3 SARS-CoV-2-specific T-cell responses in rituximab (RTX)-treated patients. (A.) Representative ex vivo interferon (IFN)-γ enzyme-linked immunosorbent spot (ELISpot) results from peripheral blood mononuclear cells (PBMCs) stimulated with spike subunit S1 and S2 peptide pools shown for one prepandemic control, one representative vaccinated healthy control and one representative RTX-treated patient. Y-axis indicates the number of spot-forming cells (SFCs) per 10^6 PBMCs. (B.) Average of SFCs/10^6 PBMCs from S1 and S2 peptide pools is shown for each subject in prepandemic (n=5) or vaccinated (n=10) healthy controls (HC). (C.) Composite ELISpot results from 45 patients divided into seroconverted (SC) and non-SC RTX-treated patients. Data show average of SFCs/10^6 PBMCs from S1 and S2 peptide pools. Dotted lines represent the cut-off as defined by the mean SFC count+three times the SD from the prepandemic controls. (D.) Scatter plot of antibodies to the receptor-binding domain of the spike protein and average of SFCs/10^6 PBMCs from S1 and S2 peptide pools with linear regression line including a 95% CI. Mean±SD deviation is shown. Av., average; neg, negative; pos, positive.

significant difference between patients with and without T-cell response was found with respect to seroconversion (p=0.371). SFC responses tended to be higher in seroconverted than non-seroconverted RTX-treated patients, but these differences did not reach statistical significance (figure 3C). In line with these data, no significant correlation between the SFC responses to S peptide pools and antibody levels against the RBD of the S protein was observed (figure 3D).

Among the 45 patients, 25 (56%) received comedication with any csDMARD (online supplemental table 2). Among them, 16

(36%) were treated with MTX and three (7%) with MMF; 12 (27%) patients received prednisone. Comparative univariate analysis revealed no difference for comedication, prednisone dose or age between patients with and without T-cell-mediated response to SARS-CoV-2 (online supplemental table 3). Of note, MMF was reported to influence the humoral and cellular immune response. In our data, exclusion of MMF-treated patients did not alter the analysis (data not shown).

Time-resolved humoral and T-cell-mediated immune responses to COVID-19 vaccination

To investigate the dynamics of humoral and T-cell-mediated immune responses, anti-RBD antibody levels and SARS-CoV-2-specific T-cell responses were analysed at two different time points. SARS-CoV-2-specific antibodies were determined on average 15 and 37 days after the second vaccination in a subgroup of 42 patients. As shown in online supplemental figure 3A, no difference in antibody levels against SARS-CoV-2 were found 5 weeks after the first laboratory testing. Likewise, no difference was observed for SARS-CoV-2-mediated T-cell responses on average 15 and 42 days after the second vaccination in a subgroup of nine patients (online supplemental figure 3B). These data suggest a robust humoral and T-cell-mediated immune response to COVID-19 vaccination over a period of 5 weeks after second vaccination.

DISCUSSION

B cells play a critical role in the development of humoral immune responses. In the presented study, we could show that B cell depletion in RTX-treated patients affects the humoral but does not necessarily abolish T-cell-mediated immune responses to COVID-19 vaccination. These data are in line with recent reports, suggesting that RTX might affect antibody responses to COVID-19 vaccination.[14 20–23] However, here, we could show that a humoral response can be mounted once peripheral B cells are present and that the numbers of peripheral B cells correlate with levels of antibodies against the RBD of the S protein. These findings suggest a qualitative and quantitative dependence of a successful humoral response to COVID-19 vaccination on peripheral B cells. Recent data indicate a role of csDMARDs on humoral immune responses.[20 21 24 25] Within our data, no clear effect on seroconversion was observed, which might be due to the small size of the patient cohort with csDMARDs. Larger cohorts are certainly needed to sufficiently address the impact of comedication on humoral immune responses. In line with recent reports, impaired humoral immune response was independent of the diagnosis.[26] Antibodies against the SARS-CoV-2 RBD significantly correlated with neutralising activity supporting a protective antibody response.

Our data also showed that a subset of RTX-treated patients could develop robust SARS-CoV-2-specific T-cell immunity in response to vaccination. T-cell-mediated immune response was observed in seroconverted and non-seroconverted patients suggesting that the absence of peripheral B cells is the primary mediator of an impaired humoral but not cellular immune response. More extensive trials will undoubtedly be needed to understand the exact role of T-cell immunity in protection against SARS-CoV-2 infection and if the current findings also pertain to other vaccines. Further analysis of additional intracellular cytokines would be beneficial for a more detailed characterisation of the T-cell-mediated immune response. Recent reports show an effect of MTX on the cellular immunity.[24] No clear statement can be made based on our data most likely due to the limited number of patients on csDMARDs.

The most recent EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases recommend that vaccines should ideally be administered before B cell-depleting biological therapy is started or, when patients are on such a treatment already, at least 6 months after the start but 4 weeks before the next course.[27] Our data suggest that a humoral immune response can be obtained once B cells have recovered, which may drive a new vaccination strategy in these individuals. However, since higher levels of peripheral B cells predict an enhanced humoral immune response, delaying RTX treatment in clinically stable patients or waiting for a robust number of peripheral B cells in treated patients with a low risk for COVID-19 may be justified. On the other hand, a T-cell-mediated immunity can be mounted even in the absence of peripheral B cells, indicating that RTX treatment may not have to preclude SARS-CoV-2 vaccination if B cell repopulation is delayed, as happens in some patients.

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High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases

SARS-CoV-2 mRNA vaccination elicited high immunogenicity in immunocompetent people in the original vaccine trials,[1 2] though recent studies have shown blunted immunogenicity in patients with rheumatic and musculoskeletal diseases (RMDs) after a single dose and case reports of non-response after two doses.[3 4] We previously detailed antibody response in patients with RMD following the first dose of SARS-CoV-2 mRNA vaccination and herein report response and factors associated with response to two-dose vaccination in a larger cohort.

As previously reported,[3] patients aged ≥18 years old with RMD were recruited to participate in this prospective, observational cohort via social media outreach to national RMD organisations between 12 July 2020 and 16 March 2021. Demographics, diagnoses and therapeutic regimens were collected via participant report through the Research Electronic Data Capture tool. One month after dose 2 (D2), participants underwent SARS-CoV-2 antibody testing on the semiquantitative Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, which measures total antibody (IgM and IgG) to the SARS-CoV-2 S receptor-binding domain (RBD) protein,[5] the target of the mRNA vaccines. Results range from <0.4 to >250 U/mL with a positive response defined as >0.79 U/mL. Associations were evaluated using Fisher's exact and Wilcoxon rank-sum tests. Participants provided informed consent.

We studied 404 participants who received two doses of the SARS-CoV-2 mRNA vaccine (online supplemental table 1). The median (IQR) age was 44 (36–57), 96% were female, 9% were non-white, 49% received the Pfizer/BioNTech vaccine and 51% received Moderna, 4% had a prevaccination history of COVID-19 diagnosis and no participant reported postvaccination COVID-19 diagnosis. Most common diagnoses included inflammatory arthritis (45%) and systemic lupus erythematosus (22%). The most frequently prescribed medications were hydroxychloroquine (42%) and glucocorticoids (29%), while 51% were on combination therapy. Participants completed anti-RBD testing at a median of 29 days after D2.

Anti-SARS-CoV-2 RBD antibodies were positive in 378/404 (94%) participants (95% CI 91% to 96%) (online supplemental table 1). Median anti-RBD titre was above the upper limit of the assay (>250 U/mL), while lower median titres were observed in participants on regimens including mycophenolate (8 U/mL) and rituximab (<0.4 U/mL) (figure 1, online supplemental table 2). Tumour necrosis factor inhibitor use was associated with a positive antibody response (100% positive, p<0.001), while regimens including mycophenolate (73% positive, p<0.001), rituximab (26% positive, p<0.001) or glucocorticoids (82% positive, p<0.001) and a diagnosis of myositis (79% positive, p=0.01) were associated with a negative response. Of note, 4/5 (80%) negative responders with myositis and 18/21 (86%) negative responders on glucocorticoids were on regimens including mycophenolate or rituximab; all eight on glucocorticoid monotherapy had an anti-RBD titre >250 U/mL.

In this study of humoral response to two-dose SARS-CoV-2 mRNA vaccination in patients with RMD, the vast majority of participants developed anti-RBD antibodies. Among negative responders, most were on regimens containing mycophenolate or rituximab. Glucocorticoid use was also associated with a negative response, though all of these individuals were on concomitant lymphocyte-depleting therapy. Compared with patients with RMD following D1 (74% seroconversion),[3] this study showed increased seroconversion following two-dose vaccination (94% seroconversion). Similarly, seroconversion for those on mycophenolate-based regimens was 73% after two doses compared with 27% after D1, while the response for those on rituximab remained poor (33% seroconversion after D1, 26% seroconversion after D2). Despite a blunted humoral response in participants on these regimens, the rate of seroconversion was comparable with those seen in the original vaccine trials and existing studies on patients with RMD.[1 2 6]

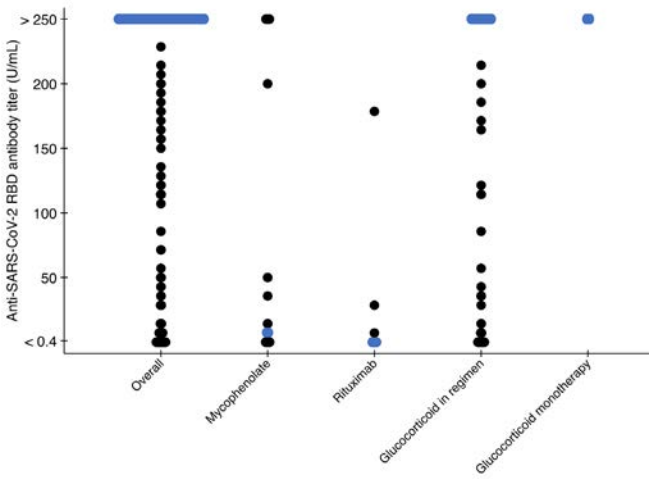

Figure 1 Anti-SARS-CoV-2 RBD antibody titre overall (n=403*) and by medications associated with a negative antibody response: mycophenolate included in regimen (n=41), rituximab included in regimen (n=19), glucocorticoid included in regimen (n=116) and glucocorticoid monotherapy (n=8) in patients with RMD after two-dose SARS-CoV-2 mRNA vaccination. Results range from <0.4 to >250 U/mL with positive antibody defined as an anti-SARS-CoV-2 RBD antibody titre >0.79 U/mL by the manufacturer; blue data points indicate median titre. *One titre value was missing from the total N (404). RBD, receptor binding domain; RMD, rheumatic and musculoskeletal disease.

Limitations of this study include a younger, generally female, racially homogenous population and limited information on immunomodulatory timing and dosage. Additionally, we did not evaluate for asymptomatic COVID-19 infection, and disease activity was not assessed.

While certain lymphocyte-depleting therapies were associated with failure to develop a humoral response, reassuringly, the majority of patients with RMD on a variety of immunosuppressive regimens had a robust antibody response to SARS-CoV-2 mRNA vaccination.

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Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City

Vaccination against SARS-CoV-2 is crucial for patients with systemic rheumatic diseases (SRDs), who may be at increased risk of severe outcomes post-COVID-19.[1] However, as patients with SRDs were not included in the mRNA vaccine trials (ie, Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273)), no data exist regarding whether these vaccines might trigger SRD flares. Sparse data suggest that other vaccines may be associated with SRD flares,[2 3] possibly from molecular mimicry triggering immune activation or non-specific adjuvant effects. As SRD flares are associated with disease deterioration, increased flares could have serious clinical implications.[4]

We report the interim results of a web-based survey evaluating SRD flare incidence post-SARS-CoV-2 vaccine. The survey was e-mailed 5 March 2021 to 3545 outpatients with SRDs seen at a large rheumatology division in New York City. ICD-10 algorithms were used to identify SRDs (online supplemental material). A self-reported disease flare was defined as 'a sudden worsening of your rheumatology condition or arthritis' within 2 weeks of the vaccine.

As of 12 April 2021, out of 1483 respondents (41.8% response rate), 1101 patients (74.2%) with SRDs reported receiving at least one dose of a SARS-CoV-2 vaccine and provided flare data (mean age: 60.8 years (14.2 years); 80.6% female; 86.0% White and 5.7% Hispanic/Latinx ethnicity). Five hundred and ninety seven patients (54.2%) received Pfizer vaccine, 483 (43.9%) received Moderna vaccine, 16 (1.5%) received Janssen vaccine and 3 (0.3%) received AstraZeneca vaccine. A total of 202 SRD flares were reported by 165 patients (14.9%). History of suspected/confirmed COVID-19 occurred in 7.9% with SRD flare and 6.7% without SRD flare. Mean age of patients reporting an SRD flare was 59.6 years (13.9 years) versus 61.0 years (14.2 years) in the non-flare group; the majority of both groups were female (89.7% vs 80.0%), White (88.5% vs 85.6%) and non-Hispanic/Latinx (95.2% vs 92.2%). 15.9% of patients receiving Moderna vaccine and 14.2% receiving Pfizer vaccine reported SRD flares.

Of the patients receiving either Pfizer or Moderna vaccines, 654 (59.4%) had received both doses. Of these patients, 113 (17.0%) flared, 26 (23.0%) flared only after the first dose, 48 (42.5%) flared only after the second dose and 37 (32.7%) flared after both doses. Flares after the first and second dose of Pfizer vaccine were 10.3% vs 10.9%, and flares after the first and second dose of Moderna vaccine were 9.6% vs 16.3%, respectively.

Both the flare and non-flare groups used medications for prevention and treatment of vaccine side effects (table 1). Most SRD flares were characterised as moderate to severe (57.3% after first vs 62.4% after second dose), and as qualitatively 'typical' SRD flares (70.9% after first dose vs 68.2% after second dose). Flares were predominantly reported as joint pain, joint swelling,

Table 1 Vaccine and flare characteristics in outpatients with systemic rheumatic diseases, stratified by flare status post-COVID-19 vaccination

	First dose vaccine N=1101		Second dose vaccine* N=626	
	Flare N=117 (10.4%)	No Flare N=984 (87.5%)	Flare N=85 (13.6%)	No Flare N=541 (86.4%)
Vaccine manufacturer, N%				
Pfizer	67 (57.3%)	530 (53.9%)	35 (41.2%)	285 (52.7%)
Moderna	47 (40.2%)	436 (44.3%)	50 (58.8%)	256 (47.3%)
Janssen	3 (2.6%)	13 (1.3%)	N/A	N/A
AstraZeneca	0 (0%)	3 (0.3%)	0 (0%)	0 (0%)
Other†	0	1 (0.1%)	0	0
Missing	0	1 (0.1%)	0	0
Medications taken for prevention of COVID-19 vaccine side effects (prior to vaccine) (N, %)‡				
No medications	104 (88.9%)	911 (92.6%)	73 (85.9%)	502 (92.8%)
Benadryl	7 (6.0%)	20 (2.0%)	2 (2.4%)	13 (2.4%)
Corticosteroids	2 (1.7%)	7 (0.7%)	3 (3.5%)	4 (0.7%)
Acetaminophen	4 (3.4%)	29 (3.0%)	7 (8.2%)	24 (4.4%)
NSAIDs/CoX-2 inhibitors	4 (3.4%)	22 (2.2%)	1 (1.2%)	11 (2.0%)
Medications taken for treatment of COVID-19 vaccine side effects (after vaccine) (N, %)‡				
No medications	64 (54.7%)	748 (76.0%)	26 (30.6%)	310 (57.3%)
EpiPen	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Benadryl	7 (6.0%)	10 (1.0%)	4 (4.7%)	13 (2.4%)
Corticosteroids	6 (5.1%)	3 (0.3%)	4 (4.7%)	5 (0.9%)
Acetaminophen	29 (24.8%)	152 (15.5%)	36 (42.4%)	166 (30.7%)
NSAIDs/CoX-2 inhibitors	25 (21.4%)	82 (8.3%)	31 (36.5%)	76 (14.1%)
Flare severity (N, %)				
Mild	50 (42.7%)		32 (37.7%)	
Moderate	49 (41.9%)		44 (51.8%)	
Severe	18 (15.4%)		9 (10.6%)	
Flare described as 'typical' (N, %)				
Yes	83 (70.9%)		58 (68.2%)	
No	18 (15.4%)		16 (18.8%)	
Not sure	16 (13.7%)		11 (12.9%)	
Flare symptoms (N, %)‡				
Fever	6 (5.1%)		9 (10.6%)	
Joint pain	98 (83.8%)		74 (87.1%)	
Joint swelling	56 (47.9%)		38 (44.7%)	
Skin rash	14 (12.0%)		10 (11.8%)	
Fatigue	62 (53.0%)		57 (67.1%)	
Muscle aches	57 (48.7%)		48 (56.5%)	
Other§	16 (13.7%)		11 (12.9%)	
Number of days after vaccine when flare started (N, %)				
1 day	30 (25.6%)		26 (30.6%)	
2–3 days	39 (33.3%)		26 (30.6%)	
4–7 days	35 (29.9%)		24 (28.2%)	
>7 days	13 (11.1%)		9 (10.6%)	
Length of flare (N, %)				
1 day	7 (6.0%)		2 (2.4%)	
2–4 days	23 (19.7%)		40 (47.1%)	
5–7 days	41 (35.0%)		16 (18.8%)	
8–21 days	28 (23.9%)		25 (29.4%)	
>21 days	18 (15.4%)		0 (0%)	
Missing	0		2 (2.4%)	

Flare defined as self-reported 'sudden worsening of rheumatology condition or arthritis' within 2 weeks of COVID-19 vaccination.
*654 patients reported receiving 2/2 vaccine doses, but 28 of these patients did not respond to second dose flare questions.
†One participant reported receiving Sinovac vaccine from China.
‡Rows not mutually exclusive.
§Other flare symptoms indicated by patients at first COVID-19 vaccine dose: paresthesias, swelling in face or feet, 'brain fog', muscle spasms, psoriasis rash, migraines. Other symptoms at second vaccine dose: paresthesias, swelling in face or feet, and muscle spasms.
CoX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammtory drugs.

muscle aches and fatigue (table 1). While 27.7% of flares started 1 day after vaccination, 61.4% began after 2–7 days and 10.9% occurred more than 7 days later (table 1). Most SRD flares resolved within 7 days of onset, but 26.2% lasted for 8–21 days and 8.9% for >21 days.

Interim data from our cohort demonstrate that >85% of patients did not report an SRD flare post-SARS-CoV-2 vaccination. This information is reassuring and can help inform vaccine decision-making for patients with SRDs. Although we did not collect laboratory studies, most SRD flares were described as 'typical', suggesting these symptoms are not vaccine's adverse effects being misreported as disease flares. However, when patients did flare, the majority of flares were reported as moderate to severe, with some lasting >3 weeks. Therefore, it will be important to follow these patients prospectively, as well as to perform analyses which incorporate potential confounders to identify predictors of SRD flares post-vaccination. Whether vaccine manufacturer is an independent predictor of SRD flare remains to be determined.

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SARS-COV-2 vaccination after stem cell transplantation for scleroderma

Autologous haematological stem cell transplantation (AHSCT) for rapidly progressive severe systemic sclerosis (SSc) is the only treatment, so far, allowing long-term improvement in overall and event-free survival.[1 2] The COVID-19 pandemic has challenged

Table 1 SARS-CoV-2 vaccination after haematological autologous stem cell transplantation for systemic sclerosis

Patient	1	2	3	4	5	6	7	Average
Age	69	59	56	39	43	49	37	50.2±11
Sex	F	F	F	F	M	F	F	86% F
Serology	Scl-70	RNAPOLIII	RNAPOLIII	Scl-70	Scl-70	Scl-70	Scl-70	
mRSS baseline	33	21	31	28	15	30	6	23±9
Lung fibrosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Cardiac involvement	No	No	No	No	Yes	Yes	Yes	
Treatment before AHSCT	CYC	MMF	MTX +MMF	MMF	MMF	MMF +ritux	MMF +ritux	
Time from AHSCT (months)	60	48	30	24	18	12	**3**	Median 24 m
Conditioning								
Cyc (total dose)	200 mg/kg	200 mg/kg	200 mg/kg	200 mg/kg	120 mg/kg	120 mg/kg	**120** mg/kg	
Influenza (total dose)	No	No	No	No	90 mg/m2	90 mg/m2	90 mg/m2	
Rabbit ATG	6 mg/kg	6 mg/kg	6 mg/kg	6 mg/kg	6 mg/kg	6 mg/kg	6 mg/kg	
CD 34+ selection	No	No	No	No	No	No	Yes	
Time to engraftment (days)	9	10	9	15	12	11	10	
Day of vaccination:								
-CD 20+ cells/mm^3 (% of lymphocytes) Normal >1%	100 (8%)	204 (15%)	152 (10%)	386 (14%)	161 (12%)	232 (11%)	220 (22%)	207±90 (13±4.5%)
-CD 4+ (cells/mm^3)	266	480	332	990	219	370	95	393±290
Adverse response	Tiredness	No	No	No	No	No	No	
SARS-COV-2 IgG AB	Yes	Yes	Yes	Yes	Yes	Yes	No	86%
Titres igG AU/mL Vaccinated (>150 AU/mL)	21 187	3903	5567	3460	24 861	5830	<21	9258±9653
Healthy controls	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Age	63	59	55	44	40	54	34	49.8±10
Sex	F	F	F	F	M	F	F	86% F
-CD 20+ cells/mm^3 (% of lymphocytes) Normal >1%	168 (12%)	234 (9%)	124 (10%)	257 (10%)	153 (10%)	206 (9%)	98 (10%)	177±58 (10%±1%)
CD 4+ (cells/mm^3)	619	1564	587	1158	690	1422	551	921±446
Adverse response	No	No	No	No	No	No	No	
SARS-COV-2 IgG AB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Titers igG AU/mL vaccinated (>150 AU/mL)	8718	60 000	24 739	3958	3274	11 167	9530	17 340±18.6

Serum antibodies after vaccination against s1 protein were evaluated by chemiluminescent microparticle immunoassay against s1 subunit of the spike protein using Abbott architect system.
AHSCT, autologous haematological stem cell transplantation; ATG, rabbit antithymocyte globulins; cyc, cyclophosphamide; F, female; flu, fludarabine; M, male; MMF, mycophenolate mofetil; mRSS, modified Rodnan Skin Score; MTX, methotrexate; ritux, rituximab; RNAPOLIII, RNA polymerase III; SCL-70, scleroderma70.

experts regarding decisions on AHSCT in these high-risk patients.[3] Increased risk for severe COVID-19 infection in SSc is related to lung and heart involvement[4] and is enhanced by high-dose immunosuppressive drugs and antithymocyte globulins used for conditioning to eliminate autoreactive cells before AHSCT and to allow reset of tolerance during the immune reconstitution period, lasting around 12 months after transplant.[1 3] Several centres have stopped AHSCT activity for SSc during the pandemic for safety considerations. Others decided to continue, believing that the benefit of AHSCT is greater than the risk of severe COVID-19 19 infection. This belief was reinforced with the introduction of SARS-COV-2 vaccines. Current european bone marrow transplantation (EBMT) guidelines recommend vaccination against SARS-COV-2, as early as 3 months after transplantation[3 5] .

Israel has been the first country worldwide to implement a national vaccination plan using the Pfizer BNT162b2 vaccine since January 2021 and 85% coverage of the adult population had been obtained in April 2021.

We report herein our experience with SARS-COV-2 vaccination in all seven adult patients with SSc treated by AHSCT in Israel, since we started the programme in 2016, compared with seven sex and aged matched healthy controls. Each patient received two doses of BNT162b2 Pfizer vaccine on days 0 and 21 (table 1), within 3–60 (median 24) months after AHSCT. No adverse reactions were reported, except fatigue lasting 2 days in patient 1.

We measured SARS-COV-2 IgG antibodies by chemiluminescent microparticle immunoassay against s1 s1 subunit of the spike protein using Abbott architect system 2 weeks after the second injection. The seven patients had normal CD20+ cell counts at time of vaccination. All but one patient, transplanted with CD34+ selected AHSCT 3 months before vaccination, who had low (95 cells/mm^3) CD4+ T cell count at time of vaccination, mounted a humoral response. All healthy controls mounted a humoral response.

CD4+ TH1-biased T-cells are important for mounting a response after vaccination.[6] The use of CD34+ selection favours treatment response but may contribute to the degree and duration of T-cell depletion after transplant which is dependent also on conditioning regimen.[1]

In conclusion, this report provides the first evidence of efficacy of SARS-COV-2 vaccination after AHSCT for SSc. Only one patient with low CD4 counts (below 200 cells/mm^3) after CD34 selection did not mount an immune response to vaccination. Systematic monitoring of immune reconstitution stage and vaccine response after AHSCT is of utmost importance to guide the time frame at which patients should be vaccinated.

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SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response

Treatment with rituximab (RTX), a monoclonal antibody targeting CD20, constitutes an important therapeutic strategy for patients with inflammatory rheumatic diseases. Some recent reports have already highlighted the risk of SARS-CoV-2 infection in patients treated with RTX.[1–4] Besides the risk of a more severe disease course during B cell depleting therapy, a major concern relates to a risk of reduced immunogenicity of vaccination. Therefore, the question arises if patients should withhold or interrupt RTX therapy around COVID-19 vaccination or delay vaccination. To address this question, we have assessed antibody response and T cell mediated immune response to the BNT162b2 (Pfizer/BioNTech) vaccine in patients undergoing RTX treatment at the end of the treatment interval.

Five patients under regular and recent RTX treatment were selected for COVID-19 vaccination with BNT162b2 (Pfizer/BioNTech). A detailed description of the methods and the patient characteristics (online supplemental table S1) can be found in the online supplemental material. The last RTX infusion was administered between 4 and 12 months ago (online supplemental figure S1). At the time of the vaccination, peripheral $CD19^+$ B cells could only be detected in two patients (online supplemental table S2). Antibodies against the SARS-CoV-2 nucleocapsid (NC) and the receptor-binding domain (RBD) of the spike protein were analysed 12–23 days following the second

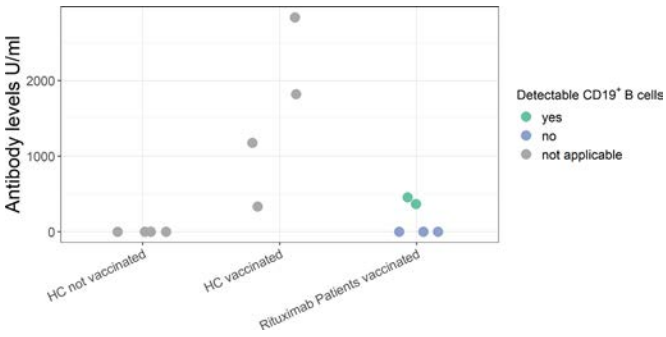

Figure 1 Humoral immune response in rituximab-treated patients. Antibodies to the receptor-binding domain (RBD) of the viral spike (S) protein was determined using an anti-SARS-CoV-2 S immunoassay. Rituximab-treated patients with detectable $CD19^+$ peripheral B cells are labelled green. Patients with no peripheral B cells are labelled in blue. Vaccinated and not vaccinated healthy individuals served as a positive and negative control group. HC, healthy controls.

dose of BNT162b2. Sex-matched healthy individuals who had received two vaccinations with BNT162b2 (n=4) and unvaccinated healthy individuals (n=4) served as controls. No antibodies against the NC were detected in either group, implying no prior SARS-CoV-2 infection (data not shown). In three patients, no antibodies against the RBD were detected. Interestingly, in two patients with detectable $CD19^+$ B cells, we determined a positive antibody response against the SARS-CoV-2 RBD, suggesting the development of a humoral immune response once peripheral B cells are repopulated (figure 1).

To determine a SARS-CoV-2 specific T cell reactivity, we measured interferon (IFN)-γ response to SARS-CoV-2 peptides in our patient cohort and control groups. All groups showed IFN-γ secretion on non-specific T cell stimulation of heparinised whole blood with mitogen. After stimulation with two different SARS-CoV-2 specific antigen mixes, IFN-γ response could be detected in the vaccinated healthy control group as well as in the patient cohort, independent of the humoral immune response (online supplemental figure S2). Of note, lower levels of IFN-γ were detected in one patient who concomitantly received intermediate prednisone dose.

In the current report, we could demonstrate that B cell depleting therapy with RTX affects the humoral immune response to SARS-CoV-2 vaccination in B cell depleted patients. However, humoral immune response was observed in patients who had measurable peripheral B cells following RTX treatment. These data are in line with very recent reports showing that RTX treatment might affect the antibody response to SARS-CoV-2 vaccination.[5 6] However, we could here reveal a T cell mediated immune response even in B cell depleted patients. It will be important to understand if T cell immunity is important or possibly even sufficient to protect patients against infection with the virus on vaccination. Our data also indicate that RTX treatment may not have to preclude SARS-CoV-2 vaccination, since a cellular immune response will be mounted even in the absence of circulating B cells. Alternatively, in patients with stable disease delaying RTX treatment until after the second vaccination may be warranted and, therefore, vaccines with a short interval between first and second vaccination or those showing full protection after a single vaccination may be preferable. Importantly, in the presence of circulating B cells also a humoral immune response may be expected despite prior RTX therapy.

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Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases

There is a paucity of data on the effect of antirheumatic drugs on serological responses to COVID-19 vaccines. Anti-CD20 therapies deplete B-cells, with reconstitution often not beginning for 6–9 months after infusion, resulting in diminished humoral immune responsiveness to recall antigens.[1–6] We retrospectively assessed response to COVID-19 vaccination in rheumatic disease patients treated with a variety of antirheumatic medications including rituximab.

A retrospective chart review of adult patients from one rheumatology practice who received at least one dose of a COVID-19 vaccine was performed. Data were collected from patients who had a clinic visit from 24 February 2021 to 8 April 2021 and were serologically screened for antibodies to the SARS-CoV-2 Spike protein.

Serological response to vaccination was assessed using a semi-quantitative anti-SARS-CoV-2 enzyme immunoassay.

Vaccination responsiveness was compared between patients receiving various antirheumatic medications. In patients treated with rituximab time between most recent administration of drug and vaccination was recorded. Exposure to rituximab was defined as having ever been treated, however, all patients were within 4.5 years (median (IQR) 0.70 (0.41–1.74)) years of last exposure. B-cell reconstitution at time of anti-SARS-CoV-2 antibodies measurement was documented, when available, for rituximab-treated patients.

Primary outcome was the presence of a serological response to COVID-19 vaccination. Descriptive statistics, box plots and bivariate comparisons using Fisher's exact test, Student's t-test and Wilcoxon rank sum tests were performed. An alpha of 0.05 was used to assess statistical significance.

Eighty-nine patients met criteria for inclusion. Eighty-three subjects (93.26%) had received both doses of a COVID-19 vaccine at the time of immunoassay. Thirty patients (34%) were treated with rituximab. Thirty-five patients (39%) were taking more than one antirheumatic medication at time of assessment (table 1).

A majority of the serologically negative results were among patients using rituximab (20/21), with the only other serologically negative patient having been treated with belimumab.

Among rituximab users, there was a significant difference in the number of days between those with a positive serological response (median, IQR 704.5 (540–1035) days) compared with those with a negative response (median, IQR 98 (64-164) days) ($p<0.001$) (figure 1A). B-cell reconstitution was available for 11 patients and there was a significant difference among those with a positive serological response (N=7) compared with those with a negative response, (N=4) ($p=0.026$) (figure 1B). When B-cell reconstitution is dichotomised, there is a statistical significance among those with a positive serological response (N=7) compared with those with a negative response ($p=0.024$).

In this study, all patients who did not demonstrate a positive serological response had been treated with rituximab, with the exception of one patient that was treated with belimumab, another B-cell targeting strategy. Longer duration from most recent rituximab exposure was associated with a greater likelihood of response. The results suggest that time from last rituximab exposure is an important consideration in maximising the likelihood of a serological response, but this likely is related to the substantial variation in the period of B-cell depletion following rituximab. In many cases, the duration of B-cell depletion and observed lack of vaccine responsiveness was longer than what is recommended in some current guidelines, and longer than the traditional interval between rituximab doses in remission maintenance regimens in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, or in the treatment of rheumatoid arthritis. Confirming B-cell reconstitution before vaccination may increase the likelihood of a positive serological response.

Patients who had even weak levels of B-cell reconstitution had higher rates of seropositive responses to vaccines, while B-cell depleted patients invariably demonstrated a negative serological response to vaccination. Importantly, absence of a detectable antibody response to COVID-19 vaccines does not imply absence of improved immunity relative to prior to vaccination in those patients, recognising that other facets of immunity may be enhanced by vaccination.[5]

Strengths of our study include the largest cohort of rituximab treated patients in whom vaccine responsiveness was assessed reported to date. Limitations of the study include small sample size and being retrospective.

These data, if confirmed in larger cohorts, could have important clinical implications regarding timing of vaccination in rituximab exposed patients. In communities with limited access to COVID-19 vaccines, confirming B-cell reconstitution prior to vaccine administration may be prudent.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Table 1 Bivariate comparisons of serological responsiveness to the COVID-19 vaccine

	Overall	Negative for antibody response	Positive for antibody response	
Factor	**N (%)**	**N (%)**	**N (%)**	**P value***
N	89	21	68	
Age, mean (SD)	61.3034 (16.081)	65.4286 (15.0916)	60.0294 (16.2692)	0.18†
Sex				0.38
Female	68 (76%)	18 (86%)	50 (74%)	
Male	21 (24%)	3 (14%)	18 (26%)	
Race				0.19
White	84 (94%)	19 (90%)	65 (96%)	
Black or African American	2 (2%)	0 (0%)	2 (3%)	
Asian	3 (3%)	2 (10%)	1 (1%)	
Primary diagnosis				
RA	23 (26%)	2 (10%)	21 (31%)	0.084
Systemic lupus erythematosus	9 (10%)	2 (10%)	7 (10%)	1.00
Sjogrens syndrome	10 (11%)	3 (14%)	7 (10%)	0.69
Systemic sclerosis	5 (6%)	3 (14%)	2 (3%)	0.083
Psoriatic arthritis	6 (7%)	0 (0%)	6 (9%)	0.33
Granulomatosis with polyangiitis	12 (13%)	6 (29%)	6 (9%)	0.031
Giant cell arteritis	2 (2%)	0 (0%)	2 (3%)	1.00
Polymyalgia rheumatica	3 (3%)	1 (5%)	2 (3%)	0.56
Microscopic polyangitis	4 (4%)	2 (10%)	2 (3%)	0.24
IgG4 disease	1 (1%)	1 (5%)	0 (0%)	0.24
Behcet's disease	2 (2%)	0 (0%)	2 (3%)	
Dermatomyositis	1 (1%)	0 (0%)	1 (1.5%)	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	1 (1%)	0 (0%)	1 (1.5%)	
Familial mediterranean fever	1 (1%)	0 (0%)	1 (1.5%)	
Mixed connective tissue disease	1 (1%)	0 (0%)	1 (1.5%)	
Osteoarthritis	1 (1%)	0 (0%)	1 (1.5%)	
Relapsing polychondritis	2 (2%)	1 (5%)	1 (1.5%)	
Retinal vasculitis	2 (2%)	0 (0%)	2 (3%)	
Systemic lupus erythematosus/rheumatoid arthritis overlap syndrome	1 (1%)	0 (0%)	1 (1.5%)	
Undifferentiated connective tissue disease	2 (2%)	0 (0%)	2 (3%)	
Vaccine type				1.00
Pfizer	51 (57%)	12 (57%)	39 (57%)	
Moderna	38 (43%)	9 (43%)	29 (43%)	
COVID-19 antibody assay				
Roche elecsys anti-SARS-CoV-2	84 (94.38%)	–	–	
Siemens healthineers SARS-CoV-2 Total Assay Atellica IM or ADVIA Centaur XP/XPT‡	5 (5.62%)	–	–	
Days from last rituximab exposure to assay among Rituximab treated patients, median (IQR), (n=30)	212 (122, 599)	153 (114, 212)	762 (599, 1064)	<0.001
Days from last rituximab exposure to second dose of COVID-19 vaccine among rituximab-treated patients, median (IQR), (n=30)	167 (79, 540)	102 (66, 167)	705 (540, 1035)	<0.001
Time from last rituximab exposure to second dose of COVID-19 vaccine among Rituximab treated patients (n=30)§				
<6 months	16 (53%)	16 (80%)	0 (0%)	<0.001
6–12 months	4 (13%)	3 (15%)	1 (10%)	
>12 months	10 (33%)	1 (5%)	9 (90%)	
Prior documented COVID infection	2 (2%)	–	–	
Medications ¶	Number and percentage of overall group	Number and percentage of group negative for antibody response	Number and percentage of group positive for antibody response	
Patients with rituximab exposure in combination with other therapy	15 (17%)	10 (48%)	5 (7%)	1.00
Patients without rituximab exposure treated with two or more medications	20 (22%)	1 (4%)	19 (28%)	0.34
Patients on two or more medications	35 (39%)	11 (52%)	24 (35%)	0.20
Non-Steroidal Anti-inflammatory Drugs	6 (7%)	0 (0%)	6 (9%)	0.33
Corticosteroids	17 (19%)	5 (24%)	12 (18%)	0.54
Non-biological DMARD **				
Sulfasalazine	1 (1%)	0 (0%)	1 (1%)	1.00
Leflunomide	3 (3%)	1 (5%)	2 (3%)	0.56

Continued

Table 1 Continued

Factor	Overall N (%)	Negative for antibody response N (%)	Positive for antibody response N (%)	P value*
Hydroxychloroquine	19 (21%)	2 (10%)	17 (25%)	0.22
Azathioprine	3 (3%)	0 (0%)	3 (4%)	1.00
Upadacitinib	2 (2%)	0 (0%)	2 (3%)	1.00
Methotrexate	13 (15%)	1 (5%)	12 (18%)	0.29
Apremilast	1 (1%)	0 (0%)	1 (1%)	1.00
Mycophenolate mofetil	7 (8%)	3 (14%)	4 (6%)	0.35
Tofacitinib	4 (4%)	0 (0%)	4 (6%)	0.57
Colchicine	3 (3%)	0 (0%)	3 (4%)	1.00
Biological DMARDs				
Adalimumab	8 (9%)	0 (0%)	8 (12%)	0.19
Secukinumab	2 (2%)	0 (0%)	2 (3%)	1.00
Mepolizumab	1 (1%)	0 (0%)	1 (1%)	1.00
Tocilizumab	2 (2%)	1 (5%)	1 (1%)	0.42
Etanercept	1 (1%)	0 (0%)	1 (1%)	1.00
Abatacept	1 (1%)	0 (0%)	1 (1%)	1.00
Belimumab	2 (2%)	1 (4.76%)	1 (1.47%)	0.42
Rituximab	30 (34%)	20 (95%)	10 (15%)	<0.001
Antibody concentration (U/mL) in rituximab-treated patients (n=30), median (IQR)	–	0 (0, 0)	251 (169, 251)	<0.001††

*All p values were calculated from a Fisher's exact test unless otherwise indicated.
†T-test was used.
‡Roche Elecsys Anti-SARS-CoV-2, specificity 99.8% sensitivity 99.5%, or a Siemens Healthineers SARS-CoV-2 total (COV2T) Assay Atellica IM, specificity 99.82% sensitivity 100% or ADVIA Centaur XP/XPT, specificity 99.81% sensitivity 100%.
§Among the four people who were negative, the specific number of days from last infusion to first vaccination were 188, 229, 230, 415.
¶Medications are not mutually exclusive. 35 (39%) patients are taking two or more medications.
**Includes both conventional and targeted synthetics.
††Wilcoxon rank sum test was used.
DMARDS, disease modifying antirheumatic drugs.

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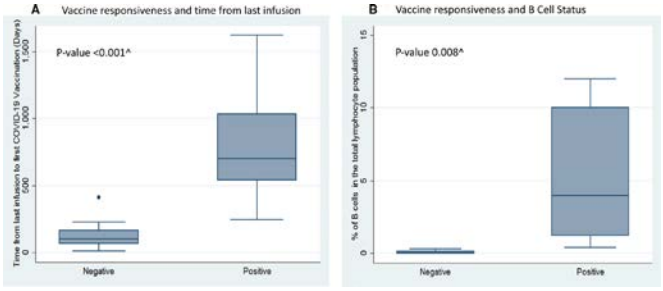

Figure 1 (A) Among patients treated with rituximab with a negative serological response (N=20), the median IQR of days from last infusion to first vaccination was 98 (64–164) days. Patients with a positive serological response (N=10) had a median IQR of 704.5 (540–1035) days. Wilcoxon rank sum test was used to calculate the p value. (B) Among N=11 people with % B-cells available, four were serologically negative and seven were serologically positive. The percentage of B-cells among the negative serological response median IQR=0 (0–0.15). Among the positive serological vaccine response group, the median (IQR) is 4 (1.2–10). The p value is from the Wilcoxon rank sum test. The y-axis is the percentage of B-cells in the total lymphocyte population as measured by flow cytometry.

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Pause in immunosuppressive treatment results in improved immune response to SARS-CoV-2 vaccine in autoimmune patient: a case report

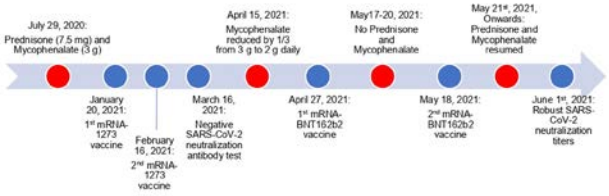
Patients on immunosuppressive drugs have been excluded from studies of SARS-CoV-2 mRNA vaccines' (mRNA-BNT162b2 and mRNA-1273) clinical trials that resulted in their Emergency Use Authorization in the USA and Europe. Since the initiation of the global vaccination campaign, it became apparent that patients on immunosuppressive drugs may not generate optimal immune response following vaccination.[1] Prednisone and mycophenalate are potent inhibitors of immune responses. Prednisone acts at many levels of immunity including the innate and

adaptive responses, whereas mycophenalate mainly targets T and B cells.[2] These and other immunosuppressive drugs used to treat patients with autoimmune disorders and organ transplant patients were shown to significantly curtail antibody responses following SARS-CoV-2 mRNA vaccines.[3–5]

We report on a 75-year-old male patient with an underlying autoimmune disorder, myasthenia gravis, which was controlled after receiving high doses of prednisone and mycophenalate for 9 months. At his first SARS-CoV-2 vaccination, he was receiving 7.5 mg prednisone on alternate days and 3 g mycophenalate daily (figure 1A). He received two doses of Moderna mRNA-1273 vaccine with a 4-week interval between doses. Neutralisation titres were measured using a pseudovirus neutralisation assay (PsVNA) as described previously.[6] No SARS-CoV-2 neutralising antibodies were detected in plasma at 4 weeks after the second mRNA-1273 vaccination. In the same assay, age-matched (65–77 years old) immunocompetent individuals (healthcare workers who were not on any immunosuppressive drugs and vaccinated with two doses of mRNA-1273 SARS-CoV-2 vaccine in Maryland) generated neutralising antibody titres (PsVNA50: 50% reduction in neutralisation titres) ranging between 1:451 and 1:3293 against the WA-1 strain following mRNA-1273 vaccination.

The patient was able to receive a second series of vaccinations with the Pfizer mRNA-BNT162b2 at 42 days and 63 days (first and second dose, respectively) following the last vaccination with mRNA-1273. Three weeks prior to the first dose of mRNA-BNT162b2, the mycophenalate dose was reduced from 3 g to 2 g daily. The day prior to the second dose with mRNA-BNT162b2 and for 3 subsequent days, the patient did not take any prednisone or mycophenalate. Thereafter (3 days post-second vaccination), the maintenance dose of 7.5 mg prednisone on alternate days and 2 g mycophenalate daily was resumed (figure 1A). No change in his clinical status related to the myasthenia gravis was observed during the study. Two weeks after the second mRNA-BNT162b2 vaccination, the patient's plasma was used to measure virus neutralisation against SARS-CoV-2 vaccine-matched WA-1 strain and multiple variants of concern. Robust virus neutralising antibody titres were measured with the highest titre against the vaccine-matched WA-1 strain and lowest against the B.1.351 SARS-CoV-2 variant strain (figure 1B).

A



B

Neutralization titers (PsVNA50) of post-vaccination plasma against SARS-CoV-2 and variants of concern

SARS-CoV-2 strain	D0 (pre-vaccine)	D56 (Post-2nd mRNA1273 vaccination)	D133 (post-2nd mRNA-BNT162b2 vaccination)
WA-1	<20	<20	4269.9
B.1.1.7	<20	<20	1589.7
P.1	<20	<20	850.6
B.1.617.1	<20	<20	423.8
B.1.351	<20	<20	290.5

Figure 1 Effect of drug treatment and SARS-CoV-2 vaccination-induced immune response in a patient with myasthenia gravis. (A) Timeline of drug treatment profile and SARS-CoV-2 vaccination of the patient with myasthenia gravis. (B) SARS-CoV-2 neutralising antibody titres as determined by pseudovirus neutralisation assay (PsVNA) in 293-ACE2-TMPRSS2 cells with SARS-CoV-2 WA-1 strain, UK variant (B.1.1.7), Japan variant (P.1), Indian variant (B.1.617.1) or South African variant (B.1.351) as described previously.[6] PsVNA50 (50% neutralisation titre) titre values are shown.

This case study exemplifies a strategy that could lead to better immune responses following SARS-CoV-2 vaccination in patients on prolonged immunosuppressive drugs. It is possible that the additional vaccination series received by the individual in this report may have been sufficient without reducing the immunosuppressive medications. Indeed, this approach is being evaluated in ongoing trials. In this regard, Werbel *et al*[7] reported that 24 of 30 (80%) of organ transplant recipients on multiple immunosuppressive regiments showed no receptor-binding domain (RBD) antibody binding response after the first vaccination series with mRNA vaccines. Among those, 67% were still seronegative for SARS-CoV-2 RBD antibodies following a third vaccination with no treatment modification.[7]

Therefore, if the virus neutralisation titres after SARS-CoV-2 vaccination are undetectable or low, it may be reasonable to consider temporary supervised reduction in the dose of immunosuppressive drugs prior and during the time of a second vaccination, to allow recovery of B and T cell function and a robust immune response to vaccination. This may be associated with risk that autoimmune diseases may relapse, or transplant rejection may occur. Careful studies need to be performed to determine whether the risk:benefit profile favours a temporary decrease in immunosuppressive drugs to allow for a successful SARS-CoV-2 vaccination-induced immune response against COVID-19.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the US Food and Drug Administration's (FDA) Research Involving Human Subjects Committee (FDA-RIHSC-2020-04-02 (252)). This study complied with all relevant ethical regulations for work with human participants, and informed consent was obtained. Samples were collected from individual who provided informed consent to participate in the study. The participant consented and is a coauthor and helped write the manuscript. All assays performed fell within the permissible usages in the original informed consent.

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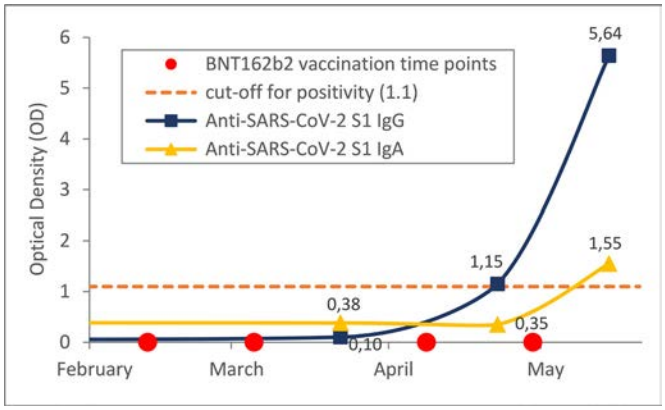

Figure 1 IgG and IgA antibody measurements against the SARS-CoV-2 spike protein (S1 domain) were performed with a semiquantitative ELISA by Euroimmun and showed a positive response after repeated vaccinations. In addition (not shown), neutralising antibodies assessed with a plaque reduction neutralization test (PRNT) were negative after the third and positive after the fourth vaccination ($PRNT_{50}$ 1:160; $PRNT_{90}$ 1:40). T-cell response against SARS-CoV-2 measured with a lymphocyte transformation test by IMD Berlin was only measured after the fourth vaccination and showed a positive result. Antibodies against SARS-CoV-2 nucleocapsid measured with an ELISA by Roche remained negative.

Successful BNT162b2 booster vaccinations in a patient with rheumatoid arthritis and initially negative antibody response

The COVID-19 pandemic poses unique challenges regarding the optimal care of patients with rheumatic diseases, who may have an increased risk of infection and hospitalisation. It is therefore highly important to ensure successful vaccination of these patients.[1] The messenger RNA vaccine BNT162b2 (Comirnaty by BioNTech/Pfizer) against SARS-CoV-2 strongly reduces infection, transmission, hospitalisation and death in immunocompetent patients. The development of neutralising antibodies after vaccination has been associated with protection from COVID-19.[2] However, a decreased immunogenicity of several vaccines has been described under immunosuppressive medication,[3] and first reports seem to confirm reduced antibody responses after vaccinations against SARS-CoV-2 in patients on some immunosuppressive medications (e.g. in one preprint rituximab, glucocorticoids and possibly JAK inhibitors).[4] This led rheumatologists to address the question of how to deal with patients who show insufficient immunogenicity after vaccination.

In this letter, we describe a case with an initially negative antibody response and seroconversion after repeated booster vaccinations without interruption of immunosuppressive medication. The patient is a 54-year-old man, with a body mass index of 30.7 kg/m². He suffers from seropositive rheumatoid arthritis (RA, since 2013), polycythemia vera and had a leucocytoclastic vasculitis in 2020, confirmed by skin biopsy, which was successfully treated with an initial dose of 100 mg prednisolone. The prednisolone dose was then decreased to 5 mg/day and eventually stopped five days before the first vaccination. Leucocytoclastic vasculitis and polycythemia vera were in remission throughout the vaccination periods. The RA had been highly active in 2020, but remained with low disease activity (Disease Activity Score 28-C reactive protein ≤3.2) since January 2021 and throughout the vaccinations under treatment with upadacitinib 15 mg/day and methotrexate 10 mg/week, both since January 2021. Both medications were not paused for the vaccinations because the risk of recurrence of disease activity was considered high, and methotrexate was even increased to 12.5 mg/week between the second and third vaccination. Previous medications included anti-tumour necrosis factor-α antibodies, but not rituximab.

After the first vaccination, the patient suffered from fever, nausea, weakness, tiredness and headache for 5 days. After the second vaccination, he described tiredness for 2 days. Antibody titres against SARS-CoV-2 spike protein did not show a titre increase from earlier testing in May 2020 to 14 days after the first two vaccinations with BNT162b2. The patient then received an additional cycle of two vaccinations with the same vaccine in a standard dose outside of our care, which led to IgA and IgG seroconversion and development of neutralising antibodies until 15 days after the fourth vaccination (figure 1). He reported only mild tiredness for 1 day after the third and fourth vaccination.

Of course, a delayed antibody response to the first two vaccinations or the longer interval between the first and fourth vaccination may have contributed to the response in this case. It is also possible that a significant T-cell response already existed after the first two vaccinations, given the clinical reactogenicity. However, after hepatitis B virus vaccinations, testing for antibodies and booster injections have been advised for immunocompromised patients with low titres of protective antibodies independent of T-cell responses.[5] Currently, American College of Rheumatology guidance does not recommend routine measurement of

antibody titres after SARS-CoV-2 vaccination,[1] and it remains unclear how to best interpret the results. The German Rheumatology Association acknowledged in a recent statement that booster vaccinations may have to be considered in patients who do not show sufficiently high or long-lasting titres of neutralising antibodies,[6] but this remains subject to an ongoing debate. Our case demonstrates that booster vaccinations in patients with an initially negative antibody response may induce a positive antibody response even without pausing immunosuppression.

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Antibody response to SARS-CoV-2 in patients receiving glucocorticoids with or without tocilizumab for COVID-19-associated hyperinflammation

Several immune mechanisms resembling a hyperinflammatory state have been critically involved in the pathophysiology of severe COVID-19, motivating the use of immunomodulatory therapies in the management of these patients. Various studies have already suggested the efficacy of immunomodulatory medication of treatment for severe COVID-19.[1–3] However, concerns have been raised about the impact of these therapies on immunity.[4 5] We analysed the presence and levels of antibodies to SARS-CoV-2 in patients recovered from severe COVID-19-associated hyperinflammation after receiving no immunomodulatory therapy, and compared them to patients who received methylprednisolone alone or methylprednisolone followed by tocilizumab.

Between March and May 2020, 197 patients were diagnosed with COVID-19-associated hyperinflammation in the Zuyderland Medical Centre. In order to meet the criteria for hyperinflammation, patients had to fulfil specific characteristics that have been previously reported in this journal.[1]

Up to the 1st of April, patients were treated with standard of care. In April and May, patients were treated according to the COVID-19 high-intensity immunosuppression in cytokine storm syndrome (CHIC) protocol with immunomodulatory therapies. This protocol included two steps: (1) high-dose intravenous methylprednisolone 250 mg on day 1, followed by methylprednisolone 80 mg intravenously on days 2–5, and an option for a 2-day extension; (2) in case of no recovery after 48 hours, escalation with tocilizumab (single-dose tocilizumab, 8 mg/kg body weight intravenous, max 800 mg).[1]

Total antibodies to SARS-CoV-2 were measured in 117 recovered patients (79.5% male, median age 64 (SD 11.4) after a median of 3 months (IQR 1), 2 months (IQR 1) and 3 months (IQR 2) after onset of symptoms in the standard of care group, methylprednisolone group and in the methylprednisolone with tocilizumab group, respectively. Seventy patients died before follow-up.

Baseline demographic characteristics and clinical status during admission of three groups were similar (data not shown). Antibodies (IgG and IgM) to SARS-CoV-2 were measured using WANTAI SARS-CoV-2 Ab enzyme-linked immunosorbent assay (Wantai Biological Pharmacy, China). This test is considered negative if the WANTAI-Index is $\leq$0.9 and positive if the WANTAI-Index is $\geq$1.1. A WANTAI-Index between 0.9 and 1.1 is considered borderline and retesting is required. The highest detectable WANTAI-index is 18. The sensitivity of this test is 95% and the specificity 100%.[6]

Neutralising antibodies were not measured.

The levels of antibodies were compared across groups with the Kruskal-Wallis test. The differences between groups of having a WANTAI-Index of 18 or <18 were compared with the χ^2 test and logistic regression analyses were used to compute predicted probabilities thereof adjusted for potential confounders.

Median WANTAI-Index in all treatment groups was 18 (IQR 0). Antibody levels were not different across the three treatment groups (p=0.486).

Ninety-one percent (106/117) of patients had the highest detectable WANTAI-Index of 18. There were no differences

Table 1 Frequency of the highest titre of antibodies (WANTAI-index of 18) in 3 treatment groups (standard care/ no immunomodulatory therapy, methylprednisolone, methylprednisolone followed by tocilizumab), and predicted probabilities thereof adjusted for possible demographic and clinical confounders

	Standard care/ no immunomodulatory therapy (N=51)	Methylprednisolone (N=42)	Methylprednisolone and tocilizumab (N=24)	
WANTAI-Index of 18 (vs <18)	48 (94%)	37 (88%)	21 (88%)	p=0.517*
Predicted probability	94%	88%	88%	
Adjusted for age (years)	94%	87%	88%	
Adjusted for gender	85%	74%	89%	
Adjusted for BMI (kg/m^2)	94%	88%	87%	
Adjusted for smoking status	98%	95%	95%	
Adjusted for hypertension	94%	88%	88%	
Adjusted for diabetes mellitus	94%	87%	88%	
Adjusted for COPD	94%	88%	88%	
Adjusted for asthma	94%	87%	88%	
Adjusted for malignancy	94%	88%	88%	
Adjusted for haematologic malignancy	94%	89%	86%	
Adjusted for cardiovascular disease	94%	89%	87%	
Adjusted for heart failure	94%	88%	88%	
Adjusted for arrhythmia	94%	88%	88%	
Adjusted for chronic kidney disease	94%	87%	89%	
Adjusted for cerebrovascular disease	94%	87%	88%	
Adjusted for peripheral vascular disease	94%	85%	90%	
Adjusted for autoimmune disease	94%	88%	88%	
Adjusted for Charlson Comorbidity Index	94%	86%	88%	
Adjusted for WHO score baseline†	92%	86%	87%	
Adjusted for oxygen support at baseline†	94%	89%	87%	

WHO score, hospitalisation requiring oxygen or hospitalisation requiring high-flow nasal oxygen therapy or non-invasive ventilation or hospitalisation requiring extracorporal membrane oxygenation, invasive mechanical ventilation or both; oxygen support at baseline, nasal oxygen or oxymask/non-rebreathing mask or high flow oxygen or mechanical ventilation.
*Calculated with Pearson χ^2.
†Baseline is at the day that patients fulfilled the criteria for hyperinflammation.
BMI, body mass index; COPD, chronic obstructive pulmonary disease.

across the treatment groups. Baseline characteristics did not influence the proportion of patients with the highest WANTAI-Index (table 1).

In 0.02% (2/117 patients) no antibodies were detected, one patient had received methylprednisolone and the other methylprednisolone plus tocilizumab. Interestingly, these two patients were being treated with rituximab for non-Hodgkin's lymphoma since before the diagnosis of COVID-19. None of the seropositive patients received monoclonal antibody therapy.

Based on these results, an effective long-term antibody response to SARS-CoV-2 infection does not seem to be impaired by immunomodulatory treatment of severe COVID-19 with hyperinflammation.

Our results may not be extrapolated to patients with milder forms of COVID-19 or patients already using (chronic) immunosuppressive agents for known underlying diseases.

In conclusion, a short-term therapy of COVID-19-associated hyperinflammation with glucocorticoids as well as with tocilizumab, given in the first weeks of the disease, will not undermine the adaptive immune response in patients with COVID-19.

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Prospective study into COVID-19-like symptoms in patients with and without immune-mediated inflammatory diseases or immunomodulating drugs

With the arrival of SARS-CoV-2, it was asked whether our patients with immune-mediated inflammatory disorders, or who had an organ transplantation (IMDT patients) and/or use immunosuppressive medication (imed) are more susceptible to SARS-CoV-2 infection and/or a severe COVID-19 disease course. In the earliest reports on COVID-19, such patients were rarely described. Most reports were retrospectively collected, in various case series or cohorts without a control group.[1–3] The Infection and Immunomodulation Inventory Initiative cohort study was started 10 March 2020 to prospectively register self-reported periods of illness with COVID-19-like symptoms (CLS) (see questionnaire in online supplemental table 1) and compare these between IMIDT patients with and without imed and controls as selected from the hospital database of the Leiden University Medical Center in March 2020. Patients were defined as being in outpatient care at the outpatient clinic for rheumatology, gastroenterology, pulmonology and/or nephrology and having an autoinflammatory or autoimmune disease or having had a solid organ transplantation with or without imed (verified from the medical records after participant's informed consent). Controls were persons who had visited these outpatient clinics in the previous 3 years and were discharged but did not have an IMIDT.

Of the 8670 individuals approached, 2110 with IMIDT and 1067 controls agreed to participate (see baseline characteristics in online supplemental table 2 and differences between the non-repliers and repliers/participants in online supplemental table 3). The most prevalent diagnoses among the participants from the IMIDT group were ulcerative colitis, Crohn's disease and seropositive rheumatoid arthritis (see online supplemental table 4). Between March and July 2020, 554 (33%) IMIDT patients and 299 (35%) controls recorded an illness episode with at least one symptom, mostly mild with a median (IQR) duration of 4 (3–6) days in both IMIDT patients and controls. Sixteen (6%) IMIDT patients with imed, 8 (3%) IMIDTs without imed and 5 (2%) controls were hospitalised with CLS (p=0.8). Logistic regression analysis showed that female gender (OR 1.45, 95% CI 1.15 to 1.82), lung disease (OR 1.50, 95% CI 1.20 to 1.88) and wearing a face mask (then not yet mandatory) (OR 1.42, 95% CI 1.13 to 1.77) were independently associated with a higher risk of experiencing CLS, whereas older age and use of imed were associated with a lower risk (see table 1).

Thus, we found a similar incidence of CLS in IMIDT patients (with or without imed) and controls. However, IMIDT patients on imeds with CLS had a slightly higher risk to be admitted to hospital, which may suggest worse symptom severity or an estimated greater risk of deterioration. We collected only self-reported symptoms mostly for logistical reasons. With 22% of participants reporting CLS, we may have overestimated the occurrence of COVID-19 and also included symptoms of influenza (season ended in March) and common colds, which, in turn, may have been over-reported during the anxious times of the 'first wave' of COVID-19. But since SARS-CoV-2 infection often results in mild influenza like symptoms only, we may in fact have come closer to the true infection rate than what has been reported in earlier observations based on hospitalisations and testing of worse cases.

Table 1 Univariable and multivariable analysis of variables associated with having CLS or not (OR with 95% CI)

	Data from n	Univariable	Multivariable*
Sex, female	2546	1.89 (1.58 to 2.25)	1.45 (1.15 to 1.82)
Age	2546	0.97 (0.96 to 0.97)	0.96 (0.96 to 0.97)
BMI	2391	0.99 (0.97 to 1.01)	1.00 (0.98 to 1.03)
Smoking (current)	2463	1.35 (1.02 to 1.78)	1.05 (0.74 to 1.50)
Daily alcohol use	2416	0.84 (0.71 to 1.00)	1.20 (0.96 to 1.50)
Solid organ transplantation	2546	0.74 (0.54 to 1.03)	0.79 (0.47 to 1.35)
IMIDT without imed†	2546	1.00 (0.82 to 1.23)	0.94 (0.72 to 1.24)
IMIDT with imed †	2546	0.79 (0.65 to 0.97)	0.68 (0.51 to 0.91)
Use of oral corticosteroids	2546	0.84 (0.66 to 1.06)	1.44 (0.95 to 2.20)
Self-reported diabetes mellitus	2381	0.69 (0.50 to 0.96)	0.89 (0.58 to 1.36)
Self-reported lung disease	2396	1.30 (1.09 to 1.54)	1.50 (1.20 to 1.88)
Self-reported heart disease	2399	0.85 (0.69 to 1.04)	1.09 (0.83 to 1.43)
Influenza vaccination‡	2415	0.71 (0.60 to 0.84)	0.96 (0.76 to 1.21)
Physical contact with family§	2220	1.47 (1.22 to 1.78)	1.22 (0.98 to 1.53)
Visiting other people (not family)	2205	1.26 (1.05 to 1.51)	0.96 (0.77 to 1.20)
Wearing a face mask	2196	1.46 (1.20 to 1.76)	1.42 (1.13 to 1.77)
Close contact (at work)	2180	1.65 (1.34 to 2.03)	1.27 (0.97 to 1.66)
Good adherence to lockdown rules	2245	1.17 (0.41 to 3.29)	2.46 (0.65 to 9.38)
Working outside the house	2435	1.39 (1.16 to 1.68)	0.92 (0.71 to 1.20)

*Number of observations: 1835.
†Control group=reference group.
‡In autumn 2019.
§Physical contact specified as 'holding/shaking hands, hugging etcetera'.
BMI, body mass index; CLS, Covid-19-like symptoms; IMIDT, with immune mediated inflammatory disorders or transplant organ.

A relatively low response rate (37%) to our invitation to participate in this study means that there is a possibility of selection bias, the effect of which we cannot estimate.

In conclusion, between March and July 2020, IMIDT patients, whether or not taking imeds, did not show an increased risk of reported CLS compared with controls. In our population, continuing immunosuppressant drugs as long as not ill, while following the Dutch COVID-19 rules, appears to be safe.

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Antibody response to the Janssen/Johnson & Johnson SARS-CoV-2 vaccine in patients with rheumatic and musculoskeletal diseases

In immunocompetent populations, the Janssen/Johnson & Johnson (J&J) SARS-CoV-2 vaccine induces antibody, CD4 + and CD8+ T cell responses and offers protection against severe and symptomatic SARS-CoV-2 infection.[1 2] This vaccine is an adenovirus serotype 26 (Ad26) vector expressing a stabilised SARS-CoV-2 spike (S) (Ad26.COV2.S), a platform without prior approval for use in the general population, or for patients with rheumatic and musculoskeletal diseases (RMD).[3] Patients on immunosuppressive therapy were excluded from the clinical trials[1 2] and early data have suggested that the J&J vaccine results in lower humoral immunity than mRNA vaccination in immunosuppressed transplant patients.[4] Given the attenuated immunogenicity to mRNA-based SARS-CoV-2 vaccines in certain patients with RMD,[5] we studied the anti-spike antibody response to J&J SARS-CoV-2 vaccination in patients with RMD and compared them to recipients of the mRNA series.

We used our prospective cohort of patients with RMD who underwent SARS-CoV-2 vaccination between December 2020 and May 2021.[5] We collected information on demographics, rheumatic diagnoses and immunosuppressive medications. One month following completion of vaccine series (J&J or mRNA), serologic testing on the semi-quantitative Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, which tests for antibodies against the receptor binding domain (RBD) of the SARS-CoV-2 S protein, was completed.

We compared the percentage of participants with detectable anti-RBD antibody in the J&J group (n=45) to the mRNA group (n=994) using Fisher's exact test (online supplemental table 1). We compared the two vaccine platforms using logistic regression adjusting for age, sex, race and use of mycophenolate, rituximab, glucocorticoid and methotrexate. We compared anti-RBD titres of the J&J group to those of the mRNA group using Wilcoxon rank-sum test.

At a median (IQR) of 29 days (28-32) after vaccination, anti-RBD antibody was detectable in 36 participants who received the J&J vaccine compared with 906 who completed the mRNA vaccine series (80% vs 92%, p=0.03). Those who received J&J vaccination had a higher odds of negative antibody response (OR: 2.57, 95% CI 1.20 to 5.52, p=0.01) compared with those who completed the mRNA series. This association remained statistically significant in the adjusted logistic regression model (aOR: 3.86, 95% CI 1.37 to 10.84 p=0.01). Consistent with prior findings, use of rituximab, mycophenolate and glucocorticoids had a statistically significant association with negative antibody response (online supplemental table 2).[5] Median anti-RBD antibody titres in the J&J group were lower than the mRNA group (9.7 vs 250 U/mL; p<0.001) (figure 1).

In this observational study, we found that patients with RMD who received J&J vaccination had a lower rate of seroconversion compared with recipients of the mRNA series. One in five participants who received J&J vaccination did not mount a detectable

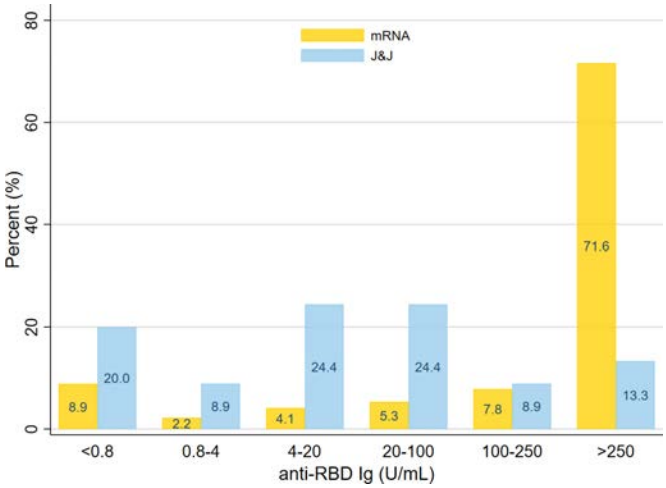

Figure 1 SARS-CoV-2 anti-RBD antibody titres among recipients of mRNA vs J&J vaccine. Titres could range from <0.4 U/mL to >250 U/mL. Positive antibody is defined as an anti-SARS-CoV-2 RBD antibody titre >0.79 U/mL. Ig, immunoglobulin; J&J, Johnson & Johnson; RBD, receptor binding domain.

antibody response. In those with a detectable antibody response, participants who received the J&J vaccine had lower antibody titres than the mRNA group. While no cut-off titre has been defined to associate with protection, there is a well-recognised role of neutralising antibodies in protection against SARS-CoV-2 infection. A recent study estimated that an antibody neutralisation level for 50% protection against detectable SARS-CoV-2 infection to be 20% of the mean convalescent level.[6]

Limitations of this study include small sample size and non-randomised design. We did not analyse peri-vaccination immunosuppression dosing or timing.

These early results suggest that patients with RMD who receive the J&J vaccine may have a more limited humoral response to J&J SARS-CoV-2 vaccination than recipients of the mRNA vaccine series. Optimisation of J&J vaccine response in patients with RMD requires additional studies with larger sample size and evaluation of deeper immunophenotyping, including memory B cell and T cell responses.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the design, conduct or dissemination of the study, though this study was motivated by questions frequently posed by the patients. The study has a public website (https://vaccineresponse.org/) and email account where we welcomed participants and the public to contact the research team. Results of the study will be shared with national RMD organisations for dissemination to their patient communities once published.

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Correspondence on 'EULAR December 2020 viewpoints on SARS-CoV-2 vaccination in patients with RMDs'

In light of their increased risk of worst outcomes following COVID-19 infection, patients with rheumatic and musculoskeletal diseases (RMDs) on immunosuppressive therapy, including systemic glucocorticoids, biological (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs), represent a vulnerable population which should be prioritised to receive vaccination. Controlled data on the effectiveness and safety of different COVID-19 vaccines on patients with RMD are not available yet. However, rheumatology providers and health professionals should be ready to offer timely guidance for the optimal use of vaccines for patients on immunomodulatory drugs. Based on the long-time experience with other non-live vaccines, the COVID-19 Task Force of the European League Against Rheumatisms (EULAR) first delivered a preliminary set of information in December 2020.[1] Overall, it is expected that the safety and immunogenicity of COVID-19 vaccines for most of the DMARDs will be comparable with that registered for the general population,[2–4] so that postponing vaccination pending more information appears unjustified. A number of independent surveys have however alarmingly reported that, among patients with RMD, potential acceptance of COVID-19 vaccines may not exceed 60%, without apparent differences in relation to specific diseases, comorbidities and type of medication.[5–8] Strategies to effectively engage high-risk patients with RMD into vaccination programmes are therefore urgently needed.

Starting from 19 March 2021, rheumatologists of the IRCCS Policlinico San Matteo University Hospital of Pavia, Italy, have been actively involved in the vaccination campaign by personally contacting, booking and administering COVID-19 vaccines to patients with RMD on b/tsDMARDs followed at our institution. In course of phone contacts, rheumatologists identify themselves and offer a vaccination date. In agreement with the most recent determination of the Italian Ministry of Health (https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=79076&parte=1&serie=null), patients are informed that they will receive alternatives to Oxford–AstraZeneca; the vaccine currently available at our hospital is the Pfizer/BioNTech. On the day of vaccination, patients are asked on their potential acceptance of other COVID-19 vaccines (Oxford–AstraZeneca, Moderna, Johnson & Johnson). Demographic and clinical characteristics are retrieved from electronic records and are detailed in online supplemental table 1. All patients provide their informed consent for the use of their anonymous data.

Table 1 Factors associated with adhesion to COVID-19 vaccination

	Acceptance of COVID-19 vaccine (Pfizer/BioNTech)				Acceptance of COVID-19 vaccine (any)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.99 (0.97 to 1.03)	0.81			1.01 (0.99 to 1.03)	0.49		
Age ≥70	0.51 (0.17 to 1.45)	0.19	0.42 (0.13 to 1.30)	0.13	0.56 (0.25 to 1.28)	0.17	—	—
Age <50	0.74 (0.30 to 1.85)	0.52			0.59 (0.31 to 1.12)	0.10	0.26 (0.08 to 0.83)	**0.02**
Male gender	2.22 (0.73 to 6.79)	0.16	2.57 (0.82 to 8.08)	0.11	1.56 (0.79 to 3.09)	0.19	4.13 (0.89 to 19.13)	0.06
Smoking	0.97 (0.20 to 4.71)	0.97			1.35 (0.42 to 4.34)	0.62		
BMI	1.06 (0.91 to 1.24)	0.45			0.95 (0.85 to 1.05)	0.30		
BMI >30	1.58 (0.18 to 13.86)	0.68			0.35 (0.09 to 1.32)	0.12	0.29 (0.06 to 1.40)	0.12
Hypertension	0.96 (0.30 to 3.08)	0.95			1.62 (0.67 to 3.89)	0.28		
Diabetes	0.36 (0.07 to 1.99)	0.24			0.35 (0.08 to 1.49)	0.15	—	—
Rheumatic diagnosis								
RA	Reference		—	—	Reference			
PsA	3.17 (0.70 to 14.46)	0.14			1.12 (0.51 to 2.47)	0.78		
SpA	1.41 (0.44 to 4.50)	0.57			0.81 (0.38 to 1.75)	0.60		
Vasculitis	1.01 (0.21 to 4.89)	0.99			1.06 (0.32 to 3.52)	0.93		
Disease duration	0.99 (0.99 to 1.00)	0.71			0.99 (0.99 to 1.00)	0.37		
Use of PDN	0.88 (0.37 to 2.10)	0.77			0.79 (0.43 to 1.45)	0.45		
PDN dose	1.01 (0.90 to 1.29)	0.41			1.03 (0.93 to 1.14)	0.55		
PDN dose ≥5 mg/day	2.28 (0.65 to 8.01)	0.19	3.36 (0.86 to 13.21)	0.08	1.14 (0.56 to 2.34)	0.71		
Use of csDMARDs	2.20 (0.83 to 5.82)	0.11	2.19 (1.03 to 5.60)	**0.04**	1.75 (0.93 to 3.28)	0.08	3.90 (0.92 to 16.56)	0.07
Type of b/tsDMARD								
Cytokine inhibitor	Reference		0.22 (0.04 to 1.15)	0.07	Reference			
CTLA4-Ig	0.95 (0.30 to 3.05)	0.93			1.19 (0.37 to 3.87)	0.77		
Anti-CD20	0.26 (0.06 to 1.12)	0.07			1.18 (0.52 to 2.71)	0.69		
JAK inhibitor	1.79 (0.22 to 14.47)	0.58			0.86 (0.21 to 3.47)	0.83		
PDE4 inhibitor	—	—			0.73 (0.18 to 3.07)	0.67		
Influenza vaccination	0.67 (0.22 to 2.41)	0.59			0.59 (0.17 to 1.35)	0.25		

The associations between demographic and clinical variables and acceptance of COVID-19 vaccine were investigated by means of univariable and multivariable logistic models including non-collinear variables with p<0.2 at the univariable analysis. Results are presented as ORs and 95% CIs. All analyses were conducted using MedCalc V.12.7.0.0, and the level of significance was set at 0.05.

BMI, body mass index; b/ts, biological/targeted synthetic; cs, conventional synthetic; CTLA4, cytotoxic T-lymphocyte antigen 4; DMARD, disease-modifying antirheumatic drug; JAK, Janus kinase; PDE4, phosphodiesterase 4; PDN, prednisone; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.

The general restrictions in vaccine supply are impacting on the rate of recruitment, with 224 patients out of a total cohort of ~900 having been contacted in the first 15 days of the campaign. Twenty-three patients (10.3%) opposed to vaccination despite extensive counselling; 23 (10.3%) had already been vaccinated (91.3% with Pfizer/BioNTech); 8 (3.5%) had recovered from COVID-19 for <3 months and, in agreement with the rheumatologist, postponed vaccination of 3 months; 35 (15.6%) expressed initial hesitancy but accepted vaccination following rheumatologists' recommendations; 135 (60.3%) immediately endorsed the vaccination proposal. Collectively, adhesion to vaccination was thus spontaneous in 70.5% of the cases (23 already vaccinated+135 agreeing to vaccinate irrespective of the rheumatologist), a proportion that increased to 89.7% (n=201) following rheumatologists' recommendations in recent COVID-19 and hesitant patients. Of the 201 patients who received at least the first dose or were willing to do so, 154 (76.6%) would have accepted any vaccine, 24 (11.9%) any apart from Oxford–AstraZeneca, 12 (6%) Pfizer/BioNTech only, and 11 (5.5%) were uncertain but ready to follow rheumatologists' advice. As a result, despite active involvement of rheumatologists, potential adherence to vaccines alternative to Pfizer/BioNTech was significantly lower (73.7% vs 89.7%, p<0.001). As shown in table 1, factors associated with acceptance of Pfizer/BioNTech were mostly related to the intensity of immunosuppression, with a significant impact of combination therapy with conventional synthetic DMARDs, a trend for higher odds for prednisone doses ≥5 mg/day and lower odds for rituximab. In contrast, factors conditioning individual preferences among vaccines were predominantly demographic, with women of younger age (<50 years) and higher body mass index (>30) more frequently expressing scepticism towards alternatives to Pfizer/BioNTech.

As real-world experience accumulates, it is not surprising that the spontaneous acceptance of COVID-19 vaccination found here is higher compared with previous studies.[5–8] However, active involvement of rheumatologists may further engage hesitant patients, allowing coverage of nearly 90% of those receiving several immunomodulatory drugs in combination. In this perspective, the constitution of dedicated task forces, such as those promoted by EULAR[1] as well as by other national and international societies,[9 10] is fundamental to assist rheumatology providers with updated guidelines on the optimal use of COVID-19 vaccines for patients with RMD. The treating rheumatologists should then be at the fore of outreach strategies aimed at engaging as many patients with RMD as possible among those followed at their centres. Still, misinformation about individual characteristics potentially affecting the efficacy and adverse reactions of different vaccines may introduce delays in a proportion of immunosuppressed patients[11] for whom efforts of the treating rheumatologists are unlikely to produce significant effects in the absence of forceful public campaigns.

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Response to: 'Correspondence on 'EULAR December 2020 View points on SARS-CoV-2 vaccination in patients with RMDs" by Bugatti *et al*

It is great to learn that these Italian colleagues take an active and effective role in promoting vaccination in their patients. The more and earlier our patients, and also the entire population, are vaccinated, the better outcomes in health and quality of life. I am quite sure this example is followed by rheumatologists and other healthcare providers in many countries.

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Correspondence on 'Immunogenicity and safety of anti-SARS-Cov-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'

We read with great interest the article by Geisen *et al*.[1] The authors reported a considerable immunogenicity of mRNA vaccines against SARS-CoV-2 in patients with chronic inflammatory diseases receiving immunosuppression; noteworthy, none was on B-cell depleting agents.

Rituximab (RTX) is one of the mainstays of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) treatment, both for induction and maintenance therapy[2]; of note, recent data have shown that RTX therapy was associated with poorer COVID-19-related outcomes in patients with rheumatic diseases.[3]

In the absence of an effective treatment, vaccination would be a promising tool to prevent severe COVID-19 in immunocompromised patients.

Only four cases addressing the issue of antibody production after SARS-CoV-2 infection in patients with AAV treated with RTX are available in literature,[4–6] while no data about antibody production after vaccination have been published yet.

We describe here the case of two AAV patients who did not produce neutralising antibodies after mRNA vaccination against SARS-CoV-2 (cases 1 and 2); we also report the case of a patient who experienced COVID-19 while B-cell depleted without seroconversion (case 3).

Case 1: a 31-year-old woman presenting with nasal crusting and saddle nose deformity, bilateral effusive otitis media, isolated microhaematuria and anti-myeloperoxidase (MPO) positive ANCA, was diagnosed with granulomatosis with polyangiitis (GPA) in February 2018. Induction therapy consisted of glucocorticoids and 4 weekly infusions of RTX (375 mg/m^2), obtaining complete remission. Subsequently, maintenance therapy was started, with four scheduled infusions of RTX (500 mg each) every 6 months. Last infusion was administered on the 26 June 2020. In January 2021, while on maintenance therapy with prednisone 5 and 2.5 mg on alternate days, she received mRNA vaccine against SARS-CoV-2. At the time of vaccination, peripheral B cell count was 0 cells/mm^3, immunoglobulin levels were normal. No anti-SARS-CoV-2 spike protein antibodies were detectable at the test performed 60 days later (March 2021).

Case 2: a 60-year-old woman was diagnosed with MPO-ANCA positive GPA in October 2014. She presented with constitutional symptoms (fever, weight loss, weakness), bilateral dacryoadenitis and episcleritis, microhaematuria and low-grade proteinuria. She received glucocorticoids and two infusions of RTX (1 g each) 2 weeks apart for remission induction. Maintenance therapy with methotrexate was then started. From November 2018, she was retreated with RTX (four scheduled infusions of 500 mg every 6 months) due to B-cell repopulation and ANCA positivity; methotrexate was withdrawn. Last RTX infusion was administered on 24 June 2020. In January 2021, she received mRNA vaccine against SARS-CoV-2. At that time, B-cell count was 0 cells/mm^3 and immunoglobulin levels normal. Maintenance therapy consisted of prednisone 5 mg/day. Sixty days later (March 2021), no anti-SARS-CoV-2 spike protein antibodies were detectable.

Case 3: a 43-year-old woman was diagnosed with biopsy proven ANCA-negative localised GPA in September 2019. She had nasal crusting and subglottic stenosis. She received glucocorticoids and four infusions of RTX (375 mg/m^2 each) for remission induction. Due to COVID-19 pandemic, a maintenance RTX infusion (500 mg) was delayed to the 26 June 2020. In September 2020, peripheral B-cell count was 0 cells/mm^3 and immunoglobulin levels normal. From the 31 October 2020, she developed fever, cough, headache and weakness. On the 4 November 2020, a nasopharyngeal swab for SARS-CoV-2 tested positive. She was treated with glucocorticoids, enoxaparin and azithromycin with complete recovery and no need for hospitalisation. In March 2021, she underwent a serological test for anti-SARS-CoV-2 spike protein antibodies and none was detected.

In patients treated with RTX, a blunted response to several vaccinations, including those against seasonal influenza, Pneumococcus and tetanus,[7 8] has already been reported.

Of note, the two patients here described did not develop neutralising antibodies after mRNA vaccine against SARS-CoV-2, even though last infusion of RTX dated back to 9 months earlier.

Data on seroconversion after SARS-CoV-2 infection in AAV patients treated with RTX are scanty but available. To date, only four cases have been published: three patients were B-cell depleted and one B-cell reconstituted (10 cells/mm^3) at the time of the infection. Of note, the latter developed IgG towards SARS-CoV-2 while, among the former three, only one showed low titre of neutralising antibodies (table 1).

Guidelines for RTX treated patients recommend to perform vaccination at least 4 weeks prior or 6 months after infusion.[9] However, in AAV patients, a more delayed B-cell repopulation has been described compared with other immunological diseases.[10] Of note, up to more than 60 months of B-cell depletion after induction with RTX has been described in AAV patients, suggesting an intrinsic dysregulation of the B-cell compartment in this disease.[11] Therefore, in addition to the timing since last RTX infusion, we believe that in this group of patients also B-cell count should be taken into account when planning vaccination.

Although results from single case reports cannot be generalised, our data raise concerns about the risk of an inadequate seroconversion after SARS-CoV-2 vaccine in AAV patients treated with RTX.

Table 1 Antibody response to SARS-CoV-2 infection in AAV patients

Reference	Age	Sex	Diagnosis	Time from last RTX (days)	B cell count (cells/mm^3)	Hypogammaglobulinaemia	Anti-SARS-CoV-2 IgG
4	73	F	GPA	45	0	Yes	Negative
4	74	F	MPA	100	0	No	Low level (39 AU/mL, cut-off >10)
5	62	F	AAV	149	0	N/A	Negative
6	64	F	MPA	82	10	No	Positive
Present manuscript	43	F	GPA	127	0	No	Negative

AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; N/A, not available; RTX, rituximab.

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Correspondence on 'Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'

We read with interest the recent report by Geisen *et al*,[1] who describe the immunogenicity and safety profile of two mRNA-based anti-SARS-CoV-2 vaccines in a cohort of 26 patients with chronic arthritides, psoriasis and other inflammatory diseases, compared with 42 healthy controls. The majority of subjects were health professionals, which makes the 14-day post-vaccinal observations provided by the authors particularly informative for high-risk settings, such as hospitals. Extensive data about the impact of anti-SARS-CoV-2 vaccines in patients with immune-mediated disorders are eagerly awaited, since people living with these diseases were excluded from registration trials,[2–4] despite constituting a risk group for severe SARS-CoV-2-realated disease (COVID-19)[5–7] and, potentially, for adverse immune-mediated post-vaccinal events.[8–11]

To contribute in filling this knowledge gap, we studied 55 consecutive patients (54 health professionals) with rheumatic diseases and primary immunodeficiencies, for a median (IQR) of 66 (42–75) days from the first and 45 (20–52) days from the second dose of the BNT162b2 vaccine[2] (detailed methods: online supplemental material 1). Thirty-eight patients (69%) had one or more comorbidities, including allergy in 22 cases (table 1).

At time of vaccination, 42/55 patients had been in remission for 20 (5–29) months. The median disease duration was 11 (5–18) years. Fifty-one patients (93%) were taking one or more immunosuppressive/immunomodulating drugs beside other treatments (online supplemental tables 1 and 2).

No patient had evidence of SARS-CoV-2 infection during follow-up. Thirty-eight patients (69%) reported at least one symptom after the first (47%), the second (56%) or both doses (35%; online supplemental table 3) with a median timing of 24 hours for onset and 48 hours for resolution. Symptoms after the first dose predicted having symptoms after the second one (OR=3.85, 95% CI 1.23 to 12.01; p=0.020). All events were mild and included more frequently constitutional symptoms (49%) and local pain at injection site (38%). Constitutional symptoms were more frequent after the second than after the first dose (38 vs 18%; p=0.033; online supplemental table 4).

Adverse events were more frequent in women than in men (78% vs 30%; p=0.006) and less frequent in IgG4-related disease (IgG4RD, 29%) than in other patients (75%; p=0.024). The median age was lower in patient with (49 (39–55) years) than in those without adverse events (58 (46–66); p=0.021). No association was found with disease duration, remission, duration of remission or previous COVID-19. All four patients with inflammatory spondyloarthropathies had adverse events after the first (χ^2=4.81; p=0.044 compared with other diseases) and second dose, with symptom severity slightly increasing across the two doses (online supplemental table 5). No other factors were associated to adverse events after the first dose. Adverse events after the second dose were more frequent in women (67% vs 10% in men; p=0.001), patients with allergy history (77% vs 42% in patients with no allergy; p=0.014), especially to drugs (82% vs 45% in patients with no history of drug allergy; p=0.017), connective tissue diseases (80% vs 48% in patients with other disorders; p=0.037) and patients without IgG4RD (65% vs 0% in IgG4RD; p=0.002).

Table 1 Clinical features of the study cohort

Item	Value
Females: n (%)	45 (82)
Age: median (IQR)	52 (45–59)
Primary immune-mediated disease: n (%)	
Connective tissue diseases	15 (27)
Systemic lupus erythematosus	11 (20)
Systemic sclerosis	1 (2)
Sjoegren's syndrome	1 (2)
Undifferentiated connective tissue disease	2 (4)
Arthritides	19 (35)
Rheumatoid arthritis	13 (24)
Inflammatory spondyloarthropathies	4 (7)
Other	2 (4)
Systemic vasculitides	8 (15)
Large-vessel vasculitides	2 (4)
Small-vessel vasculitides	3 (5)
Other	3 (5)
Autoinflammatory diseases	
Adult-onset Still's disease	1 (2)
Primary immunodeficiencies	3 (5)
IgG4-related disease	7 (13)
Sarcoidosis	1 (2)
Other	1 (2)
Immune-mediated comorbidities: n (%)	
Allergy	22 (40)
Drugs	17 (31)
Food	8 (15)
Inhalants	3 (5)
Hymenopter venom	1 (2)
Asthma	5 (9)
Chronic urticaria	7 (13)
Mastocytosis	0 (0)
Allergy	22 (40)
Other comorbidities*: n (%)	
Hypertension	8 (15)
Cardiovascular diseases	4 (7)
Cancer	2 (4)
Having received organ transplants	1 (2)
Metabolic/endocrine disorders	17 (31)
Obesity/overweight	2 (4)
Hypothyroidism	6 (11)
Dyslipidaemia	5 (9)
Diabetes	4 (7)
Osteoporosis	3 (5)
Renal diseases	3 (5)
Neurological disorders	3 (5)
Gastrointestinal disorders	9 (16)
Upper airway diseases	4 (7)
Other	2 (4)
Previous COVID-19	6 (11)

*Immune-mediated disorders causing organ dysfunction (eg, Hashimoto's thyroiditis for 'hypothyroidism' or coeliac disease for 'gastrointestinal disorders') are scored twice.

Constitutional symptoms were more frequent in patients with arthritis than in other patients (84% vs 31%; p<0.001). Specifically, these patients showed higher frequencies of fever (47% vs 11%; p=0.006), and arthralgia/myalgia (47% vs 17%; p=0.025). Constitutional symptoms were particularly frequent in patients with

rheumatoid arthritis (77% vs 40% in other patients; p=0.029), those taking methotrexate (73% vs 38% in patients with other treatments; p=0.033) and/or anti-tumour necrosis factor alpha (anti-TNF) agents (83% vs 40% in patients taking other medication; p=0.010). More generally, constitutional symptoms were more frequent among patients taking biological disease modifying anti-rheumatic drugs (70%) than other drugs (24%; p=0.001). Patients with connective tissue diseases reported local pain with a higher frequency (67%) than patients with other immune-mediated diseases (28%; p=0.012) and had a 40% prevalence of constitutional symptoms. Furthermore, no patient with systemic lupus erythematosus (n=12) or taking hydroxychloroquine (n=18) had post-vaccination fever. By contrast, fever prevalence was 30% in patients without SLE (p=0.050) and 33% in patients not taking hydroxychloroquine (p=0.005). A history of allergy was associated with both constitutional symptoms (68% vs 36% prevalence in patients with vs without allergy, respectively; p=0.029) and injection-site pain (59% vs 24% prevalence in patients with vs without allergy, respectively; p=0.012). Drug allergy history was specifically more frequent among patients with post-vaccinal fever (62% vs 21% in patients with no fever; p=0.013).

In summary, consistent with the work of Geisen *et al*[1] and others,[12 13] we provide novel real-life evidence supporting the safe and possibly effective use of the BNT162b2 vaccine in high-risk patients with primary immunodeficiencies, rheumatic disorders, allergy and multiple comorbidities, at least in the short-term, independent of disease remission and immunosuppression at time of vaccination. Furthermore, our results suggest that post-vaccinal symptoms might develop with distinct patterns according to the underlying pathogenic background and/or to the superimposed effect of treatments.

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Correspondence on 'Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'

Patients with immune-mediated inflammatory diseases (IMID) have largely been excluded in clinical trials of SARS-CoV-2 mRNA vaccines due to both disease status and immunotherapeutics used. A recent study by Geisen *et al* has shown that patients with IMID using immunotherapeutics exhibited significantly lower antibody titres against the SARS-CoV-2 spike protein (S) after full vaccination with a SARS-CoV-2 mRNA vaccine relative to vaccinated healthy controls (HCs), suggesting a compromised SARS-CoV-2 mRNA vaccine antibody response in this population.[1] Furthermore, a separate study by Boyarsky *et al* found that a proportion of patients with IMID with or without immunomodulatory therapy failed to seroconvert after the first dose with a SARS-CoV-2 mRNA vaccine.[2] Here, we quantified SARS-CoV-2 mRNA vaccine-induced anti-S and receptor-binding domain (RBD) antibodies among fully vaccinated HCs and found that antibody levels in patients with IMID using immunotherapeutics were significantly lower than HCs.

A total of 66 HCs and 8 patients with IMID who had been fully vaccinated (BNT162b2 or mRNA-1273) for at least 2 weeks were recruited. All participants received their first vaccination between 13 December 2020 and 5 February 2021 and the second dose between 3 January 2021 and 5 March 2021. Individuals with known prior SARS-CoV-2 infection were excluded. IMID diagnoses included psoriasis, rheumatoid arthritis, systemic lupus erythematosus (SLE), mixed connective tissue disease, hidradenitis suppurativa and inflammatory bowel disease. All patients with IMID were on an immunomodulatory therapy, including biologic and non-biologic disease-modifying antirheumatic drug therapy, corticosteroid or combination therapy (table 1). Demographic information is detailed in online supplemental table S1. Additionally, non-vaccinated non-convalescent healthy individuals (n=8) were included as controls. Fully quantitative anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies were measured with the COVID-SeroIndex ELISA kit (Kantaro and Bio-Techne, USA), assessing both anti-S and RBD antibodies.[3]

Table 1 Patient-level IMID diagnosis, immunotherapeutic regimen and anti-S IgG level

Age	Sex	IMID diagnosis	Immunotherapeutic regimen	Anti-S IgG (AU/mL)
30s	F	HS and LCV	Tofacitinib	16.4
40s	F	Ulcerative colitis	Infliximab and azathioprine	52.0
50s	F	RA	Hydroxychloroquine	102.8
60s	F	SLE	Methotrexate	84.8
60s	M	Psoriasis and PsA	Ixekizumab	90.5
60s	F	RA, SLE and MCTD	Mycophenolate	214.1
60s	F	SLE	Methotrexate and prednisone 5 mg	120.9
60s	F	RA and SLE	Prednisone 5 mg	Undetectable

anti-S, anti-spike protein; HS, hidradenitis suppurativa; IgG, immunoglobulin G; IMID, immune-mediated inflammatory disease; LCV, leukocytoclastic vasculitis; MCTD, mixed connective tissue disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

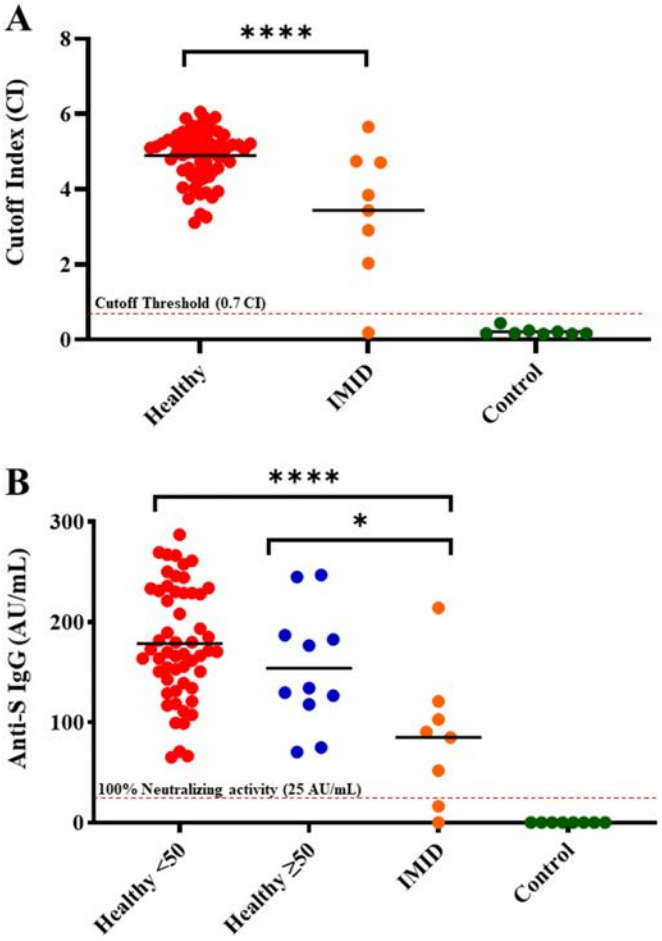

Figure 1 Patients with IMID treated with immunotherapeutics have reduced levels of SARS-CoV-2 vaccine-induced antibody. (A) Semiquantitave anti-RBD IgG levels were measured in 66 HCs and 8 IMID patients who had been fully vaccinated for at least 2 weeks. Non-vaccinated healthy participants were included as controls (n=8). The red dashed line (0.7 CI) indicates the cut-off threshold correlating to the presence or the absence of antibody per manufacturer (Kantaro and Bio-Techne). Individuals with RBD levels above the 0.7 cut-off threshold moved forward for anti-S IgG quantification. (B) Fully quantitative anti-S IgG levels were measured in the study population: healthy: <50 years old (n=55), healthy: ≥50 years old (n=11), IMID (n=8) and control (n=8). Individuals with RBD levels below the 0.7 cut-off level were assigned a value of 0. The red dashed line (25 AU/mL) indicates the threshold correlating to 100% neutralising antibody levels per manufacturer. Horizontal black bars indicate mean IgG levels. Unpaired two-tailed t-test. *p<0.05; ****p<0.0001. Anti-S, anti-spike protein; CI, cut-off index; HCs, healthy controls; IgG, immunoglobulin G; IMID, immune-mediated inflammatory diseases; RBD, receptor-binding domain.

As expected, all vaccinated HCs achieved seroconversion (anti-RBD positive), which is in line with clinical trial results from mRNA-12735 and BNT162b2.6,[4 5] while one patient with IMID and all non-vaccinated non-convalescent HCs were below the detectable limit (figure 1A). Given a mean age of 55.9 years (range: 33–68 years) among patients with IMID, HCs were split into groups of less than 50 years of age (mean age: 34.4 years (range: 21–49 years); n=55) and 50 years or older (mean age: 56.4 years (range: 50–66 years); n=11). Anti-S-IgG antibody levels were comparable between the <50-year-old and ≥50-year-old HC groups (p=0.19), with a mean of 178.7 AU/mL (95% CI, 163 to 194) and 153.8 AU/mL (95% CI, 114 to

194), respectively (figure 1B). Antibody levels among patients with IMID were significantly lower (85.2 AU/mL (95% CI, 29 to 141)) compared with two HC groups, suggesting a compromised vaccine-induced antibody response among patients with IMID (figure 1B). IMID patient-level demographics, diagnosis, immunotherapeutics regimen and individual anti-S-IgG antibody levels are outlined in table 1. One patient with SLE on low-dose prednisone failed to seroconvert, and one patient with hidradenitis suppurativa on tofacitinib had an anti-S-IgG level below the threshold of 25 AU/mL correlating to 100% neutralising antibody level.

Our study reveals that fully vaccinated patients with IMID using immunotherapeutic regimens had significantly lower levels of anti-S antibody relative to HCs, extending Geisen *et al*'s findings[1] that patients with IMID using immunotherapeutics produce lower titres of vaccine-induced anti-SARS-CoV-2 antibodies. In contrast to Giesen *et al*, where all patients with IMID had seroconversion after full vaccination, we observed one patient with IMID who did not mount a detectable antibody response after full vaccination, which was also suggested by Boyarsky *et al*,[2] although after only a single vaccination. While most patients with IMID did mount a detectable anti-S antibody response after full vaccination, it remains unknown how much protection this provides or if the response is durable. Limitations of the current study and Geisen et *al*'s findings[1] include a relatively small sample size and the absence of extended longitudinal measurements. Further investigation using greater numbers of patients with IMID and specific immunotherapeutic regimens will be required to assess antibody levels longitudinally and characterise SARS-CoV-2 memory B cell and T cell responses. These data are urgently needed to plan effective vaccination approaches for patients with IMID, including when and if booster doses will be required and if holding certain immunotherapeutics before and after vaccination may be necessary to achieve a meaningful correlate of protection.

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Contributors JV: study conception, drafting the manuscript and data analysis. KM-M:, study conception and manuscript editing. JW, TL and BZ: sample processing, data generation and analysis. IH: patient recruitment. LZ: study conception, manuscript editing and funding. Q-SM: study conception, data analysis, manuscript editing and funding.

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Correspondence on 'Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'

We read with interest the work by Geisen and colleagues[1] on the efficacy and safety of anti-SARS-CoV-2 mRNA vaccine in patients with rheumatic diseases. While substantial data on the efficacy and safety of SARS-CoV-2 vaccination have been created during the last months, it is currently unclear whether the vaccination is efficacious and safe in patients with autoinflammatory diseases (AIDs). These patients present with exacerbated innate immune responses associated with enhanced production of interleukin (IL)-1.[2]

Testing the immune response to SARS-CoV-2 vaccination in patients with AIDs is of interest, as IL-1 has been involved in the pathogenesis of COVID-19; thus, IL-1 expression is massively increased in patients with severe COVID-19.[3–5] Furthermore, COVID-19 has shown to trigger an increased inflammatory disease activity in patients with AIDs.[6 7] In addition, IL-1 inhibition has been applied in the treatment of COVID-19 and while initial uncontrolled studies revealed promising results,[8] a randomised controlled trial showed no improvement of COVID-19 on IL-1 blockade.[9] While current data suggest the immune response to SARS-CoV-2 vaccination may be reduced in certain diseases, such as rheumatoid arthritis,[10] and certain treatments such as methotrexate,[11] such data cannot be applied to AID or to IL-1 inhibitors as the underlying pathophysiology is fundamentally different. Hence, we aimed to investigate SARS-CoV-2 vaccination responses in patients with AIDs treated with IL-1 inhibitors and compared them with healthy controls (HCs).

Ten patients with AIDs, four with adult-onset Still's disease, three with familial Mediterranean fever (FMF) and each one with gout, systemic AID and tumour necrosis factor receptor-associated periodical syndrome were investigated (online supplemental table 1). Their mean age was 33±10 years, eight were women and two men. All patients with AIDs were treated with IL-1 inhibitors, eight with canakinumab and two with anakinra, administered regularly and at standard dosages of 150 mg/300 mg every 4 weeks and 100 mg/day, respectively. Two patients with FMF were additionally treated with 1 mg colchicine. None of the patients received glucocorticoids. In addition, 10 HCs were examined. All patients with AIDs and HCs received the BNT162b2 vaccine (Pfizer/BioNTech). None of the patients with AIDs and HCs did have COVID-19 before, nor did they have a positive anti-SARS-CoV-2 antibody test before vaccination.

IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were tested by CE-certified ELISA (Euroimmun, Lübeck, Germany).[12] To assess neutralisation activity of antibodies, a CE-certified SARS-CoV-2 surrogate virus neutralisation assay (cPASS, Medac, Wedel, Germany) was used. A cut-off of 30% inhibition was considered as positive, according to the manufacturer's instructions.[13] We compared binary response status of antibody levels and neutralising activity using Fisher's exact test. ODs and per cent neutralising activity of the antibodies were compared using Mann-Whitney U tests. Two-sided p values were considered significant when <0.05. Analyses were performed using the open-source R software V.4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Nine out of 10 patients with AIDs and all HCs developed SARS-CoV-2-specific IgG antibodies (OD >0.8 units). The time course of the antibody response in patients and controls was very similar (figure 1A). SARS-CoV-2-specific IgG antibodies were even higher in patients with AIDs than in HCs (figure 1B). Respective median (IQR) ODs were 7.0 (6.6 to 7.4) in HCs and 8.4 (7.3 to 8.9) in patients with AIDs (p=0.00.19, Wilcoxon rank-sum test). The neutralising activity of receptor-binding domain binding to ACE2 was 96.4% (95.4% to 97.2%) in HCs and 95.3% (87.2% to 96.2%) in patients with AIDs, respectively (p=0.21, Wilcoxon rank-sum test). Vaccination was tolerated well in all patients and controls.

These data show good responses to SARS-CoV-2 vaccination in patients with AIDs treated with IL-1 inhibitors. They support previous anecdotal reports that IL-1 inhibitors may not impair the immune response in the context of COVID-19.[14] Importantly, both IgG levels as well as neutralising capacity of the anti-SARS-CoV-2 antibodies were comparable in patients with AIDs

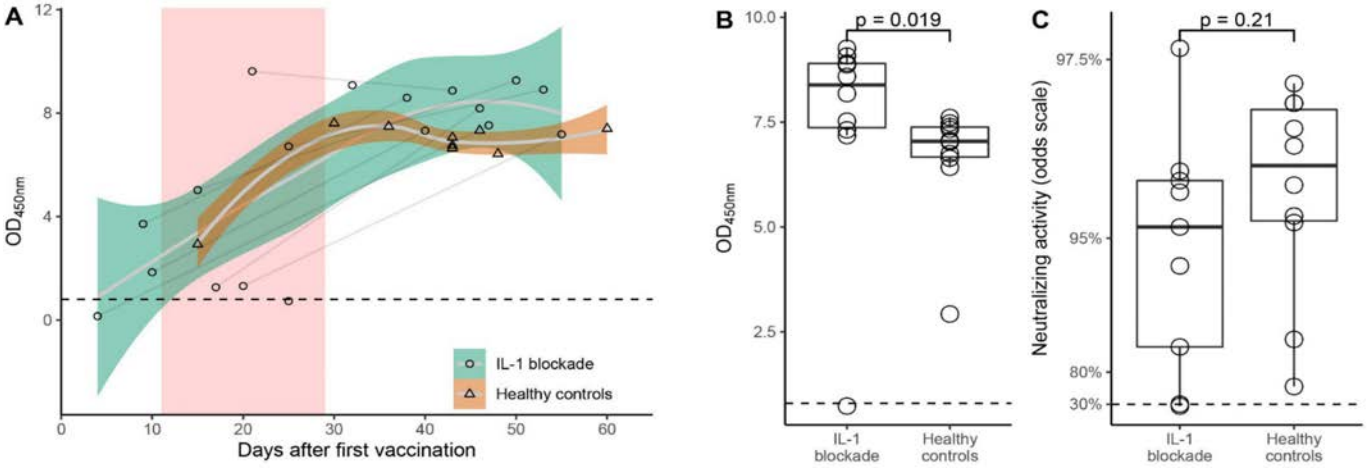

Figure 1 (A) Time course of anti-SARS-CoV-2 antibody response in patients with autoinflammatory disease receiving interleukin (IL)-1 blockade and healthy controls. Horizontal dashed line indicates the cut-off at OD 0.8. Shaded area represents the period during which second vaccine dose was administered. Dots connected by lines indicate antibody measurements from the same participants after the first and second vaccine dose. (B) Optical densities after the second vaccination, horizontal dashed line indicates the OD cut-off of 0.8. P value by Wilcoxon rank-sum test. (C) Neutralising activity of the antibodies after second vaccination. Horizontal dashed line indicates the cut-off at 30%. P value by Wilcoxon rank-sum test.

and HCs. Only one patient with gout and chronic renal failure undergoing haemodialysis did not respond to SARS-CoV-2 vaccination. The data also showed that there is no overshooting inflammatory response to SARS-CoV-2 vaccination in patients with AID. Taken together, these data support the current American College of Rheumatology guidelines for SARS-CoV-2 vaccination in patients with rheumatic diseases, including AIDs.[15]

In summary, SARS-CoV-2 vaccination in patients with AIDs receiving IL-1 inhibition is efficacious and well tolerated.

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Correspondence on 'SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response'

We read with a great interest the article published by Bonelli *et al* suggesting an inducible cellular immune response in rituximab (Rtx) treated patients.[1] The CD20-antibody Rtx is one of the most widespread biologicals worldwide with a broad spectrum of oncological and rheumatological indications. Due to its depleting effect on circulating B cells, the generation of antibodies against novel pathogens is impaired in Rtx-treated patients.[2 3] Accordingly, the last EULAR recommendations on vaccination advised that 'vaccination should be provided at least 6 months after the last administration and 4 weeks before the next course of B cell-depleting therapy'.[4] To ensure appropriate SARS-CoV-2 vaccination, the last EULAR advise was to refer to a rheumatologist.[5] The American College of Rheumatology (ACR) has recommended to vaccinate Rtx-treated patients not earlier than 5 months after the last administration with the next cycle given not earlier than 2–4 weeks thereafter.[6] In any case, the combination of B cell-depleting therapy with vaccination has been quite a challenge for patients and physicians—especially since it became clear that Rtx therapy may be associated with unfavourable outcomes in B cell-depleted patients.[7] Fortunately, very recent data by Bonelli *et al* have now suggested that a cellular response is mounted after SARS-CoV-2 vaccination in Rtx-treated patients despite a failed humoral immune response.[1] The authors demonstrated that peripheral blood cells of vaccinated patients do produce Interferon γ (IFNγ) after stimulation with SARS-CoV-2 spike (S) protein-derived overlapping peptides.[1] These results increase the scientific interest into a more detailed characterisation of vaccine-reactive T-cell immunity, which has recently been in the focus of our group as well due to a frequent Rtx application in our settings.

Applying multiparameter flow cytometry, we explored the efficacy of SARS-CoV-2 vaccination as defined by quantification and in-depth characterisation of T cell immunity in nine Rtx-treated patients diagnosed with autoantibodies against myeloperoxidase (MPO), proteinase 3 (PR3), MPO/PR overlap and immunoglobulin A (IgA) vasculitis or membranous glomerulopathy (table 1). Their mean age was 65 years, 33.3% were women, and the mean time after the last application of Rtx was 4.5 months (2–7 months). The vaccination by two doses of BNT162b2 was performed within 3 weeks. SARS-CoV-2-reactive immunity was analysed before the first dose, and 3 weeks after the first and the second dose, respectively. Vaccinated healthcare workers (n=14) served as controls.

All but two Rtx-treated patients had neglectable levels of $CD19^+$ B cells (figure 1D). Consequently, the development of antibodies to the SARS-CoV-2 S-protein was substantially impaired in Rtx group excluding two of the patients with detectable $CD19^+$ B cells, who showed seroconversion. In contrast, virus specific IgG antibodies were detected in all healthy controls.

Importantly, vaccine-reactive T cells were found in the majority of Rtx-treated patients. Due to pre-existing SARS-CoV-2-cross-reactive T cells known to be detectable in unexposed patients as demonstrated by other and our groups,[8 9] vaccine-directed T cell response was defined by a >twofold increase of SARS-CoV-2 S-protein-reactive T cell frequencies compared with the prevaccination (TP0) state. Accordingly, $CD4^+$ T cell vaccination response was observed in 78% of Rtx-treated patients 3 weeks after the first vaccination and 86% after the second vaccination (figure 1A), while $CD8^+$ T cell responses were only found in 22% and 43% of the patients after the first and second vaccinations, respectively. Of note, there were no statistically significant differences in the frequencies of vaccine-reactive $CD4^+$ and $CD8^+$ T cells between patients and controls (figure 1B). The substantial number of activated T cells produced GranzymeB, interleukin (IL)-2, interferon γ (IFNγ) or tumour necrosis factor α (TNFα) as monofunctional or polyfunctional T cells suggesting their protective function[10] (figure 1C). Again, there were no statistically significant differences between patients and controls.

T cell reactivity against SARS-CoV-2 variants of concern (VOC), including B1.1.7 and B1.351 strains, after vaccination with the Wuhan wild type S-protein are of special interest. Importantly, 75% of Rtx-treated patients had T cells directed against the S-protein derived from both mutant strains after the second vaccination, respectively (figure 1B). These T cells were able to produce several cytokines simultaneously suggesting antiviral potential of these polyfunctional T cells[10] (figure 1C). Again, the magnitude and functionality of B1.1.7 and B1.351 S-reactive T cells were not significantly different between patients and controls (figure 1B), with a tendency towards lower frequencies in the former.

In conclusion, despite the lack of seroconversion in most patients, Rtx-treated patients are able to raise T cells reactive not only to SARS-CoV-2 wild type strain but also to B1.1.7 and B1.351 VOC. Although not a confirmation of antiviral protection of vaccine-reactive T cells, their polyfunctional properties suggest an antiviral potential.

Table 1 Patient characteristics

	Age	Sex	Body mass index (kg/m²)	Months since rituximab	Overall rituximab treatment duration	Aetiology	GFR (CKD-EPI; mL/min/1.73²)
1	73	F	21.5	2	8	MPO	31.7
2	65	M	32.2	2	26	PR3	38.6
3	60	M	35.4	7	26	IgAV	17.3
4	57	M	23.3	6	6	MPO	47.1
5	74	M	32.1	7	7	MGN	45.2
6	79	M	25.1	5	27	MGN	43.7
7	52	F	25.7	4	17	MPO/PR3	43.2
8	64	M	27.5	4	21	PR3	27.5
9	64	F	34.6	4	10	PR3	47.9

GFR, glomerular filtration rate
; IgAV, IgA–associated vasculitis; MGN, membranous glomerulonephritis; MPO, myeloperoxidase; PR3, proteinase 3.

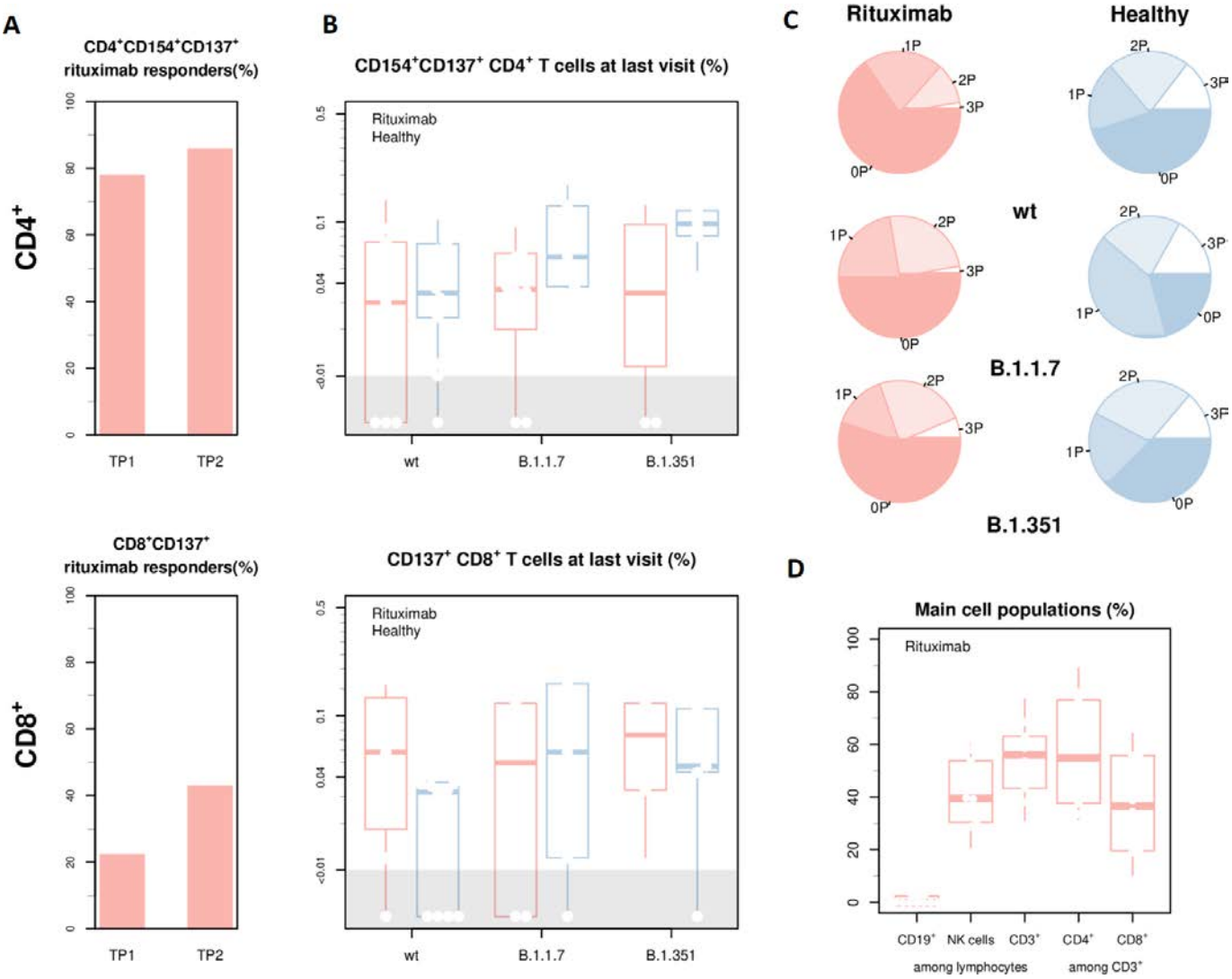

Figure 1 Robust polyfunctional T cell response directed against spike (S) wild type (wt) and variants of concern (VOC) strains can be detected in rituximab (Rtx) treated patients following SARS-CoV-2 vaccination. (A) Incidence of Rtx-treated patients responded to the vaccination 3 weeks after the first dose (TP1) and 3 weeks after the second dose (TP2). Vaccine-directed T cell response was defined as >twofold increase of S-reactive T cell frequencies as compared with the prevaccination (TP0) T cell response ($CD4^+$ T cells top; $CD8^+$ T cells bottom). (B) The relative frequency of SARS-CoV-2 reactive $CD4^+$ and $CD8^+$ T cells directed against S-protein of wt, B.1.1.7 and B.1.351 VOC strains in Rtx-treated patients and healthy donors. For $CD4^+$ T cells, activation is defined by $CD154^+$ and $CD137^+$ double expression (top) and for $CD8^+$ T cells by $CD137^+$ (bottom). Presented are data obtained from the last visit (3–5 weeks) after the second vaccination dose. For wt strain, 9 Rtx-treated patients and 14 controls were available. For VOC strains, eight Rtx-treated patients and five controls were available. PBCMs were isolated 3–5 weeks after the second BNT162b2 dose and stimulated overnight with SARS-CoV-2 S-protein of wt, B.1.1.7 and B.1.351 strains, respectively. T cell reactivity was determined by flow cytometry as $CD154^+$, $CD137^+$ and $CD137^+$ for CD4+ and CD8+, respectively, together with antibodies for Granzyme B, IFNγ, TNFα and IL-2. (C) Total frequency of monofunctional (1P), bifunctional (2P) or trifunctional (3P) T cells concurrently producing one, two or three cytokines or no cytokines (0P), respectively, in response to S-protein from wt, B.1.1.7 or B.1.351. PBCMs were isolated 3–5 weeks after the second BNT162b2 dose and stimulated overnight with SARS-CoV-2 S-protein from wt, B.1.1.7 and B.1.351. T cell reactivity was determined by flow cytometry as $CD154^+$ and $CD137^+$ together with antibodies for Granzyme B, IFNγ, TNFα and IL-2. (D) Reduced CD19+ but normal frequencies of other lymphocytes in Rtx-treated patients. The frequencies of $CD19^+$, NK, $CD3^+$, $CD4^+/CD3^+$ and $CD8^+/CD3^+$ were evaluated in fresh whole blood by flow cytometry. Each point signifies a patient. IFNγ, Interferon γ; IL, interleukin, NK, natural killer, TNFα, tumour necrosis factor α.

The role of SARS-CoV-2-specific antibodies in COVID-19 is not well established: reports indicate an increased risk of severe COVID-19 infections in Rtx-treated patients,[7] whereas other data have suggested that B cells are dispensable for resolving such infections.[11] The here presented data indicate that polyfunctional antiviral T cell responses are raised after SARS-CoV-2 vaccination in this high-risk population suggesting protection in the absence of virus-specific antibodies.

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Response to: 'Correspondence on 'SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response" by Westhoff *et al*

We have read the correspondence of Westhoff *et al* to our article[1] with great interest. The authors confirm our finding of an impaired humoral immune response in rituximab-treated patients by showing that also their rituximab treated patients did not develop antibodies to the SARS-CoV-2 spike protein after two doses of SARS-CoV-2 vaccinations with BNT162b2.[2] In line with our data, the authors provide evidence for a maintained cellular immune response in rituximab-treated patients. In addition, Westhoff *et al* could quantify the presence of a CD4 and CD8 T cell response in 78% and 43% of the rituximab-treated patients, respectively. The finding of a dissociated humoral and cellular immune response is adding an important piece to the understanding of the scope of secondary immunodeficiency induced by rituximab. Nevertheless, this specific scientific field is strongly driven by questions about clinical relevance, and it remains not sufficiently clear what leg of the immune system is essential for successfully fighting a SARS-CoV-2 infection. However, to date, the clinical relevance of these findings remain elusive, as large vaccination studies with clinical endpoints for this patient population are challenging and quite unlikely, even in the currently very active research field.

For now, given the uncertainty on these details, the conclusion for patients on rituximab treatment can only be that vaccination is not without potentially protective effects, even if antibodies cannot be detected. Future studies would need to investigate what level of B cell repopulation is necessary to also achieve a humoral immune response to vaccination, and whether such response may be elicited, even in the absence of such repopulation, through an additional boost vaccination.

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Correspondence on "SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response" by Bonelli *et al*

SARS-CoV-2 vaccination elicited high levels of immunogenicity in immunocompetent people in the original vaccine trials[1 2] though recent studies have shown blunted immunogenicity in patients with rheumatic diseases treated with lymphocyte depleting agents.[3 4] B-lymphocytes have been implicated in the pathogenesis of anti-neutrophil cytoplasmic antibidy (ANCA)-associated vasculitis (AAV) and B-cell-targeted therapy with rituximab is recognised as an established induction and maintenance strategy in management.[5 6] SARS-CoV-2 infection in patients with AAV has been associated with severe outcomes,[7] while rituximab has been associated with worse outcomes among patients infected with SARS-CoV-2.[8 9] A recent study by Bonelli *et al* found evidence of an ameliorated humoral response but possible inducible cellular response in five patients treated with rituximab.[10]

We studied the tolerability and humoral response to the SARS-CoV-2 vaccine series in 48 patients with a diagnosis of AAV. Patients underwent SARS-CoV-2 antispike antibody testing to assess humoral response. Antibody testing was performed using antispike IgG enzyme immunoassay (Roche Elecsys via Quest, DiaSorin Liaison assay via LabCorp or Euroimmun via Hopkins lab). Demographics, clinical information including immunosuppressive therapy were extracted from medical records. Time from last rituximab administration to receipt of the first dose of the vaccine was recorded. We recorded serum creatinine, white blood cell count, serum immunoglobulins, Cluster of CD19 and ANCA status. CD19 reconstitution was defined as CD19-positive B cells greater than 0/mm^3. Hypo-IgG and hypo-IgM were defined as less than the lower limit of normal for the lab. Patients were asked solicited questions about local and systemic adverse events after each vaccine dose (D1, D2) to assess tolerability. Descriptive statistics and bivariate comparisons were performed using χ^2 and Fischer's exact tests for categorical variables and t-tests and Wilcoxon rank-sum tests for continuous variables. All analyses were conducted in SAS V.9.4 (SAS Institute).

We studied 48 patients with AAV (table 1). Most patients (98%) had renal involvement, while 77% had extrarenal involvement. Immunosuppressant regimens included rituximab (44 patients; 92%), prednisone (14 patients; 30%) and mycophenolate mofetil (6 patients; 12%). The median (IQR) daily dose of prednisone was 4 mg (2–8 mg). The indications for rituximab included induction (1 patient) and remission maintenance (43 patients). The median (IQR) interval from the time of last rituximab administration to receipt of vaccine was 200 days (124–425 days).

Only 18 (37%) developed detectable humoral response. No recipient of Johnson & Johnson vaccine (0/4) had evidence of humoral response. Among those treated with rituximab (online supplemental table 1), absence of serologic response was associated with vaccine type (p=0.024), lack of CD19 reconstitution (p<0.0001), hypo-IgM (p=0.03) and shorter interval from last rituximab infusion (p=0.002) (online supplemental figure 1). Nineteen (43%) of those treated with rituximab had evidence of B-cell reconstitution, of whom fifteen had detectable humoral response (p<0.0001). Of the four patients who did not have a humoral response despite B-cell reconstitution, one was undergoing treatment for lung cancer with Navelbine, one was on concurrent mycophenolate mofetil and two were on subcutaneous immunoglobulin.

Thirteen patients (27%) reported adverse events after D1, while 17 (39%) patients reported adverse events after D2. Fatigue (n=9) and headache (n=9) were the most reported events. There was no association of either local or systemic adverse events with humoral response. No AAV relapses were reported. Two patients without humoral response developed severe SARS-CoV-2 infection. The first patient required mechanical ventilation and died on day 10 of hospitalisation. The second patient required hospitalisation for 1 week.

In this study, only 37% of participants had detectable humoral response to SARS-CoV-2 vaccination. The majority (92%) of patients were on rituximab maintenance therapy. Longer duration from rituximab exposure, as well as B-cell reconstitution, was associated with a greater likelihood of response. In this study, no patient who received Johnson-Johnson vaccine mounted a detectable humoral response, though our analysis is limited by the small sample size. While this single dose vaccine has induced immunogenicity in healthy individuals, patients on immunosuppression were not well represented in the trials[11 12] and this warrants additional study.

Vaccine-associated side effects were similar to those reported in the clinical trials.[1 2] There were no reports of disease relapse following vaccination. Two patients developed severe SARS-CoV-2 infection following vaccination; one of these patients died.

Similar to other reports,[3 13] we demonstrated a limited humoral response to SARS-CoV-2 vaccination in patients treated with rituximab. No safety concerns were identified. Patients treated with rituximab are more likely to experience poor outcomes if they are infected with COVID-19,[14] and should be aware of the potential for limited vaccine response. It is critical that providers continue to recommend risk-minimisation strategies and ongoing vigilance in preventative measures. These high-risk patients may benefit from alternative vaccination strategies such as additional booster doses or combination of vaccine types to enhance immunogenicity, although more studies are needed to define an optimal strategy in this vulnerable population.

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Table 1 Patient demographics stratified by presence or absence of SARS-CoV-2 antispike antibody

	Total cohort n=48	Spike antibody positive n=18	Spike antibody negative n=30	P value
Age, years				
Median (IQR)	69.0 (62, 74)	70.5 (62.0, 74.0)	69.0 (59.0, 73.0)	0.38
Gender, n (%)				0.82
Female	17 (35.4)	6 (33.3)	11 (36.7)	
Male	31 (64.5)	12 (66.7)	19 (63.3)	
Race, n (%)				0.76
White	37 (77.0)	15 (83.3)	22 (73.3)	
African American	6 (12.5)	1 (5.6)	5 (16.7)	
Hispanic	2 (4.2)	1 (5.6)	1 (3.3)	
Other	3 (6.3)	1 (5.6)	2 (6.7)	
ANCA type, n (%)				0.34
PR3	16 (33.3)	4 (22.2)	12 (40.0)	
MPO	32 (66.7)	14 (77.8)	18 (60.0)	
Organs involved with ANCA, n (%)				
Renal	47 (97.9)	18 (100)	29 (96.7)	1.00
Extrarenal	37 (77.0)	15 (83.3)	22 (73.3)	0.50
Comorbidities, n (%)				
Hypertension	42 (87.5)	16 (89.9)	26 (86.7)	1.00
Diabetes	8 (16.7)	3 (16.7)	5 (16.7)	1.00
Heart disease	8 (16.7)	4 (22.2)	4 (13.3)	0.45
Lung disease	7 (14.6)	3 (16.7)	4 (13.3)	1.00
ESRD	8 (16.7)	3 (16.7)	5 (16.7)	1.00
Renal transplant	4 (8.3)	1 (5.6)	3 (10.0)	1.00
Vaccine type, n (%)				0.02
Pfizer	19 (39.6)	4 (22.2)	15 (50.0)	
Moderna	25 (52.1)	14 (77.8)	11 (36.7)	
Johnson & Johnson	4 (8.3)	0 (0.0)	4 (13.3)	
Patient-reported side effects, n (%)				
1st dose of vaccine	13 (27.1)	5 (27.8)	8 (26.7)	0.93
2nd dose of vaccinePI	17 (38.6)	7 (38.9)	10 (38.5)	0.98
Immunosuppressant regimen, n (%)				
Rituximab	44 (91.7)	17 (94.4)	27 (90.0)	1.00
Prednisone	14 (29.2)	4 (22.2)	10 (33.3)	0.52
MMF	6 (12.5)	2 (11.1)	4 (13.3)	1.00
Tacrolimus	4 (8.33)	1 (5.6)	3 (10.0)	1.00
SCIg	2 (4.2)	1 (5.6)	1 (3.3)	1.00
Others	1 (2.1)	0 (0.0)	1 (3.3)	1.00
RTX administration, n (%)				
Within 4 months*	15 (31.9)	0 (0.0)	16 (55.2)	0.0002
Within 6 months*	22 (46.8)	3 (16.7)	19 (65.5)	0.002
Lab work (SD)				
White cell count	7.1 (1.9)	6.4 (1.8)	7.5 (1.9)	0.07
eGFR	39.7 (19.3)	35.6 (17.8)	42.1 (20.1)	0.28
IgG				
Median (IQR)	653.5 (443.5, 831.5)	742.0 (417,1008)	627.0 (450, 809)	0.273
IgM				
Median (IQR)	36.2 (18, 49)	37.0 (22.5, 56.5)	25.0 (25.0, 44.0)	0.113
IgA				
Median (IQR)	126.0 (83,182)	105.5 (75.5, 149.5)	147.0 (88.0, 228.0)	0.134
CD19 Reconstituted, n (%)	19 (43.2%)	15 (88.4%)	4 (14.8%)	<0.001
Per cent CD19 count				
Median (IQR)	0.0 (0.0, 2.8)	4.0 (1.1, 5.1)	0.0 (0.0, 0.0)	<0.001
Low IgG, n (%)	18 (40.9)	5 (29.4)	13 (48.2)	0.22
Low IgM, n (%)	21 (47.7)	4 (23.5)	17 (63.0)	0.015

*Within 4, 6 months: 1 frequency missing.
ANCA, anti-neutrophil cytoplasmic antibody; CD 19, cluster of differentiation 19; eGFR, estimated glomerular filtration rate; ESRD, end stage kidney disease; MPO, myeloperxoidase; MWF, Monday, Wednesday, Friday; PR3, proteinase 3; RTX, rituximab; SCIg, subcutaneous.

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Correspondence on "SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response" by Bonelli *et al*

Bonelli *et al* recently reported reduced humoral responses to the BNT162b2 mRNA vaccine in five patients on rituximab therapy; in two patients with repopulated B cells, a low-level Spike protein antibody response occurred, but three patients with no detectable B-cells had no measurable antibody response to the vaccine.[1] Of great interest, they reported that interferon-γ T-cell responses to SARS-CoV-2 Spike peptides were present in all five patients, irrespective of the antibody response to the vaccine.

It has been reported that patients on B-cell depleting therapy are at increased risk for hospitalisation and death from SARS-CoV-2 infection.[2] In February 2021, the American College of Rheumatology (ACR) COVID-19 Taskforce published consensus guidelines regarding vaccine timing in immunosuppressed patients, despite the paucity of data available at that time on vaccine efficacy in patients on targeted B cell therapy.[3] Moreover, the guidelines specifically recommended against antibody testing. There is also a public perception that vaccinated patients have minimal risk of infection and can resume a normal lifestyle. However, emerging data from patients on targeted B cell therapies suggest a more cautious approach.

Here, we report an additional 15 patients on targeted B-cell therapy from our institution who mounted no detectable anti-Spike IgG protein levels in response to vaccination (table 1). Several of these patients were on concomitant T-cell immunosuppression and/or methotrexate therapy. Anti-Spike antibodies were detected using the EUA Euroimmun assay (IgG binding SARS-CoV-2 spike protein S1 including the RBD domain) in a CLIA-certified laboratory. Results from this assay have been shown to correlate with viral neutralisation titers and have been used to quantify antibody levels following COVID-19 infection.[4] Unlike the Bonelli *et al* study, this cohort depicts real-life clinical scenarios where patients pursued vaccination prior to or without knowledge of the ACR COVID-19 vaccine guidance recommendations. In the vast majority of cases, the decision to measure anti-Spike antibody levels was driven by the patient, who expressed concern regarding his/her level of protection during treatment with targeted B-cell suppression. It is worth noting that 2 of the 15 patients had CD19+ B cell levels measured at the time of anti-Spike IgG testing, and in both cases, CD19+ B cell levels were found to be nearly absent (case 1 with CD19+ absolute count 0.022×10^3/μL (2%) and case 8 with 0.000/μL (0%); normal range $0.160–0.390\times10^3$/μL).

These data raise concern for the safety of our patients on targeted B-cell therapy, particularly for those on additional immunosuppressive agents. Data regarding potential T-cell responses to the vaccine that might be important for protection remain unclear. However, knowing a patient's serological antibody response to vaccination could be helpful in two respects: (1) for clinicians, knowledge of antibody titres may prioritise such individuals for booster doses and influence the decision to administer therapeutic monoclonal antibody in the event of SARS-CoV-2 infection and (2) for patients, knowledge of low antibody levels may provide value in self-regulation of high-risk activities. It is likely that evaluation of CD19+ B cell levels may help guide vaccination timing, as suggested by the Bonelli *et al* data. Until more information is available, we recommend that patients on targeted B-cell depleting or suppressive therapy follow local guidelines on COVID-19 prevention as if they were not vaccinated.

Table 1 Characteristics of 15 patients on targeted B-cell therapy with undetectable anti-SARS-CoV-2 Spike IgG levels after COVID-19 vaccination

Case	Age/sex	Disease	BCDT dose at last administration*	Concomitant immunosuppression	Vaccine type†	Days from BCDT dose to vaccine‡	Days from last vaccine to anti-Spike IgG testing§
1	41/M	AAV	RTX 500 mg	–	mRNA	206	59
2	67/M	AAV	RTX 1000 mg	Prednisone 10 mg one time a day	Viral vector	185	28
3	64/F	AAV	RTX 1000 mg	–	mRNA	60	68
4	72/F	AAV	RTX 500 mg	Prednisone 5 mg one time a day	mRNA	65	60
5	67/M	RA	RTX 1000 mg	MTX 15 mg weekly	mRNA	109	13
6	53/F	RA	RTX 1000 mg	Prednisone 10 mg one time a day	mRNA	88	23
7	53/M	RA	RTX 1000 mg	Prednisone 5 mg one time a day. HCQ 200 mg one time a day	mRNA	43	66
8	66/M	RA	RTX 1000 mg	MTX 20 mg weekly	mRNA	36	80
9	62/F	SSc	RTX 1000 mg	MMF 1000 mg two times a day	mRNA	110	43¶
10	57/F	SSc	RTX 1000 mg	HCQ 300 mg one time a day	mRNA	13	39
11	64/F	SSc	RTX 1000 mg	Prednisone 5 mg one time a day MMF 1500 mg two times a day MTX 17.5 mg weekly	mRNA	12	20
12	45/F	SLE	RTX 1000 mg	HCQ 300 mg one time a day	mRNA	39	9
13	34/F	SLE	BEL 200 mg	MMF 1500 mg two times a day	mRNA	5	15
14	47/F	IgG4-RD	RTX 1000 mg	Prednisone 8 mg one time a day	mRNA	54	41
15	27/F	IgA vasculitis	RTX 1000 mg	–	mRNA	67	4

No patient had a history of SARS-CoV-2 clinical infection and/or testing by PCR.
*BCDT dose refers to the dose last received prior to COVID-19 vaccination.
†mRNA refers to Pfizer-BioNTech vaccine (two doses) or Moderna vaccine series (two doses); viral vector refers to Johnson & Johnson Janssen vaccine (one dose).
‡Vaccine refers to first/initial vaccine dose date, if series.
§Vaccine refers to second/last vaccine dose, if series; anti-Spike IgG assessment as detected by Euroimmun IgG assay.
¶As detected by DiaSorin Liaison SARS-CoV-2 S1/S2 IgG assay (LabCorp Seattle).
AAV, ANCA-associated vasculitis; BEL, belimumab; HCQ, hydroxychloroquine; IgG4-RD, IgG4-related disease; MMF, mycophenolate mofetil; MTX, oral methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

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Correspondence on "SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response" by Bonelli *et al*

We have read the interesting research by Bonelli *et al* on the role of rituximab in vaccination for SARS-CoV-2. In the data on five patients, two had repopulated B cells and had antibodies to SARS-CoV-2 RBD after vaccination.[1] In our experience, we evaluated a group of patients with rheumatoid arthritis who had received the last infusion of rituximab 6 months earlier (group A, four patients), a group of patients who had received the last dose of rituximab 9 months earlier (group B, five patients) and finally a group of patients who had received rituximab 12 months earlier (group C, five patients). All patients received two doses of SARS-CoV-2 mRNA BNT162b2 vaccine 21 days apart. Patients underwent evaluation of the lymphocyte subpopulations with determinations of the B-lymphocyte population (CD27-naive, CD27+ memory, CD38+, CD20+ and CD19+) evaluated by flow cytometry (FACS CANTO II, BD Biosciences), before the vaccination and 3 weeks after the second dose of vaccine. The value of anti-SARS-CoV-2 Spike RBD IgG antibodies (IgG antibodies against S1-protein quantified by FEIA ThermoFisher, Uppsala, Sweden) was determined 3 weeks after the second vaccine dose. All patients were in clinical remission at the time of vaccination and discontinued methotrexate in the week of the first and second vaccine administrations according to published recommendations.[2 3] Table 1 shows the characteristics of the sample of the 14 patients. The median levels (min–max) of anti-SARS-CoV-2 Spike RBD IgG antibodies levels (binding antibody units (BAU)/mL) were in the different groups as followings: group A 294 (0.70–569), group B 764 (164–1632), group C 638 (0.70–16320). Differences between the three groups were not statistically significative (p=0.536). Statistical analysis performed with Pearson's correlation coefficient highlighted the following correlations between antibody quantitative levels and lymphocyte subpopulations: IgG anti-SARS-CoV-2 RBD/CD19 cells/mcl=0.7126, p=0.0039; IgG anti-SARS-CoV-2 RBD/CD20 cells/mcl=0.599, p=0.0236; IgG anti-SARS-CoV-2 RBD/CD27-naive cells/mcl=0.557, p=0.386. In the multiple linear regression model, only CD19 cells' mcl levels maintained a significance as a predictor of IgG anti-SARS-CoV RBD levels with an estimated beta coefficient of 4.105 (p=0.004). A previous study in 126 patients focused on the role of rituximab in vaccination for SARS-CoV-2.[4] Another recent study published in the *Annals of the Rheumatic Diseases* shows that only patients who had repopulated for B lymphocytes exhibited an immune response to the SARS-CoV-2 vaccine. In the study, 11 patients repopulated but only 7 responded.[5] The data from our study show that the time of 9 months since the last infusion of rituximab is sufficient to achieve an immune response, and this can be assessed by the reappearance of circulating CD27-naive CD20+CD19+B lymphocytes. Another aspect to evaluate is the number of treatment exposure cycles in our series 6.07±2.27, which can limit the repopulation of B lymphocytes over time. In conclusion, careful evaluation of peripheral B cell maturation may help the clinician to determine the right time to vaccinate patients treated with rituximab for rheumatic diseases.

Table 1 Demographic, clinical and laboratory charateristics of patients under RTX treatment

	Group	Overall
n		14
Female/male		13/1
Age (years), mean (SD)		57.36 (13.19)
CD3/cells/mcl, mean (SD)		1376.93 (583.76)
CD3/CD4/cells/mcl, mean (SD)		838.36 (422.43)
CD3/CD8/cells/mcl, mean (SD)		451.57 (307.68)
CD3/CD56/CD16/cells/mcl, mean (SD)		286.21 (101.39)
CD19/cells/mcl, median (min–max)		31 (2.20–383)
CD20/cells/mcl, median (min–max)		25.50 (1–491)
CD27/memory cells/mcl, median (min–max)		8.50 (2–19)
CD27/naive cells/mcl, median (min–max)		40(8–476)
CD38/cells/mcl, median (min–max)		14.50(2–236)
MTX dose, median (min–max)		10(10–15)
Prednisone dose, median (min–max)		5 (2.50–5)
Number RTX cycle, mean (SD)		6.07 (2.27)
RTX week before mean (SD)		40.64 (12.71)
Months since last RTX (%)	6–9	4 (28.6)
	9–12	4 (28.6)
	>12	6 (42.9)
IgG anti-SARS CoV-2 RBD BAU/mL, median (min–max)		418 (0.70–1632)

MTX, methotrexate.

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Response to: Correspondence on "SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response" by Bonelli *et al*

We have read the correspondence of Chung *et al* to our article[1] with great interest. The authors measured anti-SARS-CoV-2 spike IgG levels after COVID-19 vaccination in 15 patients on B cell-depleting therapy. In accordance with our data no detectable anti-spike IgG levels in response to vaccination were found. Therefore, the authors suggest that these patients should be prioritised for booster vaccinations and that patients on B cell-depleting therapy should follow local guidelines for COVID-19 vaccination, since data on the importance of a T cell-mediated immune response are still missing.[2] We certainly agree with the authors; however, we could recently show that a T cell-mediated immune response can be mounted in up to 60% of rituximab-treated patients in the absence of a humoral immune response.[3] Patients under B cell-depleting therapy have an increased risk of more severe disease courses and persistent viraemia on SARS-CoV-2 infection.[4–7] Although data on the exact role of a cellular immune response for protection of severe disease courses are missing, our data indicate that vaccination in high-risk patients such as those treated with rituximab should not be withheld.

Another important aspect that should be considered is the number of peripheral B cells. Benucci *et al*[8] analysed humoral immune response in 14 rituximab-treated patients and evaluated B lymphocyte populations in parallel. The authors observed a significant correlation between neutralising antibody levels and CD19 and CD20 positive lymphocyte populations, suggesting that evaluation of peripheral B cell numbers may help for the right timing of SARS-CoV-2 vaccination in rituximab-treated patients.

These data are supported by Connolly *et al*,[9] who evaluated tolerability and humoral immune response to SARS-CoV-2 vaccination in 48 patients with ANCA-associated vasculitis. Among the rituximab-treated patients (n=44) absence of humoral immune responses was associated with lack of CD19-positive cell reconstitution and a shorter interval from last rituximab infusion. The majority of the patients with detectable humoral immune response had evidence of B cell reconstitution. In line with these data, we could recently show that circulating B cells correlate with levels of antibodies against SARS-CoV-2; however, patients with low numbers of B cells also mounted humoral immune responses to SARS-CoV-2 vaccination.[3]

In summary patients under rituximab treatment are at high risk of severe disease courses on SARS-CoV-2 infection and we still do not fully understand the exact role of immunosuppressive therapies and comedication on humoral and cellular immune responses. Recent evidence points to a role of an additional booster vaccination in patients with no humoral immune response to SARS-CoV-2 vaccination. More studies are needed to understand if an additional boost affects humoral and T cell-mediated immune responses and if this is associated with a higher protection against COVID-19 infection.

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Correspondence on 'SARS-CoV-2 vaccine hesitancy among patients with rheumatic and musculoskeletal diseases: a message for rheumatologists'

We read with great interest the letter recently published in *Annals of the Rheumatic Diseases* by Priori *et al*,[1] who carried out an online survey among patients with rheumatic diseases to explore their willingness to receive the SARS-CoV-2 vaccination. An alarming high hesitancy was observed in nearly half of these patients.

This is particularly concerning as patients with autoimmune inflammatory rheumatic diseases (AIIRDs) are regarded as at higher risk for developing severe COVID-19 and, for this reason, they should be vaccinated with priority.[2 3]

To date, four vaccines have been approved in Italy for COVID-19 but only three are currently available (ie, Pfizer/BioNTech, Moderna and AstraZeneca). Importantly, the European Alliance of Association for Rheumatology stated that all these vaccines can be used safely in patients with AIIRDs as well as in patients receiving immunosuppressive treatment.[4] Similarly, the Italian Society of Rheumatology (Società Italiana di Reumatologia) produced a document (last update: 13 March 2021) to confirm the safety of all the SARS-CoV-2 vaccines for patients with AIIRDs.[5]

In recent weeks, AstraZeneca vaccine is undergoing an unprecedented media firestorm following reports on its possible association with venous thromboembolism.[6] With this regard, the European Medicines Agency has stated that the overall benefits of AstraZeneca vaccine in preventing COVID-19 outweigh the risks of side effects in the general population.[7]

Our aim was to explore the willingness to receive SARS-CoV-2 vaccines among patients with AIIRDs, as well as their eventual reasons for declining and preferences on the different available vaccines.

From 1 April to 13 April, we performed a phone survey among patients with AIIRDs followed-up at the Rheumatology Unit of "Carlo Urbani" Hospital in Jesi (Ancona, Italy), Polytechnic University of Marche. All patients provided their informed consent for the use of their anonymous data. For statistical analyses, Mann-Whitney test, χ^2 test and multivariate logistic regression analysis were used (two-sided, significance level <0.05). The analyses were performed with SPSS (V.26).

The following questions were asked to the patients:

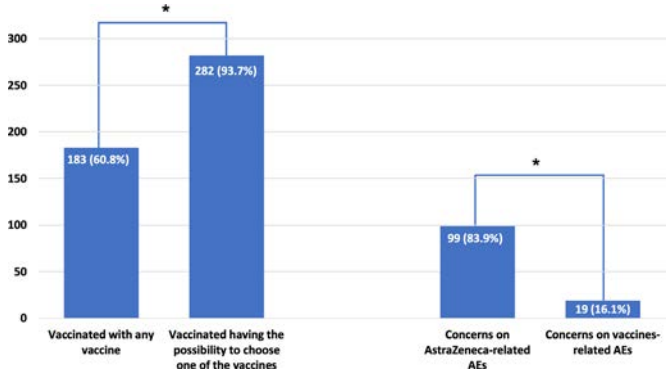

Figure 1 Vaccination acceptance among patients with autoimmune inflammatory rheumatic diseases (on the left) and main reasons for declining (on the right). All the comparisons (*) are significant (p<0.01). AEs, adverse events.

- Would you agree to be vaccinated with any of the SARS-CoV-2 vaccines currently available in Italy (ie, Pfizer/BioNTech, Moderna and AstraZeneca)?

In case of negative answer, the following questions were asked:

- Why not?
- Would you agree to be vaccinated having the possibility to choose one of the SARS-CoV-2 vaccines among those currently available in Italy? If YES, which one(s) would you choose?

A total of 301 patients agreed to participate in this survey. Demographic and clinical data are shown in online supplemental table S1. The willingness to potentially receive any of the SARS-CoV-2 vaccines was reported by 183 out of 301 (60.8%) patients, similarly to what observed by Priori *et al*.[1] Concerns about AstraZeneca-related adverse events were the main reason for declining; indeed, 99 out of 118 (83.9%) patients who declined would have accepted to be vaccinated if they were given the option to choose a different vaccine (Pfizer/BioNTech or Moderna) (figure 1). Only 19 patients declined because of fear of vaccines-related adverse events (16.1%).

The decision of accepting or declining vaccination was not associated with any of the demographic and clinical variables evaluated (eg, age, gender and education) (online supplementary table S2).

The main result of our survey is that the decision of accepting or declining vaccination is heavily influenced by the type of vaccine. While the great majority of patients would accept the possibility to get vaccinated either with Pfizer/BioNTech or Moderna (93.7%), almost one-third would refuse vaccination because of concerns regarding AstraZeneca vaccine (32.9%).

Our data clearly highlight the discrepancy between what is perceived by patients with AIIRDs and the recommendations coming from international scientific societies regarding the safety of AstraZeneca vaccine. This might be explained by the uncertainty generated by conflicting messages from mass media, social media and controversial decisions by political institutions. The prevalence of AstraZeneca-related venous thromboembolism is low (approximately four cases per million[7]) and its prevalence does not seem to exceed the expected incidence rate in the general population.[8]

Our results raise the need of promoting initiatives to defeat AstraZeneca vaccine scepticism among patients with AIIRDs. Rheumatologists should actively inform their patients on benefits and risks of SARS-CoV-2 vaccine, as recommended by national and international scientific societies. In this context, two recent studies have demonstrated that rheumatologists have the potential to increase the willingness of patients with AIIRDs to receive vaccination; in these studies, 9%–20% of patients with AIIRDs would have reconsidered their refusal of vaccination on recommendation by their treating physician.[9 10] Moreover, Priori *et al* showed that patients with AIIRDs would be significantly more willing than healthy controls to reconsider their decision if they were provided more medical education.[1] This is particularly relevant in view of the fact that one of the possible future scenarios includes the need for periodical revaccination.[11]

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Response to: 'Correspondence on 'SARS-CoV-2 vaccine hesitancy among patients with rheumatic and musculoskeletal diseases: a message for rheumatologists" by Smerilli *et al*

We appreciate the comments by Smerilli *et al*[1] in response to our letter[2] about the willingness to vaccination among patients with rheumatic and musculoskeletal diseases (RMDs).

By the time we had performed our survey, only the Pfizer–BioNTech vaccine was available for the administration to healthcare personnel, therefore we could not assess whether, among the reasons for refusal, the kind of vaccine might have affected willingness to vaccinate. After some months, once other vaccines became available, Smerilli *et al*, confirming a rate of acceptance to COVID-19 vaccination similar to ours, had the opportunity to observe that the decision of accepting or declining vaccination is heavily influenced by the type of vaccine.

We can now corroborate Smerilli's results. In fact, during the last few weeks, our tertiary referral centre has organised the vaccination campaign by starting to contact our extremely vulnerable patients by telephone call (according to the definition of our Minister of Health those subjects with autoimmune diseases and an immunodeficiency secondary to treatments or with severe lung involvement) (https://www.salutelazio.it/documents/10182/59078875/allegato+1_COV19_12-03-2021.pdf/5a4f445b-31d8-6426-2dd5-ffe53ea6c8f3 (accessed 25 April 2021)) to make an appointment for vaccination with the Pfizer–BioNTech product. Only 54 (5.2%) out of the 1027 subjects contacted so far have declined, which is a lower percentage than that previously reported in January[2] when vaccination was only a still far possibility and not a real opportunity, in line with those observed in the USA by Nguyen *et al*.[3] Other kinds of vaccines were not available for such prioritised category of patients, so we could not check if proposing Vaxzevria or others would have increased refusals.

Across all countries, vaccines and population groups, the leading cause of concerns for vaccinations is vaccine safety,[4] in the peculiar case of COVID-19 it appears that safety concerns linked to the type of vaccine, more than to vaccination itself, outweigh the perceived disease risks.[5]

This type of concern is probably unprecedented in the history of vaccination campaigns and is possibly linked to an overabundance of information concerning this topic, some of which are potentially harmful because untrue. Vaccine acceptance is a complex decision-making process influenced by a wide spectrum of factors among which communication and media environments play an important role.[6] We, as physicians, have the responsibility and the duty to increase our patients' willingness to vaccinate on the ground of solid scientific evidence about risk and benefits, trying to fight this unique and overwhelming COVID-19 infodemic. In this context, we are planning calls between specialists and their patients with RMDs who had refused vaccination to verify if a personal contact might increase awareness and willingness to vaccinate.

Roberta Priori ,[1,2] **Greta Pellegrino** ,[1] **Serena Colafrancesco** ,[1] **Cristiano Alessandri** ,[1] **Fulvia Ceccarelli** ,[1] **Manuela Di Franco**,[1] **Valeria Riccieri** ,[1] **Rossana Scrivo** ,[1] **Antonio Sili Scavalli**,[1] **Francesca Romana Spinelli** ,[1] **Fabrizio Conti** [1]

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Correspondence on 'Influence of COVID-19 pandemic on decisions for the management of people with inflammatory rheumatic and musculoskeletal diseases: a survey among EULAR countries'

We read with interest the article by Dejaco *et al* recently published in *Annals of the Rheumatic Disease* on the influence of the COVID-19 pandemic on decisions on the management of individuals with rheumatic diseases.[1] One issue not touched on in this article is attitudes to vaccination, particularly influenza vaccination, in the COVID-19 era. Seasonal influenza infection is a major cause of morbidity and mortality in selected individuals with altered immune response.[2] Influenza vaccination is recommended for the majority of individuals with autoimmune inflammatory rheumatic diseases.[3]

Previous studies of patients with autoimmune diseases in general and rheumatologic conditions in particular have demonstrated low uptake for influenza vaccine.[4 5] The median vaccination coverage rate was 47.1% for 3 seasons in 2015–2018 among older age groups within Europe.[5] Various reasons have been suggested for low influenza vaccination uptake, from patient belief that the vaccination is ineffective, perceived financial cost, concerns regarding adverse side effects of vaccination, lack of patient education, to a patient's own underestimation of their own health risk profile.[6–9]

In the current context of the COVID-19 global pandemic, public perception of and interest in vaccination programmes has rarely been of a higher concern. Influenza vaccination uptake has emerged as a public health concern of even greater importance in 2020–2021 winter season in order to minimise additional burden on already overstretched healthcare system.

We did a cross-sectional study in St James's Hospital, Ireland. A questionnaire was given to all patients attending a general rheumatology clinic over the course of 3 months (October–December 2020). This questionnaire consisted of self-reported information regarding socio-demographic characteristics, personal history of chronic illnesses, previous personal uptake of the influenza vaccine in 2019 and personal interest in undergoing vaccination for influenza in 2020/2021. This 14-item questionnaire was self-designed based on variables identified in a literature review. Criteria for inclusion included all adult patients who attended outpatient rheumatology clinic appointments during the specified time period. Those who declined to be part of the study were excluded. The study was approved by the St James's Hospital's Research and Innovation Office. The data were summarised using descriptive analyses.

A total of 200 patients completed the survey, 136 (68%) were women and the median age was 59 years, the majority were non-smoker (60%). Eighty-five patients (42.5%) documented actively taking immunosuppressive treatment. The most common comorbidities reported were hypertension: 40/200 (20%), followed by chronic obstructive pulmonary disease (COPD): 18/200 (9%), diabetes: 17/200 (8.5%) and cardiovascular disease: 14/200 (7%). Eighty one (40.5%) of the studied population did not receive influenza vaccination in 2019 due to various reasons, including fear of adverse reaction (n=15), perceived good health (n=15), personal lack of belief in the vaccine effectiveness (n=11), a reported history of side effects (n=10), a lack of recommendation from healthcare workers (n=6), lack of access to the vaccine (n=5), high cost of the vaccine (n=5), needle phobia (n=2) and others provided no reason for their decision (n=12). Among those that did not engage with influenza vaccination in 2019, 39 (48%) opted to receive vaccination in 2020.

The primary aim of this study was to capture patient's perception of influenza vaccination during the COVID-19 pandemic; in relation to this, the overall percentage of vaccination is comparable to previous studies carried out in Ireland.[10 11] A study in Southern Denmark looked at influenza vaccine uptake among 192 rheumatoid arthritis patients. Self-reported uptake was found in 59%. In this study, the most common factor associated with low uptake of vaccination was fear of adverse effects.[12] According to our results, the most common factors affecting the level of vaccination were fear of adverse reactions, perceived good health, personal lack of belief in the vaccine and a history of adverse reaction; there were slight differences in ranking compared with prior studies but shared common themes.

The strength of this study was the good sample size and high response rate. There are a number of limitations of this study. These include a selection bias featuring exclusively those attending rheumatology outpatient clinics, a population more likely to receive healthcare recommendations of vaccination uptake compared with the average population. The self-reported nature of the questionnaire introduces some limitations with regards to the comprehensiveness of our data. There was some variability with regards to patient's response and completion of the questionnaire.

Influenza vaccine is an important step to alleviate global health burden associated with seasonal influenza virus and its negative sequelae during COVID-19 pandemic. The study highlights suboptimal uptake in at risk population seen at our general rheumatology clinic. It indicates the need for a greater emphasis to address concerns surrounding vaccination in our vulnerable patients.

Shamma Al Nokhatha,[1,2,3] **Neil MacEoin,**[3] **Richard Conway**[3]

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Response to: 'Correspondence on 'Influence of COVID-19 pandemic on decisions for the management of people with inflammatory rheumatic and musculoskeletal diseases: a survey among EULAR countries' by Nokhatha *et al*

The letter from Al Nokhatha *et al* nicely complements our study whose primary purpose was to investigate how COVID-19 related closure of services influenced decisions of rheumatologists and health professionals in rheumatology regarding the management of patients with inflammatory rheumatic and musculoskeletal diseases (RMD).[1 2] In contrast to the study by Al Nokhatha *et al*, we did not include data on vaccinations, which were at that time still far away.

The authors of this letter correctly point out that vaccination is fundamental to our patients in order to protect them from adverse outcomes of (certain) infections. However, many patients with inflammatory RMD are immunocompromised, and it is well known that in such a clientele, vaccination is challenging regarding both efficacy and safety. Paget *et al* recently concluded that influenza vaccination should continuously be promoted during COVID-19 pandemic as a central public health measure.[3] The reason is that the evidence accrued so far clearly indicates that the management of the coronavirus pandemic can greatly benefit from influenza vaccination, for example, by facilitating differential diagnosis and by avoiding an overload of health services and hospitals associated with influenza infections.[3 4] Also, influenza vaccination protects elderly people which are particularly vulnerable to COVID-19. Al Nokhatha *et al* noted that there are some barriers to receive influenza vaccination that might also be relevant for ongoing vaccination against SARS-CoV-2: peoples' fear of adverse reactions, perceived good health, personal lack of belief in the vaccine effectiveness, a reported history of side effects, a lack of recommendation from healthcare workers or lack of access to the vaccine.[1] The authors of this correspondence have experienced some additional obstacles during COVID-19 pandemic such as patients' fear to enter health service structures, lack of manpower to adequately organise and conduct vaccination, lack of vaccine and patients' fear that influenza vaccination might lower the defence against COVID-19.

Given the vulnerability of patients with inflammatory RMD to infections, we need to make sure that our patients undergo influenza and SARS-CoV-2 vaccinations. We should develop strategies to address patients' specific concerns about the new vaccine, such as the fact that the vaccines have not been specifically tested in patients with autoimmune disease or that possible long-term consequences of SARS-CoV-2 vaccination are unknown yet.

In accordance with a recent statement from 'European League Against Rheumatism,[5] we think that rheumatologists should be the primary experts to discuss these issues with their patients. Moreover, national societies of rheumatology should launch public programmes influencing mass opinion in order to convince patients with RMD, their relatives and friends, that vaccination against SARS-CoV-2 is the only way to protect people from COVID-19.

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