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nature reviews rheumatology

TREAT-TO-TARGET
Moving towards implementation of a T2T strategy for SLE

JAK-targeting therapies in rheumatology
A mechanisms-based approach

HIPPOCRATES: improving diagnosis and outcomes in psoriatic arthritis

Oliver FitzGerald ✉ *and Stephen R. Pennington*

Combining the diverse expertise of clinical and scientific researchers from across Europe as well as patient representatives and pharmaceutical industry partners, the HIPPOCRATES consortium aims to characterize the molecular pathways underlying psoriatic arthritis in order to improve early diagnosis and precision treatment strategies for the disease.

Despite many years of progress in understanding the molecular pathways underpinning psoriatic arthritis (PsA) and in the management of this disease, it is evident that considerable clinical needs remain unmet[1]. HIPPOCRATES, a new European research programme funded by the Innovative Medicines Initiative, aims to address these needs by investigating the mechanisms and biomarkers associated with PsA, with the intention of improving diagnostic and therapeutic options for people living with the condition. In this commentary, as coordinating partner, we represent the views of the HIPPOCRATES consortium.

Unmet clinical needs in PsA

PsA is a chronic immune-mediated inflammatory disease that, together with skin involvement, affects joints and other components of the musculoskeletal system, in an estimated 1–2% of the general population[2]. PsA is associated with an increase in mortality and a reduction in quality of life, both likely to be related to the burden of inflammatory disease and to comorbidities[3].

Current approaches to diagnosis and treatment of PsA can result in poor short-term and long-term outcomes. As there are no diagnostic criteria or tests available, patients commonly experience a delay in diagnosis, which in turn contributes to a delay in establishing effective treatment. A delay in diagnosis of as little as 6 months, compared with an early diagnosis, is associated with worse radiographic outcomes and increased functional disability[4]. Thus, the early identification of those patients with psoriasis who are developing features of PsA is an important unmet need, as is the diagnosis of PsA in patients with early, undifferentiated inflammatory arthritis. Improved tools are also required to predict the emergence of PsA in patients with psoriasis, as the validation of candidate biomarkers and the development of a combined risk model for progression to PsA (including clinical, genetic and molecular risk factors) is a critical step for the development of a strategy aimed at PsA prevention. The ability to identify at baseline those patients with PsA whose disease will progress is also needed for the development of a stratified treatment approach. To date, there are no validated biomarkers or clinical algorithms that predict which patients with PsA will develop bone or joint damage.

Despite the emergence of new treatments for PsA that target a variety of molecular pathways, overall response rates have not improved; ~40% of participants in randomized controlled trials (RCTs) of such treatments fail to achieve an ACR20 response, and only ~25% meet more stringent disease response measures, such as ACR70 response, low disease activity or remission[5]. For a patient with active PsA, their disease might progress while the treating rheumatologist, without any reliable clinical or biochemical markers to guide them, tries one treatment after another. The identification and validation of biomarkers that predict an individual patient's response to treatment will underpin future precision treatment strategies.

The HIPPOCRATES approach

The ambitious, overarching aim of HIPPOCRATES is to characterize the key pathophysiological mechanisms that contribute to the development of PsA in patients with psoriasis and that define outcomes in patients with PsA. We anticipate that an improved, more detailed description of psoriatic disease endotypes and a better understanding of the molecular pathways resulting in these endotypes will enable individual patient profiles to inform therapy choice.

A key element of HIPPOCRATES is that it brings together and provides access to the largest and highest quality PsA cohorts in Europe, including 25,000 patients with psoriasis who will participate in a prospective, observational study. Also accessible will be data, images and biosamples provided by the HIPPOCRATES European Federation of Pharmaceutical Industries and Associations (EFPIA) partners (for example, from the OPAL Broaden (NCT01877668) and OPAL Beyond (NCT01882439) studies of tofacitinib for PsA, which involved more than 700 study participants). With these combined datasets, HIPPOCRATES can address a major shortcoming of previous PsA research, in which dataset sizes were not large enough to account for the

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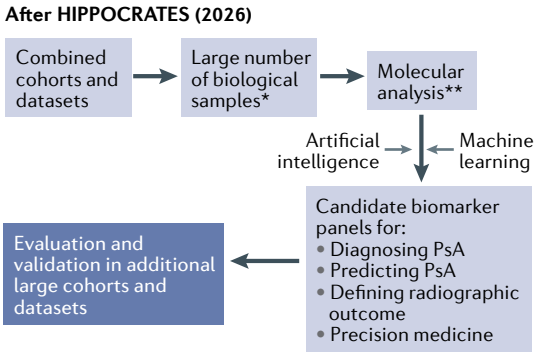

Fig. 1 | **Progress in psoriatic disease biomarker development after HIPPOCRATES.** To date, most biomarker discovery research in psoriatic disease is performed in cohorts from one centre, with no candidate biomarkers sufficiently evaluated or further validated. By the time the HIPPOCRATES project is completed in 2026, we aim to have moved the state-of-the art such that data from multiple, large cohorts will have been curated and combined with subsequent molecular analyses interrogated using artificial intelligence and/or machine learning statistical methods. This approach should yield candidate biomarker panels for areas of key unmet clinical need, which can be validated in other large datasets. *With consideration of pre-analytical variables. **Including quality control measures. PsA, psoriatic arthritis.

heterogeneity of the disease and hence support robust conclusions and implementable solutions. A centralized database is being established that will facilitate data integration and provide a unique opportunity, for both HIPPOCRATES investigators and future research programmes, to address areas of unmet need at scale.

Another important feature of HIPPOCRATES is that a wide range of cutting-edge analytical technologies will be deployed by experts at partner research centres to produce new molecular data. To identify relevant molecular pathways, patients with psoriasis and patients with PsA at various disease stages will be deeply phenotyped using biofluids and tissue; the biofluids will be used for 'omics'-based discovery, which will focus on epigenomics, proteomics, metabolomics and lipidomics, and tissue samples will be used for a range of analyses, including toponomics and single-cell analysis (for example, CyTOF and EpiTOF). All participants in these deep-phenotyping studies will be genotyped so that the results can be stratified according to genotype data.

The use of machine learning and artificial intelligence tools to interpret complex datasets should enable the identification of endotypes and the generation of important new insights, new diagnostic algorithms and prototypes of both diagnostic and therapeutic decision support tools (FIG. 1).

Central to the HIPPOCRATES ethos is that patients contribute to defining the research priorities and to the interpretation and implementation of the results that are obtained. From its initial conception, HIPPOCRATES has had direct, active and ongoing engagement with highly experienced patient research partners (PRPs), who are represented on the HIPPOCRATES management team and on each of the work packages, in addition to forming a patient advisory council. By demonstrating the pervasive benefit of the patient voice, HIPPOCRATES will be an example to future health research projects.

Critical to long-term success will be the ability to validate diagnostic and outcome algorithms in large, independent cohorts. Although the integrated HIPPOCRATES database might be used for such purposes, we have also reached out to investigators beyond the HIPPOCRATES partners through the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), which has access to such cohorts. GRAPPA is now registered in Europe (GRAPPA-EU[6]) thus facilitating such access and providing some funding.

The way forward

By meticulously combining and sharing information from some of the most extensive and well-studied PsA cohorts across Europe and integrating diverse skills, the transdisciplinary HIPPOCRATES consortium has an exciting opportunity to address key research questions at scale and to validate biomarkers for clinical implementation (FIG. 1)[7]. This important opportunity will be enhanced by aligning HIPPOCRATES with international research efforts, including a complementary Accelerating Medicines Partnership-Autoimmune and Immune-Mediated Diseases (AMP-AIM) programme in psoriatic disease[8].

In summary, by integrating the strongest PsA clinical and research teams from across Europe, with the engagement, support and skills of EFPIA partners, the experience of PRPs and connection and integration with other international efforts, HIPPOCRATES should maximise the opportunity to extract critical clinical and molecular data from patient cohorts, thereby enabling development of diagnostic and prognostic tools to support patient stratification for precision treatment strategies.

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Competing interests
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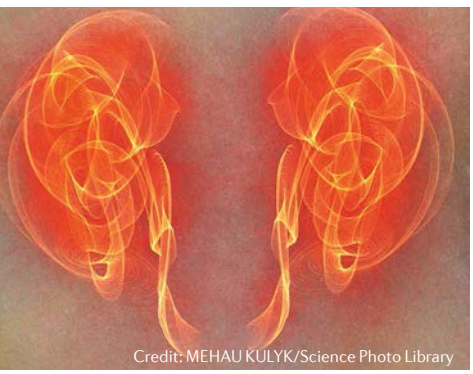
LUPUS NEPHRITIS

CD6 is a therapeutic target for LN

New research confirms that activated leukocyte cell adhesion molecule (ALCAM), a CD6 ligand, is a urinary biomarker of active renal involvement in systemic lupus erythematosus (SLE). Blockade of CD6 in animal models of SLE prolongs survival and reduces disease activity, demonstrating its potential as a therapeutic target.

Lupus nephritis (LN) is a common complication of SLE that causes morbidity and mortality. The CD6–ALCAM pathway is thought to contribute to the pathogenesis of LN via its involvement in T cell activation and trafficking, as previously indicated by identification of upregulation of urinary ALCAM in patients with SLE and LN.



Credit: MEHAU KULYK/Science Photo Library

In a new study, concentrations of urinary ALCAM in 1,038 individuals were highest in those with SLE and LN, intermediate in those with SLE and active nonrenal disease or inactive SLE, and lowest in healthy individuals. This pattern of urinary ALCAM concentrations was observed in independent analyses of African American, Asian, Hispanic and white individuals. "This is an important observation given the disparate burden of LN in minority ethnic groups," notes Chaim Putterman, corresponding author of the study.

Further investigation of the CD6–ALCAM pathway in renal cell populations by single-cell RNA sequencing identified higher numbers of $CD6^+$ leukocytes (primarily T cells) and $ALCAM^+$ leukocytes (primarily antigen-presenting cells) and epithelial cells in biopsy samples from 24 patients with LN than in those from nine healthy individuals.

> Blockade of CD6 in animal models of SLE prolongs survival and reduces disease activity

An anti-CD6 antibody was investigated in relevant mouse models of lupus. "Blockade of CD6 was able to prolong survival, decrease infiltrating immune cells, lower cytokine levels, and reduce renal pathology in a manner comparable to mycophenolate mofetil and cyclophosphamide, both potent immunosuppressors used in the treatment of LN," explains Putterman. "By specifically targeting CD6 on T cells, not only was there a decrease in T cell infiltration and activity but this led to decreased activity of other immune cell types including inflammatory macrophages and neutrophils." These results suggest the CD6–ALCAM pathway is a therapeutic target in SLE, and notably, the anti-CD6 antibody itolizumab is currently being evaluated in clinical trials for the treatment of LN.

Robert Phillips

ORIGINAL ARTICLE Chalmers, S. A. et al. The CD6/ALCAM pathway promotes lupus nephritis via T cell-mediated responses. *J. Clin. Invest.* **132**, e147334 (2022)

DEGENERATIVE DISC DISEASE

Kindlin-2 reduces IVD inflammation

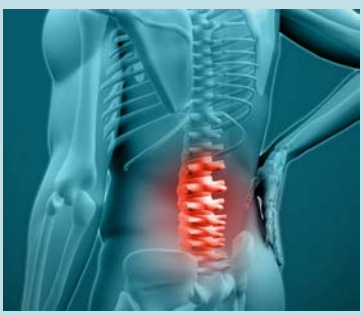
Intervertebral disc (IVD) degeneration (IVDD) is a major cause of lower back pain, although the molecular mechanisms are poorly defined. Chen et al. show that kindlin-2, a focal adhesion protein, acts to inhibit inflammatory signals to maintain IVD homeostasis and could be a therapeutic target for IVDD.

The researchers first examined tissue samples from patients with IVDD of varying severity. They found that kindlin-2 is localized to cells of the nucleus pulposus (NP) — the central region of the IVD — and that its abundance was reduced in patients with the most severe forms of IVDD. Similarly, kindlin-2 levels in the NP were lower in aged mice, which exhibit IVDD, than in young mice. Thus, loss of kindlin-2 might be implicated in the development of IVDD.

To confirm a role for kindlin-2 in IVDD, the researchers created a conditional knockout (cKO) of the gene encoding kindlin-2, *Fermt2*, specifically within NP cells of adult mice. Histological experiments revealed that loss of kindlin-2 caused spontaneous IVDD within the lumbar regions and accelerated coccygeal IVDD when mice were subjected to abnormal mechanical loading. At the molecular level, the degeneration in cKO mice mirrored features of IVDD observed in patients, including NP cell death and decreased synthesis of extracellular matrix (ECM). These findings reveal a previously unappreciated role of kindlin-2 in IVD homeostasis.

> Kindlin-2 … acts to inhibit inflammatory signals to maintain IVD homeostasis

The researchers next sought to define the mechanisms at play. Immunofluorescence microscopy revealed that the NLRP3 inflammasome is upregulated in NP cells of cKO mice, suggesting that kindlin-2 normally acts to suppress inflammasome activation. Initiation of the inflammatory response in turn downregulates kindlin-2, creating a feedback cycle that promotes ECM catabolism and NP cell death. Therapeutically, pharmacological inhibition of the inflammasome, or administration of kindlin-2 directly using adeno-associated virus-mediated expression of kindlin-2, prevented these deleterious effects in human primary NP cells and alleviated IVDD in rats.



Credit: Wavebreakmedia Ltd/Wavebreak Media/Getty Images Plus

"[Our work] identifies a novel mechanism that leads to IVDD and may define a novel target for the prevention and treatment of IVDD", concludes co-corresponding author Guozhi Xiao.

Michael Attwaters

ORIGINAL ARTICLE Chen, S. et al. Kindlin-2 inhibits Nlrp3 inflammasome activation in nucleus pulposus to maintain homeostasis of the intervertebral disc. *Bone Res.* **10**, 5 (2022)

IN BRIEF

RHEUMATOID ARTHRITIS

Low-dose rituximab can go even lower

A pre-planned secondary analysis of data from the REDO trial demonstrates similar effectiveness of the ultra-low rituximab doses 1,000 mg, 500 mg and 200 mg in patients with rheumatoid arthritis, with 11%, 21% and 13% of patients treated with these doses not meeting response criteria. The lower doses resulted in lower drug concentrations, but did not affect concentrations of anti-drug antibodies or counts of B cells. The lack of a dose–response suggests that even lower doses of rituximab could be effective in these patients.

ORIGINAL ARTICLE Wientjes, M. H. M. et al. Drug levels, anti-drug antibodies and B-cell counts were not predictive of response in rheumatoid arthritis patients on low dose rituximab. *Rheumatology* https://doi.org/10.1093/rheumatology/keac024 (2022)

OSTEOARTHRITIS

PPIs linked to increased risk of knee replacement

Proton pump inhibitors (PPIs) prescribed to counter gastrointestinal effects of NSAIDs can affect serum magnesium concentrations and, in turn, osteoarthritis (OA) progression. In a UK study that showed an increase in PPI prescription rates in patients with knee OA from 12.7% in 2000 to 44.0% in 2017, the risk of knee replacement was higher in patients treated with the PPIs omeprazole (HR 1.21; 95% CI 1.01–1.44) or pantoprazole (HR 1.38; 95% CI 1.00–1.90) than in patients treated with histamine 2 receptor antagonists. Treatment with lansoprazole, rabeprazole or esomeprazole was not associated with increased risk of knee replacement.

ORIGINAL ARTICLE Zeng, C. et al. Proton pump inhibitor therapy and risk of knee replacement surgery: a general population-based cohort study. *Osteoarthritis Cartilage* https://doi.org/10.1016/j.joca.2021.12.010 (2022)

GOUT

No benefit to intensive urate lowering in gout

Results from a 2-year, double-blind, randomized controlled trial of 104 patients with erosive gout suggest there is no benefit to assigning an intensive (<0.2 mmol/L) rather than a standard (<0.3 mmol/L) serum urate target. Patients in the intensive-target group achieved lower serum urate concentrations, but required higher doses of allopurinol and greater use of combination therapy than those in the standard-target group. The intensive-target and standard-target groups did not differ in terms of bone erosion scores, OMERACT core outcome domains or adverse event rates.

ORIGINAL ARTICLE Dalbeth, N. et al. Intensive serum urate lowering with oral urate-lowering therapy for erosive gout: A randomized double-blind controlled trial. *Arthritis Rheumatol.* https://doi.org/10.1002/art.42055 (2021)

UNDIFFERENTIATED ARTHRITIS

Imaging for prediction of RA development

The usefulness of MRI of the hands and feet for prediction of progression to rheumatoid arthritis (RA) has been assessed in 405 patients who meet the current definition of undifferentiated arthritis by fulfilling neither the 1987 nor the 2010 criteria for RA and having no alternative diagnosis. Over a 1-year follow-up, 21% of these patients developed RA. MRI-detected synovitis and tenosynovitis were predictive of development of RA, whereas RA was less likely in individuals with negative MRI findings, particularly in the subgroup with autoantibody-negative oligoarthritis.

ORIGINAL ARTICLE den Hollander, N. K. et al. Hand and foot MRI in contemporary undifferentiated arthritis: in which patients is MRI valuable to detect rheumatoid arthritis early? – a large prospective study. *Rheumatology* https://doi.org/10.1093/rheumatology/keac017 (2022)

COVID-19

B cells: deplete, repopulate, vaccinate

Credit: Photodisc

Immunosuppression is essential for treatment of autoimmune rheumatic disease (AIRD), but it can have negative effects on the generation of effective immune responses. B cell depleting therapy (BCDT) is of particular concern, as it is known to affect the serological response to vaccination. With the continuing threat of the COVID-19 pandemic, rheumatologists are striving to determine how to get the best outcomes from both BCDT and SARS-CoV-2 vaccination in patients with severe AIRDs. Results from three new studies provide further evidence of the importance of the interval between rituximab treatment and vaccination, and suggest that B cell reconstitution is a biomarker for the probability of seroconversion.

In a study of 24 patients with AIRD who were treated with the BCDT rituximab, 35 with AIRD and other immunosuppressant therapy and 26 healthy individuals, 28 days after second doses of SARS-CoV-2 mRNA vaccines, neutralizing antibodies were present in 29%, 80% and 92% of participants in the respective groups. No patient treated with rituximab in the 6 months prior to vaccination had a neutralizing antibody response, and time since last rituximab infusion was associated with humoral response. Rituximab treatment did not affect T cell responses.

In a second study of 56 patients with AIRD who were all treated with rituximab and who all received two doses of SARS-CoV-2 mRNA vaccine, time from last rituximab infusion (<6 months, 6–12 months or >12 months) was associated with rates of serological response (antibodies to the viral spike protein were detected in 14%, 45% and 87%, respectively). In addition, among the 39 participants whose B cell status was assessed, the seropositivity rate was 91.3% in those with detectable B cells who were vaccinated ≥6 months after rituximab treatment. According to corresponding author Robert Spiera, these results "suggest that B cell measurement could provide complementary information to timing that could help inform strategies to increase the likelihood of achieving a serological response in rituximab-treated patients with AIRD."

In the third study, among 19 patients with AIRD and rituximab treatment, 12 with AIRD and other therapy and 30 healthy individuals, researchers identified the minimum concentration of B cells in the peripheral circulation of individuals who underwent seroconversion in response to SARS-CoV-2 vaccination. Corresponding author Thomas Dörner suggests that this concentration, of 10 B cells/μl, "is a candidate biomarker for a high likelihood of humoral vaccination response, and may support optimization of vaccination protocols among this vulnerable patient group."

Robert Phillips

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OSTEOARTHRITIS

Electric scaffolds charge cartilage repair

As currently available tissue engineering strategies cannot fully regenerate hyaline cartilage, novel approaches are being tested, including the use of electrical stimulation to promote cartilage regeneration. A new study reports that use of a biodegradable piezoelectric scaffold in combination with physical exercise promotes chondrogenesis and cartilage regeneration in osteochondral defects in rabbits, suggesting it could have potential for the treatment of osteoarthritis.

Cartilage is known to be sensitive to electrical stimulation. The 3D scaffold used in the study is an assembly of piezoelectric poly(L-lactic acid) (PLLA) nanofibres that generate electricity under applied force, such as the force from exercise-induced joint motion. Implanted into damaged joints, the scaffold would thus serve as a battery-less electrical stimulator to accelerate cartilage growth.

In vitro, use of the piezoelectric PLLA scaffold and applied physical force promoted chondrogenic differentiation of rabbit adipose-derived stem cells. Further experiments showed the scaffold influenced chondrogenesis by attracting extracellular matrix proteins, triggering calcium ion influx and inducing secretion of TGFβ by the stem cells.

In vivo, the piezoelectric scaffold was implanted into critical-sized osteochondral defects in rabbit knees. Rabbits treated with treadmill exercise for 1–2 months (after a 1-month recovery period) had substantial healing and hyaline cartilage regeneration in the defects, with abundant chondrocytes and expression of type II collagen; subchondral bone volume was also increased. By contrast, rabbits treated with non-piezoelectric scaffolds and exercise, or with piezoelectric scaffolds and no exercise, had less regeneration and limited healing.

Further studies will seek to elucidate the mechanisms by which the scaffold achieves cartilage regeneration, as well as optimize the exercise regimen and the functional life of the biodegradable scaffold.

Sarah Onuora

ORIGINAL ARTICLE Liu, Y. et al. Exercise-induced piezoelectric stimulation for cartilage regeneration in rabbits. *Sci. Transl. Med.* **14**, 627 (2022)

SPONDYLOARTHRITIS

Neutrophils implicated in early enthesitis

Neutrophils have previously been implicated in the pathogenesis of spondyloarthritis (SpA)-related conditions such as psoriasis, psoriatic arthritis, uveitis and inflammatory bowel disease, but new research published in *Arthritis Research & Therapy* suggests these innate immune cells could also have a role in the early phase of enthesitis in SpA.

The investigations involved SKG mice, an IL-17–IL-23-dependent model of SpA that is accelerated by exposure to fungal adjuvant. SKG mice developed inflammation at axial and peripheral entheseal sites (in the spine and ankle, respectively) as early as 1–2 weeks after administration of curdlan. An abundance of neutrophils within the entheseal inflammatory infiltrates was confirmed by immunohistochemical staining for myeloperoxidase (MPO).

Gene array analysis demonstrated upregulation of neutrophil-associated genes and pathways at axial and peripheral entheseal sites in the SKG mice. Notably, gene and protein expression of S100A8 and S100A9, alarmins that are abundantly expressed by neutrophils, was highly upregulated at both sites.

The researchers also demonstrated the presence of neutrophils in non-inflamed human entheseal tissue from the axial skeleton of healthy individuals. MPO-expressing neutrophils were present in peri-entheseal bone and were also found in entheseal soft tissue, where they were localized to the blood vessels.

In vitro, human enthesis-derived neutrophils produced the pro-inflammatory cytokine IL-23 after administration of fungal adjuvant. Furthermore, fungal adjuvant-stimulated fibroblasts isolated from human entheseal tissue produced chemokines including IL-8, a neutrophil chemoattractant.

Together, the results suggest that entheseal neutrophils could be an important source of IL-23 in the early stages of SpA pathogenesis.

Sarah Onuora

ORIGINAL ARTICLE Stavre, Z. et al. A role for neutrophils in early enthesitis in spondyloarthritis. *Arthritis Res. Ther.* **24**, 24 (2022)

PSORIATIC ARTHRITIS

Risankizumab improves PsA

New data from the KEEPsAKE 1 and KEEPsAKE 2 phase III randomized controlled trials (RCTs) indicate that risankizumab improves the signs and symptoms of psoriatic arthritis (PsA). The results suggest that risankizumab, which targets the p19 subunit of IL-23, could offer an additional option for the treatment of PsA.

Both RCTs were international, multicentre studies that randomly allocated participants to receive treatment with risankizumab 150 mg or placebo at weeks 0, 4 and 16. In each study, the primary end point was the proportion of patients achieving 20% improvement according to ACR criteria (ACR20) at week 24. Secondary efficacy end points included assessments of disease activity in key clinical domains of PsA.

The KEEPsAKE 1 trial involved 964 patients who had active PsA despite treatment with at least one conventional synthetic DMARD (csDMARD). At week 24, 57.3% of those who received risankizumab achieved an ACR20 response, compared with 33.5% of those in the placebo group ($P < 0.001$).

The KEEPsAKE 2 trial compared risankizumab with placebo in 444 patients with active PsA who had a history of inadequate response to, or intolerance of, at least one csDMARD and/or up to two biologic DMARDs (bDMARDs); 206 of the 444 participants had a history of bDMARD treatment. At week 24, 51.3% of those treated with risankizumab achieved an ACR20 response, compared with 26.5% in the placebo group ($P < 0.001$).

In both RCTs, greater improvements in enthesitis, dactylitis, nail and skin psoriasis and physical function were also observed in patients treated with risankizumab compared with those who received placebo. Rates of adverse events were similar in the risankizumab and placebo groups across both RCTs, although injection site reactions were more common in those who received risankizumab.

Sarah Onuora

ORIGINAL ARTICLES Kristensen, L. E. et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2021-221019 (2021) | Östör, A. et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2021-221048 (2021)

How the COVID-19 pandemic has affected rheumatology research

Paula Alba Moreyra, Francis Berenbaum, Debashish Danda, Bettina Grötsch, Simon R. Stones and Sowmya Viswanathan

The COVID-19 pandemic has put pressure on researchers around the world. In this Viewpoint, six rheumatology researchers at different career stages and from different regions discuss the difficulty of conducting research during the pandemic, and also reflect on how the pandemic has changed their attitudes towards research and their plans for the future.

Since the COVID-19 pandemic began, what have been the biggest challenges to conducting your research?

Simon R. Stones. As a qualitative researcher in rheumatology and a patient living with rheumatic and musculoskeletal diseases, there have been several challenges to conducting research in my field. Prior to the UK Prime Minister's request to stop non-essential contact and travel in March 2020, there was great confusion, and I was often conflicted between my researcher and patient roles. As a researcher, I was committed to my research participants and wanted to proceed as planned with data collection; however, my vulnerability as an immunocompromised patient caused great anxiety — both for my own wellbeing and for that of immunocompromised research participants.

Bettina Grötsch. When the German federal and state governments decided on measures to contain the spread of coronavirus in March 2020, I was still on parental leave with my second child and only came back to my normal work routine in June 2020 when the daily COVID-19 case numbers had declined. At that point, everyone was instructed to work from home whenever possible to stick to the contact restrictions. However, as I had to take care of my students in the lab, working from home was not a good solution for me. I really appreciated that our whole lab tried to continue our work at the bench-side in a normal way, but as it is quite hard to keep your distance in a small lab with many people around, a part of me was always afraid of becoming infected and especially of bringing this virus back home to my family. I have also had to deal with closed day care facilities and several quarantine isolations for both of my children that repeatedly forced me to coordinate my work from home with two small children around me.

Paula Alba Moreyra. The Argentine government had instituted a full lockdown by the end of March 2020 that affected the whole country when the first cases of COVID-19 were reported. My professional life and clinical practice has completely changed since then. During the first 3 months after the full lockdown, all routine appointments were cancelled and an emergency clinic was available twice a week. I work in an academic institution, not only running clinics but also doing clinical and basic research and educating both undergraduate and postgraduate students. The academic work was adapted to a web-based learning process and we continued with our clinical research with a lot of changes and difficulties.

Debashish Danda. Our research activities outside of COVID-19-related areas have been greatly affected in India, as patients with autoimmune and rheumatic diseases were unable to reach hospital unless they faced a rheumatological or COVID-19-related emergency. Therefore, our clinical and translational research were substantially curtailed owing to a shortage of clinical and biological materials. Another big challenge we faced was a drastic cut in research funding for non-COVID-19 areas as the bulk of existing funding was diverted to COVID-19-related research. As all of our younger staff were on COVID-19 duties and some research staff were unable to attend work owing to lockdowns and fear of exposure to COVID-19 in hospital, human resources were also compromised. In addition, all international and national visits related to collaborative research were and still are badly affected, which has been one of the biggest personal losses for many, including me.

Francis Berenbaum. The effects of the COVID-19 pandemic on the activity of my research laboratory have been phenomenal. We conduct experimental research that requires the handling of biological products and of small animals. Moreover, we use fresh joint tissues coming from patients at the time of joint replacement. As this type of surgery was withdrawn for many months, we had to stop doing this kind of research. The successive confinements that we experienced in France forced the majority of my team to stay at home. We managed to negotiate with our university the possibility for our PhD and post-doc students to come to the laboratory. To interrupt research for several months is to risk having to postpone one's professional project and sometimes also any associated private projects, so you can imagine the level of anxiety that these students had, given that their careers essentially depend on their publications.

Sowmya Viswanathan. As a scientist working in Canada on cellular and immune therapies for the treatment of osteoarthritis, being in a hospital setting (our institute is located within a hospital complex) has been a mixed blessing. Re-opening has been faster for us, but we have had stricter restrictions on spacing, shift work and capacity limits than our university-based counterparts. When we re-opened at 25% of normal capacity in June 2020 to 6-h shift work, it took an incredible amount of detailed planning and coordination between lab members for each experiment to be performed. My lab works on primary tissues

and cells, and these certainly do not respect any shift-work boundaries. Funding has also been tight. Many of the new calls for proposals both from governments and from industry are rightly focused on COVID-19 research, but this means that fundamental and translational research on chronic diseases such as osteoarthritis has become a lower priority. Philanthropic funding, which can always be unreliable, has also been difficult to come by owing to cancelled fundraising events. Fortunately, government subsidies for trainee stipends have helped to cover some of the costs, particularly during the full shutdown.

How have your research activities changed? What adaptations have you put in place?

Simon R. Stones. During the initial period of the UK lockdown, the National Institute for Health Research's Clinical Research Network paused the set-up of new or ongoing studies that were not nationally prioritized COVID-19 studies. All parts of the research system were encouraged to help these COVID-19 studies to progress and to enable clinicians to be redeployed to support frontline care. Alongside the added pressures caused by the pandemic, such as home schooling, the most logical and sensitive action for my research was to stop recruitment of study participants and continue data collection online. Meetings initially stopped for several weeks as people adjusted to life in lockdown. My research activities used to involve frequent travel to other countries too, so that all stopped.

Paula Alba Moreyra. Our research activities have completely changed since the start of the COVID-19 pandemic. Telemedicine became a partial medical solution to respond to the pandemic in some aspects and to help clinical research. We had to introduce remote patient assessment, as well as local routine laboratory evaluation. Although it was very difficult to recruit new patients to trials and clinical and basic studies, we were able to continue with the patients we had already recruited. Some evaluations and disease activity assessments of our patients with rheumatoid arthritis or systemic lupus erythematosus were not done in the full lockdown and were instead scheduled for after lockdown was partially lifted. In spite of the fact that we could not get the samples we needed for our clinical research, we were able to use telemedicine for other evaluations, such as health-related quality of life assessment. All research laboratories were closed during 2020 and all the samples from our collaborative research were stored and not sent for analysis by the core laboratory until the second COVID-19 wave was under control.

Debashish Danda. The COVID-19 pandemic has been and still continues to be the nightmare of our lifetime. The fear and panic kept most senior rheumatologists home-bound (especially those aged over 60 years) before vaccination was available, and many had to adopt an alternative plan to maintain their academic pursuits. Ongoing lab-based research with stored samples could be sped towards completion, if support staff were available. I decided to write up some of my pending manuscripts when the data were ready and strengthen my knowledge by reading COVID-19-related literature, particularly about its possible biological effects on autoimmune rheumatic diseases and other sequelae. Reviewing the existing literature and writing some narrative reviews was another strategy[1]. Questionnaire-based data generation with my existing cohorts of patients with autoimmune rheumatic diseases was another strategy, and I am currently trying to create some short communications and correspondences on the basis of that data. As a senior rheumatologist, I was also part of a couple of task forces and was involved in Delphi exercises and recommendations related to rheumatic diseases, anti-inflammatory treatment and vaccination-related issues, some of which have been published[2].

Sowmya Viswanathan. As a team, we had to be nimble and responsive. The morning shift would often prime and harvest cells and tissues that would then be run in experimental set-ups by members of the afternoon shift; students would help each other on completely unrelated projects. This teamwork and collaboration was a happy by-product of the pandemic-imposed restrictions, and resulted in my lab members becoming more versatile and cross-trained in various techniques and concepts compared with when we worked on siloed projects. Another key crunch on resources was the availability of primary cells and tissues. We rely on healthy volunteers to donate blood and bone marrow, and on patients with arthritis for joint tissues. The second and even deadlier third waves in

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Canada meant that all elective surgeries were cancelled, and we had no access to patient samples. Normal hospital visits were non-existent, and research staff were only on site to conduct essential experiments. No one had the time or interest to consent to and donate tissue for research. We had to be creative and come up with alternative solutions, such as using stem cells to derive the primary cells needed for our in vitro models, re-framing research questions and shifting our focus, working with cell lines or jumping straight into animal models, or having to purchase primary cells from commercial vendors, which was an expensive option.

Bettina Grötsch. My research activities did not really change during the pandemic situation. Our lab was lucky that the pandemic did not affect our research. Hence, I continued my work in the field of osteoimmunology. Only at the beginning of 2021 did we face some delivery shortages for our consumables, especially those containing filters. This shortage has forced us to use our consumables sparingly and to organize our lab space, which is actually a positive development. In addition, like many labs, we have moved all our meetings and educational work to virtual work environments. Hence, research and education have become much less interactive and it has been a big challenge to accommodate this change. As a result of these virtual meetings, interaction between the students in the lab has been lost, and we are realizing that this is quite hard to re-establish.

Has the COVID-19 pandemic affected the quality of your research or your ability to publish? If so, what adaptations or allowances do you think are needed to account for the effects of the pandemic?

Simon R. Stones. I do not believe that the quality of my research has been affected by the pandemic, although I would attribute this to an inherent resilience in the face of adversity, which I share with many researchers forced to adapt to new and evolving situations. However, I do believe that the pandemic has influenced my findings. On the one hand, the pandemic has shed light on pertinent issues that might not have previously been discussed. On the other hand, I have had fewer opportunities to interact with research participants. As a qualitative researcher, building a rapport with participants is an essential part of the research process; ensuring that they feel comfortable sharing their experiences, while minimizing the researcher–participant power imbalance[3]. Although online methods can support these interactions, especially as more people become familiar with using the technology, it can be difficult to replace human interactions in a face-to-face setting, where non-verbal signs of communication can be interpreted. Although I have not personally observed a direct effect on publishing, I do think that the pandemic has revealed several flaws in the current peer-review process, which relies heavily on the generosity and capacity of already stretched clinicians and researchers — although that is a topic for a separate discussion entirely!

Sowmya Viswanathan. Fundamentally, the pandemic restrictions have shifted how research is planned and conducted in my lab. I had always emphasized planning and mapping out all experiments, but these exercises have become even more critical now as we have had so little time to do experiments, and every hour in the lab had to count. Additionally, even as the lab capacity limits grew to 50% of normal, shortages of reagents became a major work-stoppage issue. My lab relies on PCR as a readout. Reagents such as RNA isolation kits, PCR master mixes, PCR plates and pipette tips, which would normally be available immediately or within 24 h, were now at a 6-week minimum, or worse, indefinite, delay. This delay meant switching reagents mid-experiment and essentially repeating the first half to get uniform, interpretable results, or waiting out the delay to prevent re-doing half the dataset. The necessity of every experiment was called into question. How would the results from this experiment advance our learning? Did it support our fundamental hypotheses? Would it help us to fill in missing gaps for a manuscript in preparation? I had to be a ruthless tactician and cut down any 'let's see what happens'-type experiments (which, as most researchers know, generate serendipitously promising results), and only allow the most informative, urgent and useful experiments to proceed.

Bettina Grötsch. For me personally, the COVID-19 pandemic did not affect the quality of my research that much. I was even able to successfully apply for a research grant during the pandemic. However, in general, the turnaround time for research applications and for publications has slowed. Furthermore, our whole research group realized that it has become quite difficult to publish non-COVID-19-related research in high-quality journals during the past 2 years. Of course, research articles that help to understand or even show how to fight coronavirus are of great importance right now. However, from my point of view, we should not forget that there are still more diseases out there that urgently need basic and clinical research to improve the quality of life of those affected. Therefore, all journals need to adapt to the new situation and create space for both COVID-19 and non-COVID-19 research.

Francis Berenbaum. Thankfully, there has been no effect as such on our ability to publish, but we have had to be extremely reactive and orient our research forces towards a brand new theme — SARS-CoV-2 infection — as specific grants were allocated for this topic by our university. From osteoarthritis to COVID-19, it was not an obvious move!

Will the COVID-19 pandemic change your research activities for good, or will you return to business as usual once the situation is back to 'normal'?

Debashish Danda. Life will not be same again, especially for senior rheumatologists, as crucial time has been lost. Once the situation changes back to normal, we can try to be back to business as usual (in terms of research), if opportunities are provided. However, some of the modalities of research activities that were adopted during the COVID-19 pandemic can be continued too, as these adaptations have indeed been proven to be newly discovered opportunities during these challenging times. For example, real-world research that makes use of digital technologies, telemedicine or databases might become an ongoing activity in the future. COVID-19-related clinical research might also continue in many fields, including rheumatology, for the next few years, even after the pandemic ends[4,5]. Interesting ongoing research questions include COVID-19 as a trigger for the onset of autoimmunity, as well as how exposure to COVID-19 and COVID-19 vaccinations will change the outcome of autoimmune rheumatic diseases.

Paula Alba Moreyra. Now that advances have been made in the vaccination programme, we are returning to usual research and clinical activities while maintaining all protective measures. Technological innovations have become an important resource for the care of

patients with rheumatic diseases, for continuing medical education online and for maintaining research networks during the pandemic. However, in spite of the important role of telemedicine during the pandemic, we welcome the return to face-to-face appointments, particularly for those patients with severe or difficult to treat disease. Although the time we have been able to devote to research activities has not been enough, new research opportunities have opened up, such as the study of the prevalence, clinical manifestations and outcomes of COVID-19 infection in patients with rheumatic diseases. The Argentine Society of Rheumatology has developed two registries, the first to learn the effect of SARS-CoV-2 on patients with rheumatic diseases in Argentina, and the second to evaluate the safety and efficacy of COVID-19 vaccines in this population. Our rheumatology unit has actively participated in these two projects and in other projects at the Universidad Nacional de Córdoba.

Sowmya Viswanathan. For my lab, the pandemic has changed our approach to research. It has increased, not diminished, the quality of research, as we have had to be razor-focused on our research questions and have been careful to design every run of experiments with appropriate controls to generate useable and interpretable data. We have trimmed all excesses. The restrictions imposed by shift work, limited reagents and the availability of cells and tissues have also made us re-evaluate experimental approaches and re-examine and question hypotheses, as well as foster more critical thinking. This mind-set is now being passed on to new trainees joining the lab, and even though shift-work restrictions have eased, we are very mindful that small changes in how the pandemic is managed could reverse all gains. Our experiments will continue to be planned and executed around rationed resources and, ultimately, I think that this makes us better researchers.

Francis Berenbaum. Not everything has been negative: collaborations have been set up with teams we would never have imagined working with before the pandemic. For example, our expertise on the biology of prostaglandins led us to collaborate with a team that was working on the antiviral properties of an NSAID[6]. Similarly, our expertise on the cholinergic system led to a joint publication with researchers from the Pasteur Institute and the Cochin Hospital on the role of this system in the hyperinflammatory state of patients with COVID-19 (REF.[7]). Not to mention the wonderful international exchanges I have had within the framework of the COVID-19 Global Rheumatology Alliance registry[8]. The pandemic has also expanded our communication capabilities. Thanks to improvements in the quality of videoconferencing platforms, we realized that certain small working meetings between disseminated research teams could be held remotely without any loss of quality and with considerable time savings as travel was avoided. However, this pandemic has also shown us that virtual large meetings will never replace the usual face-to-face meetings. Indeed, even if virtual meetings allow us to present our work to the rest of our research community, the lack of user-friendliness and interactivity greatly reduces their interest. Research is also done around the coffee machine!

Simon R. Stones. I do not think that we will ever get back to normal, only to a 'new normal' that we all must learn to embrace. I believe that COVID-19 has made many individuals reassess their work–life balance. Pre-pandemic, I was travelling excessively for various meetings. As much as I despised the national lockdowns that were imposed in 2020, those periods of confinement enabled me to reflect on my life and its fragility, as I witnessed so many people prematurely lose their lives. I also believe that this forced change has come at a time when we must collectively take greater action to tackle pressing issues such as climate change. Admittedly, some of the meetings I would travel abroad for can quite easily be conducted online. Not only is this better for the environment, but it also saves me a considerable amount of time and effort and can be more economical too. That is not to say that all meetings should become virtual, but I do think that greater attention is required during the planning process. In terms of how research is conducted, I believe that the pandemic has accelerated the use of innovative methods in research, many of which were once described as too complex, showing that anything is possible. I also believe that greater flexibility and choice are just two reasons why a more open and dynamic approach to research could be beneficial for everyone involved.

Q *Looking to the future, how do you think that the COVID-19 pandemic will affect your career? Has it made you consider alternative career paths or created unexpected opportunities?*

Bettina Grötsch. The COVID-19 pandemic has indeed slowed down my career plans owing to a combination of the restrictions in the lab, the long processing times for applications and publications, as well as taking care of my children during the lockdown in the winter months. However, I am still a young researcher and have only just started my independent academic career. Therefore, I am really looking forward to a future without COVID-19 restrictions, not only for pushing my career forward but also for improving the work–life balance for all families.

Debashish Danda. I am not sure if the COVID-19 pandemic has created any alternative career paths for me; if anything, it has made my current path more difficult. I was looking forward to several international collaborations, research sabbatical opportunities and exchange visits to strengthen my research. At over 60 years of age and with 2 years lost, my academic career has been badly affected, particularly by the loss of assistants. Government and private research funding to very senior researchers is highly restricted, if not non-existent, in India. This is a painful fact that is often not given any consideration by many institutes, funding bodies and even colleagues. One of the most crucial periods of my career has been washed away by the COVID-19 pandemic; therefore, I think that career paths need to be assessed from a pre-COVID-19 time-point, rather than being counted chronologically. I am looking forward to a career now where I can build new academic, teaching and training facilities with some lead research roles, and to opportunities to catch up the time lost by upskilling myself appropriately for this new scenario. Societal leadership and social research related to my speciality is another area where I wish to contribute, if opportunities arise.

Simon R. Stones. During the COVID-19 pandemic, I have defended my PhD thesis and transitioned from academia to the pharmaceutical industry as a medical writer. I feel blessed to be able to work remotely from home in a role that offers flexibility, although I know that this is not the case for many. The pandemic provided countless opportunities for me to reflect and consider how I could best use my skills and experiences to have the greatest possible influence, which guided me into medical communications. Different experiences throughout the pandemic have shown how much people rely on different media to digest health-related information, and so

I now see it as part of my duty to help craft and disseminate accurate information in an accessible format for everyone, regardless of their background.

Francis Berenbaum. Being a professor with a tenured position, this pandemic will not affect my career as such. But it has definitely created new interactions with teams outside my usual field of research. The future is indeed interdisciplinary!

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Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach

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Abstract | The four Janus kinase (JAK) proteins and seven signal transducer and activator of transcription (STAT) transcription factors mediate intracellular signal transduction downstream of cytokine receptors, which are implicated in the pathology of autoimmune, allergic and inflammatory diseases. Development of targeted small-molecule therapies such as JAK inhibitors, which have varied selective inhibitory profiles, has enabled a paradigm shift in the treatment of diverse disorders. JAK inhibitors suppress intracellular signalling mediated by multiple cytokines involved in the pathological processes of rheumatoid arthritis and many other immune and inflammatory diseases, and therefore have the capacity to target multiple aspects of those diseases. In addition to rheumatoid arthritis, JAK inhibition has potential for treatment of autoimmune diseases including systemic lupus erythematosus, spondyloarthritis, inflammatory bowel disease and alopecia areata, in which stimulation of innate immunity activates adaptive immunity, leading to generation of autoreactive T cells and activation and differentiation of B cells. JAK inhibitors are also effective in the treatment of allergic disorders, such as atopic dermatitis, and can even be used for the COVID-19-related cytokine storm. Mechanism-based treatments targeting JAK–STAT pathways have the potential to provide positive outcomes by minimizing the use of glucocorticoids and/or non-specific immunosuppressants in the treatment of systemic immune-mediated inflammatory diseases.

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Cytokines have critical roles in the pathogenesis of immunological and inflammatory diseases and can be targeted therapeutically. Targeted, small-molecule therapies that inhibit Janus kinase (JAK) proteins (essential signalling mediators that act downstream of pro-inflammatory cytokines) have gained traction as efficacious options for the treatment of rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), spondyloarthritis, psoriasis, atopic dermatitis and inflammatory bowel disease (IBD). RA is a systemic autoimmune disease that is characterized by persistent destructive synovitis and extra-articular manifestations, which can lead to severe disability and even mortality. Timely and appropriate treatment is essential to control joint damage, because rapid destruction occurs in the early phase of RA, resulting in joint deformity and irreversible functional impairment. The use of DMARDs, and particularly the development of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), theoretically enables remission to be the goal of therapy in all patients. In addition, these drugs can prevent progression of joint damage and physical dysfunction in the long term[1–3].

JAK inhibitors are an important class of tsDMARDs. The rationale underlying the use of these inhibitors is that JAKs have pivotal roles in particular pathological mechanisms, so that their targeted inhibition can result in effective disease control. Clinical results support this rationale, and JAK inhibitors have been approved for the treatment of RA and other systemic or organ-specific autoimmune diseases (TABLE 1). In this Review we describe the progress in JAK-targeting therapies for autoimmune rheumatic diseases, with a focus on the mechanisms of action, and discussion on a disease-by-disease basis.

What are JAK inhibitors?

In contrast to bDMARDs, which are large molecules that must be administered parenterally, tsDMARDs are orally available small molecules that enter cellular cytoplasm and directly regulate intracellular signalling by inhibition of kinases or phosphodiesterases. Protein kinases are important regulators of cellular functions that constitute a diverse family, with 518 kinase-encoding genes identified by the Human Genome Project. JAKs belong to the tyrosine-kinase family[4,5]. Binding of a number of

Key points

- Mechanism-based targeting of receptor-mediated signalling via Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathways in refractory systemic autoimmune diseases can potentially minimize glucocorticoid and non-specific immunosuppressant use.
- JAK–STAT pathways are important for cellular interaction during rheumatoid arthritis pathological processes, causing synovial inflammation, autoantibody production, synovial proliferation and joint destruction, which are potential targets for JAK inhibition.
- Inflammatory processes involving JAK–STAT signalling pathways are involved in the pathology of spondyloarthritis (including psoriatic arthritis), and are targets for JAK inhibition.
- Innate immune system cytokines signal through JAK–STAT to adaptive immune mechanisms involving autoreactive T cells, B cell activation and autoantibody production, which are potential therapeutic targets in systemic lupus erythematosus.
- Cytokines contribute to various pathophysiological mechanisms of organ-specific autoimmune diseases, and JAK inhibitors can target multiple aspects of inflammatory bowel diseases, alopecia, allergic disorders and cytokine storm.
- Use of JAK inhibitors requires careful consideration of their multi-target effects, with adequate prior screening and regularly planned monitoring during treatment for infection, cardiovascular disorders, thrombosis and malignancy.

cytokines and growth factors to their receptors results in phosphorylation of receptor-associated JAKs. Phosphorylation activates the JAKs, and they, in turn, phosphorylate intracellular components of the receptors, which enables recruitment of transcription factors of the signal transducer and activator of transcription (STAT) family. Activated STAT proteins translocate to the nucleus and induce transcription. Intracellular signal transduction involves combinations of four JAK isoforms (JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)) and seven STAT family members. The usage of individual JAKs depends on their selective interactions with particular cytokine receptors. Evidence from genetic studies with mutated cell lines, animal models and humans established the essential role of JAKs in signalling by a subset of cytokines that use type I and type II cytokine receptors. More than 50 soluble factors, including IL-2, IL-3, IL-4, IL-5, IL-6 and IL-12, as well as interferons, endocrine factors (including growth hormone, prolactin and leptin) and colony-stimulating factors including erythropoietin, thrombopoietin and granulocyte–macrophage colony-stimulating factor (GM-CSF), exert their effects through specific combinations of JAKs[6–11] (FIG. 1).

JAK inhibitors selectively interfere with the ATP-binding site of JAKs, resulting in suppression of downstream signalling pathways, which can have immunomodulatory effects in a wide range of pathological processes. Cytokines work in networks, with type I and type II cytokines inducing or being induced by TNF-family cytokines, and in mouse models, JAK inhibitors can inhibit production of TNF, which is a major component in the pathogenesis of RA[12]. Theoretically, the selectivity of each JAK inhibitor determines its effects on particular inflammatory responses, including those that promote RA[9–15]. Five JAK inhibitors (tofacitinib, baricitinib, peficitinib, upadacitinib and filgotinib) are currently approved by different agencies for the treatment of RA, and are categorized as tsDMARDs. In results from clinical trials in patients with RA, tsDMARDs (either as monotherapy or in combination with methotrexate) had multi-target, rapid and robust effects that were equivalent to or superior to those of bDMARDs[16–23].

Tofacitinib was developed as a small-molecule drug that competitively binds to the ATP-binding site of JAK3. Tofacitinib was initially thought to selectively inhibit phosphorylation of JAK3, but it is now considered to inhibit JAK1, JAK2 and JAK3 to varying degrees in vitro and in vivo[16,17,24]. All of the currently approved JAK inhibitors are competitive antagonists. However, the in vitro assays used in preclinical studies to obtain selectivity data are not identical, and relating these data to in vivo efficacy and adverse events is not a simple matter. Selectivity to JAKs can be determined by the use of purified enzymes, or via a variety of cellular models using cytokine stimulation of cells, with assessment of STAT phosphorylation. To illustrate the difficulties with direct comparison of these methods, in vitro kinase assays demonstrate that tofacitinib is a potent inhibitor of JAK1 and JAK3, but that it is less active against JAK2 and TYK2, whereas baricitinib is a selective JAK1 and JAK2 inhibitor, and upadacitinib and filgotinib are selective JAK1 inhibitors[8–10]. However, in direct comparisons in cell-based assays, the ability of each JAK inhibitor to inhibit a specific cytokine-signalling pathway could not be readily inferred using preclinical selectivity data[25–28]. For example, baricitinib and tofacitinib similarly suppress the JAK–STAT-mediated differentiation of plasmablasts, T helper 1 (T_H1) and T helper 17 (T_H17) cells, as well as the capacity of dendritic cells to stimulate T cells[25,26]. In addition, the effects of JAK inhibitors on cytokine-receptor signalling are all generally similar when comparing the clinically effective doses for RA, suggesting that differentiation on the basis of pharmacological properties with individual JAKs comes with substantial caveats[28]. By contrast, in an industry-sponsored study of filgotinib, upadacitinib, tofacitinib and baricitinib, although JAK1-dependent pathways were the most potently affected by all four inhibitors, filgotinib demonstrated relatively little inhibition of the JAK2-dependent and JAK3-dependent pathways, compared with the other inhibitors[27]. The apparent selectivity of filgotinib might have benefits in terms of safety profiles, and there is preliminary evidence of a lower incidence of herpes zoster infection and venous thrombotic events with filgotinib from side-by-side tabulation of across-trial data[28,29]. However, any potential differences in safety profiles need to be confirmed with rigorously designed head-to-head studies and more real-world experience.

Although the downstream effects of JAK inhibition in vivo are not fully understood, JAK-dependent cytokine signalling in vivo is known to be influenced by individual variation in factors such as single-nucleotide polymorphisms (SNPs) affecting STAT isoforms, the penetration and distribution of drugs into tissues, the expression patterns of JAKs at sites of inflammation and the dynamic balance of T follicular helper (T_{FH}) cells, T peripheral helper (T_{PH}) cells, T_H17 cells and regulatory T (T_{reg}) cells[7,8]. Furthermore, specific aspects of particular experimental approaches could differentially

Table 1 | **Progress with Janus kinase inhibitors for autoimmine, allergic and inflammatory diseases**

Indication	Approved	In phase III or IV trials[a]	In phase II trials[a]
Rheumatoid arthritis	Tofacitinib; baricitinib; peficitinib; upadacitinib; filgotinib	NA	Ritlecitinib (NCT02969044)
Polyarticular juvenile idiopathic arthritis	Tofacitinib	Baricitinib (NCT03773978)	NA
Systemic juvenile idiopathic arthritis	NA	Tofacitinib (NCT03000439); baricitinib (NCT04088396)	NA
Atopic dermatitis	Baricitinib; abrocitinib; topical delgocitinib	Upadacitinib (NCT03569293); topical ruxolitinib (NCT03745638)	Tofacitinib (NCT02001181); gusacitinib (NCT03531957); brepocitinib (NCT03903822)
Hidradenitis suppurativa	NA	NA	Upadacitinib (NCT04430855); PF-6826647 (NCT04092452); brepocitinib (NCT04092452); topical ruxolitinib (NCT04414514)
Alopecia areata	NA	Tofacitinib (NCT03800979); baricitinib (NCT03899259); ritlecitinib (NCT04006457); topical ruxolitinib (NCT03745638)	Ruxolitinib (NCT01950780); brepocitinib (NCT02974868)
Psoriasis	NA	Tofacitinib (NCT01815424); deucravacitinib (NCT04036435)	Baricitinib (NCT01490632); peficitinib (NCT01096862); PF-6826647 (NCT03895372); brepocitinib (NCT03850483); gusacitinib (NCT02969018); ruxolitinib (NCT00617994)
Psoriatic arthritis	Tofacitinib; upadacitinib	Filgotinib (NCT04115748)	Brepocitinib (NCT03963401); deucravacitinib (NCT03881059)
Ankylosing spondylitis	Upadacitinib	Tofacitinib (NCT03502616)	Filgotinib (NCT03117270)
Axial spondyloarthritis	NA	Upadacitinib (NCT04169373)	Tofacitinib (NCT03738956)
Polymyalgia rheumatica	NA	NA	Tofacitinib (NCT04799262); baricitinib (NCT04027101)
Active ulcerative colitis	Tofacitinib	Upadacitinib (NCT03653026); filgotinib (NCT02914522)	Peficitinib (NCT01959282); deucravacitinib (NCT03934216); brepocitinib, ritlecitinib (NCT02958865)
Crohn's disease	NA	Upadacitinib (NCT03345836); filgotinib (NCT02914561); izencitinib (NCT03758443)	Tofacitinib (NCT01393899); deucravacitinib (NCT03599622); brepocitinib, ritlecitinib (NCT03395184)
Pouchitis	NA	NA	Tofacitinib (NCT04580277)
Primary biliary cholangitis	NA	NA	Baricitinib (NCT03742973)
Non-infectious uveitis	NA	NA	Tofacitinib (NCT03580343); filgotinib (NCT03207815)
JIA-associated uveitis or chronic anterior antinuclear antibody-positive uveitis	NA	Baricitinib (NCT04088409)	Brepocitinib (NCT03845517)
Systemic lupus erythematosus	NA	Baricitinib (NCT03616964)	Upadacitinib (NCT03978520); deucravacitinib (NCT03252587); brepocitinib (NCT03845517)
Cutaneous lupus erythematosus	NA	NA	Tofacitinib (NCT03288324); filgotinib (NCT03134222)
Lupus membranous nephropathy	NA	NA	Filgotinib (NCT03285711)
Lupus nephritis	NA	NA	Deucravacitinib (NCT03943147)
Sjögren syndrome	NA	NA	Tofacitinib (NCT04496960); filgotinib (NCT03100942)
Systemic sclerosis	NA	NA	Tofacitinib (NCT03274076); itacitinib (NCT04789850)
Idiopathic inflammatory myositis	NA	NA	Baricitinib (NCT04208464)
Takayasu arteritis	NA	Tofacitinib (NCT04299971); upadacitinib (NCT04161898)	NA
Giant cell arteritis	NA	Upadacitinib (NCT03725202)	Baricitinib (NCT03026504)
NNS/CANDLE, SAVI and AGS	NA	Baricitinib (NCT04517253)	Baricitinib (NCT04517253)
Kidney transplant	NA	NA	Tofacitinib (NCT00106639)
Diabetic kidney disease	NA	NA	Baricitinib (NCT01683409)
COVID-19	Baricitinib	Tofacitinib (NCT04469114)	Ruxolitinib (NCT04414098)

AGS, Aicardi-Goutières Syndrome; NA, not applicable; NNS/CANDLE, Nakajo–Nishimura Syndrome/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; SAVI, STING-associated vasculopathy with onset during infancy. [a]Information from clinicaltrials.gov.

affect results relating to the selectivity of inhibitors for JAK isoforms. In this Review, we discuss the potential of JAK inhibitors on a disease-by-disease basis.

JAK inhibition in RA

In genome-wide association studies (GWAS) of SNPs in patients with RA, among disease-susceptibility genes such as *PTPN22*, *CTLA4* and *STAT4*, *HLA-DRB1* had the strongest association. *HLA-DRB1* alleles encode protein chains that include the shared epitope motif, and they are associated with production of anti-citrullinated protein antibodies. Although specific autoantigens have not been identified, the interaction of genetic and environmental factors, as well as citrullination of extracellular matrix molecules such as filaggrin and fibrinogen, induces autoimmunity in RA through epigenetic modification and conformational changes that disrupt immune tolerance to antigens. As a result, autoreactive T cells and B cells accumulate in synovial tissue, leading to angiogenesis, vasodilation and proliferation of synovial cells. In addition, differentiation of naive T cells to T_H1 cells, T_H17 cells, T_{FH} cells and T_{PH} cells, as well as activation of B cells, leads to the formation of lymphoid-follicle-like structures and germinal-centre-like structures, which induce the production of autoantibodies. Close cell–cell interaction results in excessive production of pro-inflammatory cytokines, leading to RA. Monocytes differentiate into immature dendritic cells in a process that is dependent on IL-4 and GM-CSF, and then can differentiate into dendritic-cell-derived osteoclasts in the presence of macrophage colony-stimulating factor (M-CSF) and RANKL (FIG. 2). Rheumatoid synovial fibroblasts also produce an excess of pro-inflammatory cytokines (mainly IL-6). The nature of these and other pathological processes in RA indicate that multiple cytokines, including IL-6, interferons and GM-CSF, are direct targets for JAK inhibitors, whereas the production of other cytokines, such as TNF, can be indirectly affected[1,2,30,31] (FIG. 2).

An animal model of RA (SCID-HuRAg) was created by transplantation of synovium and cartilage from patients with RA into severe combined immunodeficiency mice. Continuous administration of tofacitinib to these mice using an osmotic minipump suppressed production of human IL-6, IL-8 and matrix metalloproteinase-3 (MMP-3) from the transplanted synovium, leading to a reduction of synovial inflammation and cartilage destruction compared with untreated SCID-HuRAg mice. In this model, tofacitinib also directly inhibited the production of IL-17 and IFNγ and the proliferation of $CD4^+$ T cells, which in turn inhibited the production of MMP-3, IL-6 and IL-8 by synovial fibroblasts and $CD14^+$ monocytes and suppressed cartilage destruction. These results demonstrated the important roles of JAK signalling for $CD4^+$ T cells, T_H1 cells and T_H17 cells in synovial inflammation in RA[32] (FIG. 2).

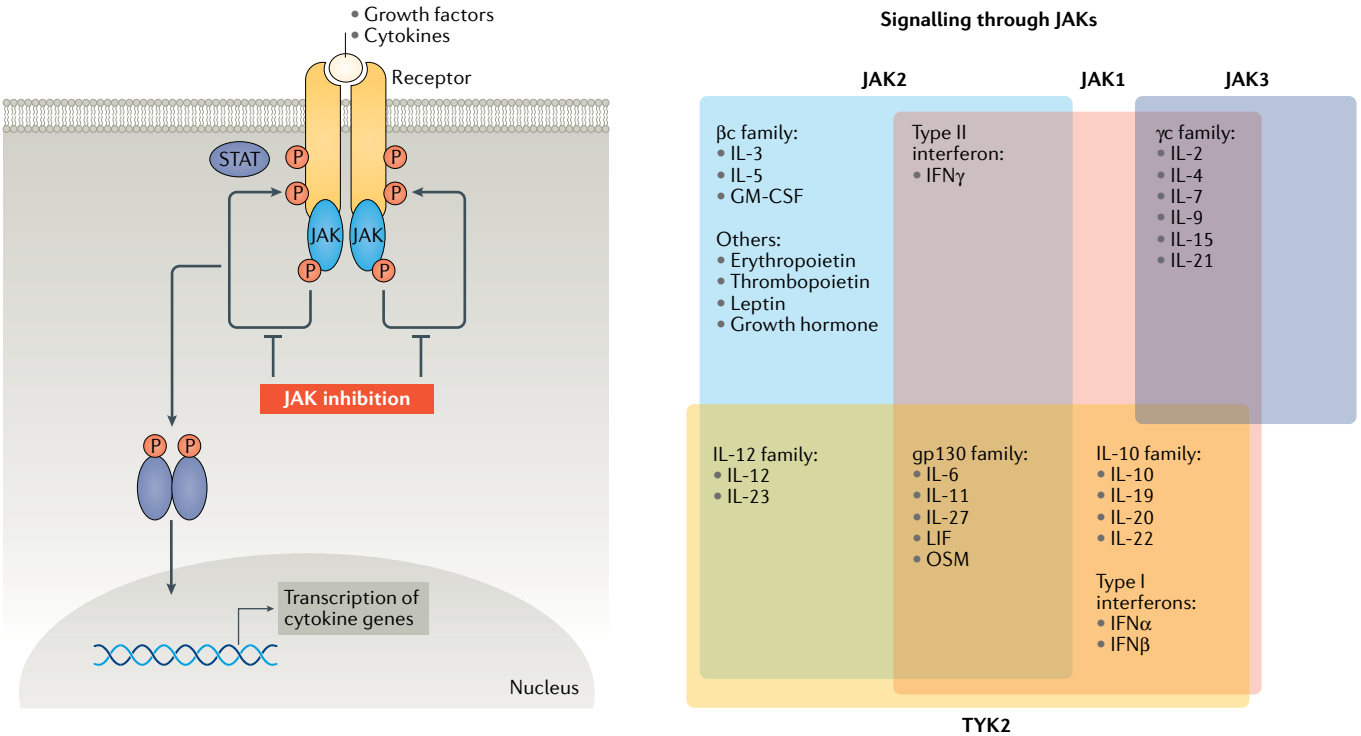

Fig. 1 | **What are JAK inhibitors?** Extracellular binding by a number of cytokines and growth factors to their receptors results in intracellular phosphorylation of receptor-associated Janus kinases (JAKs). Activated JAKs in turn phosphorylate the intracellular components of the receptors, enabling recruitment of signal transducer and activator of transcription (STAT) transcription factors. Activated STATs accumulate in the nucleus and induce transcription. Intracellular signals are transduced through combinations of four JAK isoforms, JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), and seven STAT family members. The involvement of particular JAKs depends on their selective interactions with cytokine-receptor families. JAK inhibitors suppress the effects of cytokines by inhibiting STAT-mediated and other downstream signalling pathways. GM-CSF, granulocyte–macrophage colony-stimulating factor; LIF, leukaemia inhibitory factor; OSM, oncostatin M.

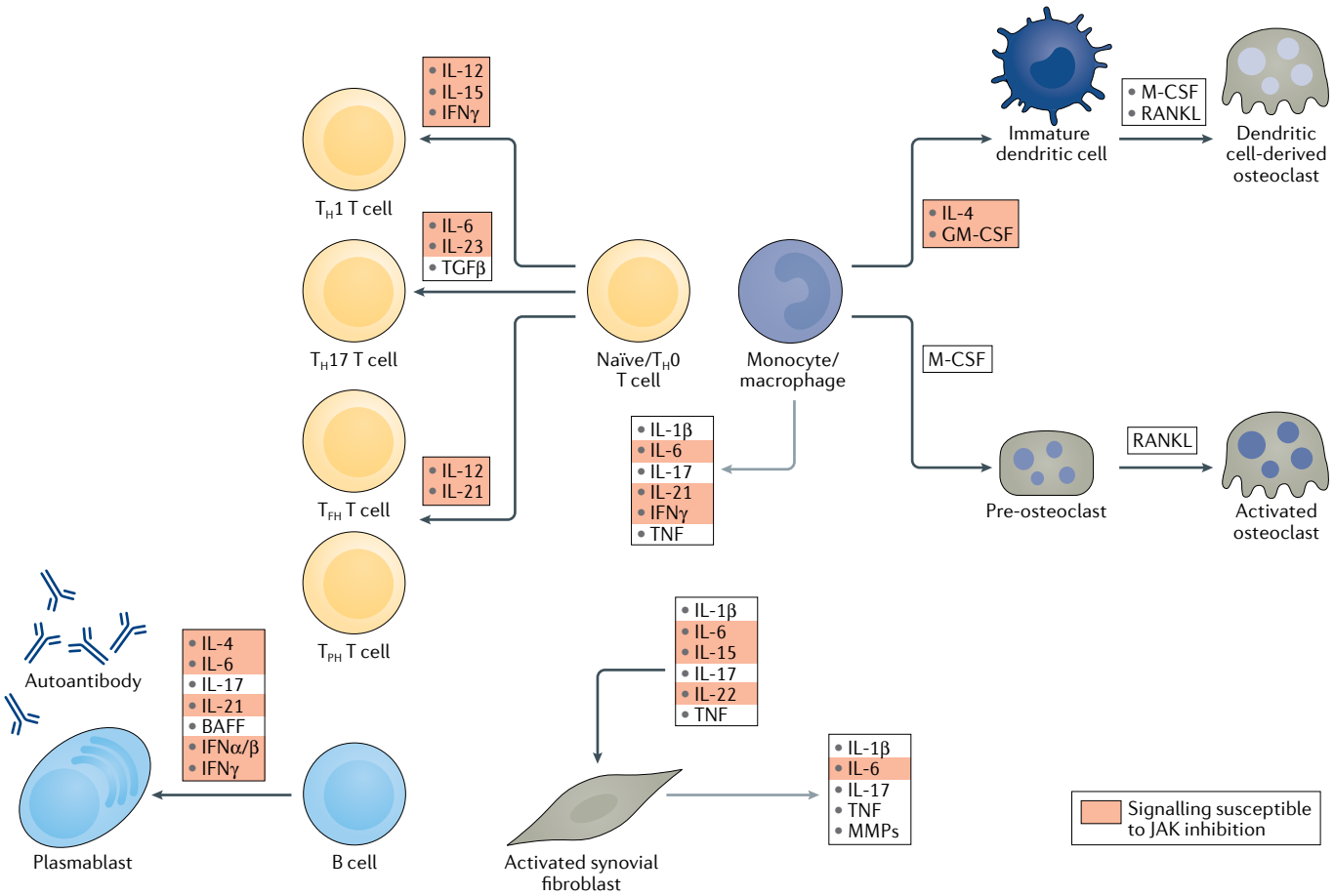

Fig. 2 | **Cytokine involvement in rheumatoid arthritis.** The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling pathways have pivotal roles in intracellular signalling in the pathogenesis of rheumatoid arthritis (RA), including synovial inflammation, autoantibody production, synovial proliferation and joint destruction, which are potential targets for JAK inhibition. Differentiation of naive T cells to T helper 1 (T_H1), T helper 17 (T_H17), T follicular helper (T_{FH}) and T peripheral helper (T_{PH}) cells, and differentiation of B cells to plasmablasts leads to production of autoantibodies. This close cell–cell interaction, including B cell differentiation to plasmablasts induced by T_{FH} in lymphoid organs or T_{PH} in peripheral inflamed tissue, results in high expression of pro-inflammatory cytokines. Monocytes differentiate into osteoclasts in a process dependent on macrophage colony-stimulating factor (M-CSF) and RANKL. Monocytes also differentiate into immature dendritic cells in the presence of IL-4 and granulocyte–macrophage colony-stimulating factor (GM-CSF), and stimulation with M-CSF and RANKL further differentiates the cells to activated osteoclasts (dendritic cell-derived osteoclasts). Synovial fibroblasts produce an excess of pro-inflammatory cytokines, mainly IL-6. These pathological processes provide evidence that multiple cytokines, including IL-6, TNF, interferons and GM-CSF, are good targets for JAK inhibitors in RA. BAFF, B cell activating factor; MMP, matrix metalloproteinase; TGFβ, transforming growth factor-β.

Phase III clinical trials have demonstrated robust and rapid effects of JAK inhibitors compared with placebo in patients with RA who are methotrexate naive or who have an inadequate response to methotrexate or to bDMARDs[15–23]. Baricitinib 4 mg daily dosage, compared with TNF inhibitor adalimumab in a head-to-head phase III trial, achieved superiority in the primary outcome, the ACR20 response rate (20% improvement in the number of tender and the number of swollen joints, along with 20% improvement in three criteria among patient global assessment, physician global assessment, functional ability measure, visual analogue pain scale and erythrocyte sedimentation rate or C-reactive protein) at 12 weeks[18]. However, it should be noted that baricitinib 4 mg daily dosage for treatment of RA has approval in Europe, but not in the USA. Upadacitinib is more effective than adalimumab with regard to ACR20, ACR50 and ACR70 response rates, but only the ACR50 comparison demonstrates multiplicity-controlled statistical superiority[20]. Upadacitinib is superior to the selective T cell costimulatory modulator abatacept with regard to the mean change of DAS28-CRP (disease activity score in 28 joints using C-reactive protein concentrations) at 12 weeks (the primary outcome) and the remission rate[22]. Filgotinib 200 mg once-daily dosage (but not 100 mg once-daily dosage) is non-inferior to adalimumab[21]. In patients with RA who have an inadequate response to methotrexate, monotherapy with upadacitinib results in improvements in clinical and functional outcomes compared with continuation of methotrexate[23]. In the EULAR management guidelines for RA of 2019, the recommendation for JAK inhibitors was raised to the same level as for bDMARDs, that is, for use as second-line and third-line agents[3]. On the basis of the treat-to-target principle, JAK inhibitors should be used in combination with conventional synthetic DMARDs in patients with RA.

The JAK inhibitors upadacitinib and filgotinib are therapeutically effective in patients with difficult-to-treat RA, and exert their effects even in patients who have previously been treated with at least two bDMARDs[33,34]. Although there have been no direct comparative studies between JAK inhibitors in RA in general, results from a propensity score-based study indicate that baricitinib is more effective than tofacitinib[35]. We also showed in a network meta-analysis that peficitinib is comparable with baricitinib and tofacitinib in terms of efficacy[36].

JAK inhibitors result in robust inhibition of bone erosion in RA. Relative to placebo, baricitinib inhibited joint inflammation and the progression of radiographic joint damage in patients with RA during phase III studies, and these effects were comparable with those observed with adalimumab[37]. These efficacies against joint destruction are supported by results from preclinical studies showing that baricitinib promotes mineralization of osteogenic cells and has osteoprotective effects[38]. Pathological bone erosion occurs when inflammatory granulation tissue, including proliferating and stratified synovial cells, grows until it contacts bone, at which point multinucleated osteoclasts destroy and resorb the bone and cause joint destruction. IL-6 and TNF induce proliferation of synoviocytes and expression of RANKL on synoviocytes and lymphocytes, thereby inducing the maturation and activation of osteoclasts. JAK inhibitors directly or indirectly inhibit osteoclast maturation by suppressing IFNβ-mediated signalling in osteoclasts and IL-6-mediated RANKL expression in synovial fibroblasts. Dendritic cell-derived osteoclasts stimulated by IL-4, GM-CSF, M-CSF and RANKL promote bone resorption as osteoclasts and T cell activation as antigen-presenting cells in the pathogenesis of chronic inflammatory and destructive synovitis, suggesting that dendritic cell-derived osteoclasts are also targets for JAK inhibitors in the suppression of bone erosion in RA[39,40] (FIG. 2).

JAK inhibition in spondyloarthritis

Genetic, cellular and molecular mechanisms contribute to the pathogenesis of spondyloarthritis (SpA). In SpA, dysregulation of skin and gut barriers, caused by alteration of bacterial exposure and/or by genetic factors, is responsible for inflammation in the skin, gut and joints. Immune cells migrate from the peripheral blood to the inflamed joints. Invasion of immune cells such as dendritic cells, macrophages, innate lymphoid cells, mucosal-associated invariant T cells and mast cells into the tissue results in the production of numerous additional inflammatory mediators. Thus, various cytokines such as IFNγ, IL-6, IL-12, IL-17, IL-23 and TNF have important roles in pathogenesis.

IL-12 and IL-23 are produced in large quantities by all antigen-presenting cells, such as dendritic cells, monocytes and macrophages. IL-12 is important for the induction of T_H1 cells, which produce IFNγ, TNF and other cytokines, and IL-23 is important for the induction of T_H17 cells that produce, among others, IL-17A, IL-17F and IL-22 (FIG. 3). IL-17 is produced by T_H17 cells, CD8 T cells, γδ T cells and type 3 innate lymphoid cells. These cytokines work in synergy to perpetuate persistent inflammation by interacting with a variety of cells, including chondrocytes, osteoblasts, osteoclasts and fibroblasts, leading to disease manifestations and complications[41–46] (FIG. 3).

Approvals for JAK inhibitors beyond RA are being extended to various rheumatic and autoimmune diseases, including SpA. Results from phase III trials in ankylosing spondylitis (AS), the prototypic axial SpA (axSpA), indicate that the overall magnitude of response to tofacitinib is similar to that reported for TNF inhibitors[47]. Upadacitinib at 15 mg daily was assessed in the phase II/III placebo-controlled trial SELECT-AXIS 1, and more patients had an ASAS40 response (improvement of ≥40% and absolute improvement of ≥10 units in three or more of the domains: patient global assessment, pain assessment, function and inflammation) at week 14 in the upadacitinib group than in the placebo group[48]. Upadacitinib has been approved for treatment of AS by the European Medicines Agency. Overall, the efficacy of JAK inhibitors in AS seems to be comparable with that of TNF inhibitors, and the patterns of adverse events and changes in laboratory outcomes are similar to previous findings in other indications.

Among individuals with psoriasis, 30–40% have SpA, resulting in the designation psoriatic arthritis (PsA). However, only a subset of the heterogeneous PsA population develops axSpA, which is considered to differ from classic axSpA or non-radiographic axSpA by type of spinal involvement, disease characteristics and responses to therapy. PsA initially occurs as enthesitis associated with immune abnormalities, and subsequently the inflammation persists or spreads to synovitis. Because inflammation and new bone formation result in progressive and irreversible functional disability affecting peripheral joints and/or the spine, appropriate and timely treatment is a prerequisite for inhibition of damage progression. Other notable clinical manifestations of PsA include dactylitis, inflammation of the nails and entheses, eye lesions such as anterior uveitis, keratoconjunctivitis sicca and iritis, aortic regurgitation, interstitial lung disease and intestinal inflammation[41–46,49].

Targeting effector cytokines with bDMARDs and JAK inhibitors can help to resolve enthesitis and subsequent arthritis, as well as spine and joint damage in PsA[41–46]. Tofacitinib is approved for PsA in multiple countries. In the phase III trial OPAL Broaden, tofacitinib had a comparable efficacy and safety profile to adalimumab in patients with PsA who had inadequate response to at least one conventional synthetic DMARD and were TNF inhibitor-naive[50]. In another landmark phase III trial, OPAL Beyond, tofacitinib was effective in patients with PsA who had previously had an inadequate response to TNF inhibitors[51]. Notably, 10 mg tofacitinib was not approved for PsA because of concerns regarding its safety–benefit ratio. Also, tofacitinib was not approved for patients with psoriasis but without PsA. The clinical development of baricitinib for PsA has been halted, possibly because of results in a phase II trial in patients with psoriasis, in which responses were only seen at the higher doses of 8 mg and 10 mg[52]. In a comparison of the efficacy and safety of upadacitinib with those of placebo or adalimumab in patients with PsA,

the proportion of patients achieving ACR20 response at week 12 was greater with upadacitinib 15 mg or 30 mg than with placebo, and the 30 mg (but not 15 mg) dose of upadacitinib was superior to adalimumab. Adverse events were more frequent with upadacitinib than with placebo. In patients with active PsA and with inadequate response to bDMARDs, upadacitinib (15 mg or 30 mg) was more effective than placebo over 24 weeks for improvement of the signs and symptoms of PsA[53,54]. Brepocitinib, an inhibitor of TYK2 and JAK1, is effective for treatment of PsA, with a therapeutic response beginning as early as 4 weeks after commencement and maintained to 52 weeks[55].

Deucravacitinib (BMS-986165) is a selective TYK2 inhibitor. Unlike currently approved inhibitors that all bind to the JAK catalytic domain, deucravacitinib targets the pseudokinase or regulatory domain, potentially resulting in higher selectivity[56]. Deucravacitinib was developed for multiple indications including psoriasis, PsA, systemic lupus erythematosus (SLE) and IBD[57]. Deucravacitinib is superior to both placebo and apremilast (an inhibitor of phosphodiesterase 4) in treating moderate to severe plaque psoriasis, according to results from a pivotal phase III trial[58]. Results from a phase II trial demonstrate that it also has favourable efficacy and safety in the treatment of active PsA[59].

JAK inhibition in SLE

SLE is a multisystem autoimmune disease that is more common in women (particularly those of reproductive age) than in men, and that can affect the skin, joints, heart, kidneys, serosa, nerves and blood vessels, presenting with a variety of clinical symptoms. It is pathologically characterized by activation of autoreactive T cells and production of autoantibodies by B cells[60–63]. Glucocorticoids and conventional immunosuppressants are widely used treatments, but their targets are non-specific, and effective targeted therapies are needed.

Many SLE disease-susceptibility genes identified by GWAS are highly expressed in adaptive immune cells, including B cells, and B cell activation processes and overproduction of autoantibodies are notable pathological features of SLE[64]. B cells stimulated by T_{FH} cells or autoreactive T helper cells undergo class switching,

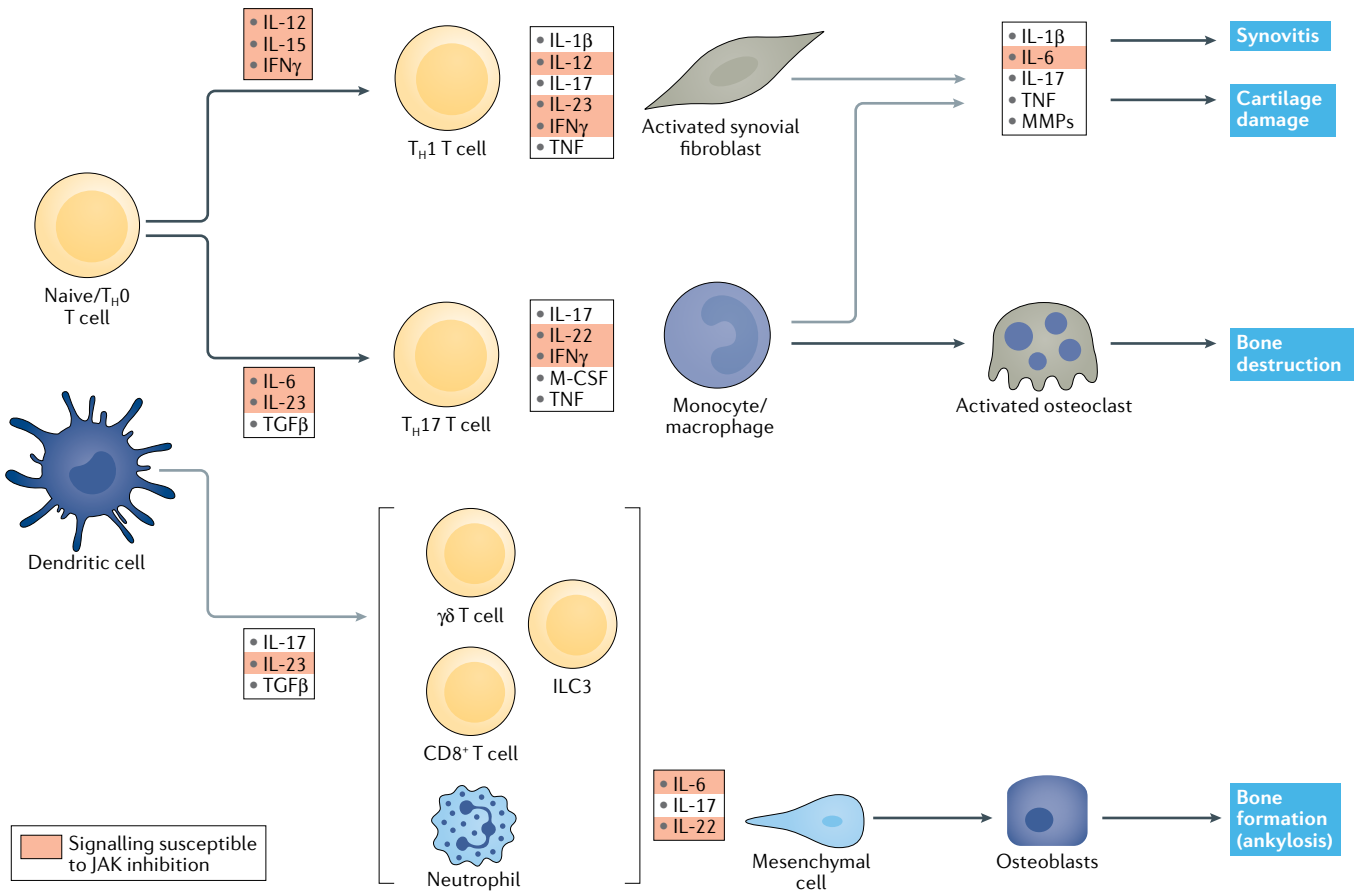

Fig. 3 | **Cytokine involvement in spondyloarthritis.** During pathological processes of spondyloarthritis, invasion of immune cells such as dendritic cells, T cells, type 3 innate lymphoid cells (ILC3) and neutrophils into the tissue results in the production of numerous additional inflammatory mediators. Thus, various cytokines, including IFNγ, IL-6, IL-12, IL-17, IL-23 and TNF, have important roles in pathogenesis, with involvement of multiple signalling pathways including the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathways among several types of immune and non-immune cells. Various cytokines work in synergy to perpetuate persistent inflammation by interacting with a variety of cells, including fibroblasts and monocytes/macrophages. Propagation of autoinflammation involves diverse cytokines, leading to disease symptoms and complications. Targeting these effector cytokines with JAK inhibitors can help to resolve arthritis and cartilage damage, as well as spine and joint damage in spondyloarthritis. M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; TGFβ, transforming growth factor-β; T_H, T helper.

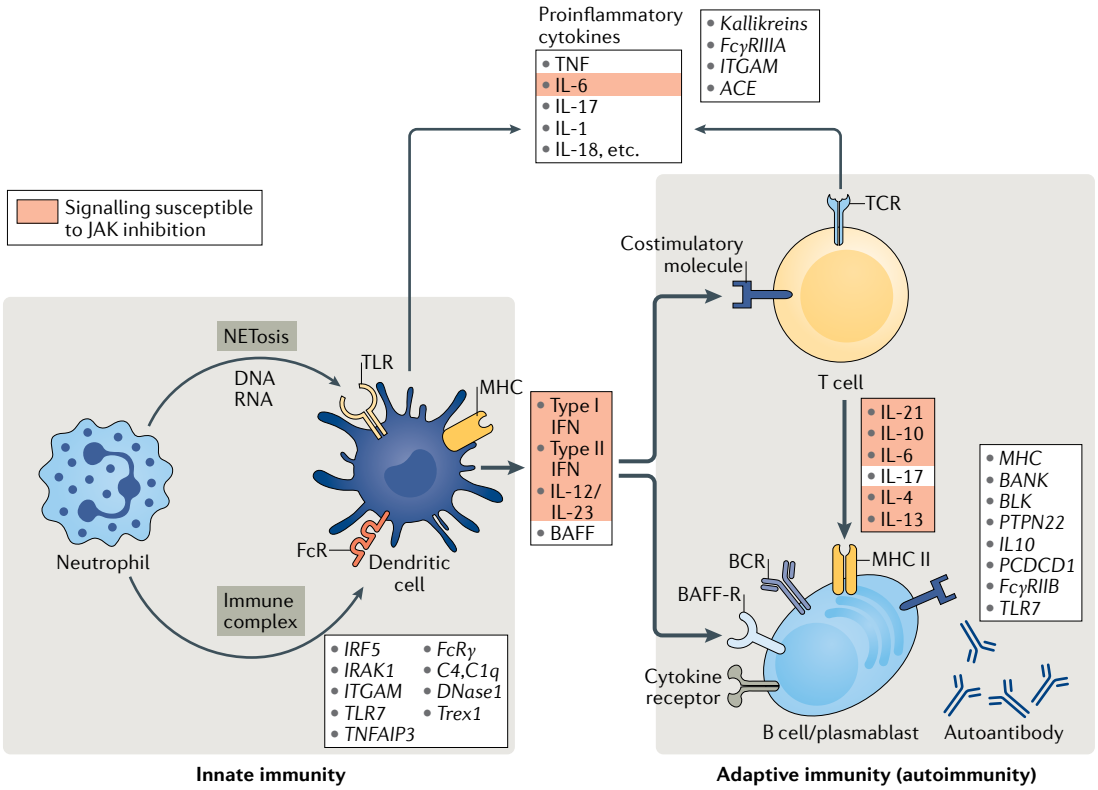

Fig. 4 | **Cytokine involvement in systemic lupus erythematosus.** Genome-wide association analysis has identified disease-susceptibility genes for systemic lupus erythematosus (SLE), including genes encoding Toll-like receptor (TLR) 7 and interferon regulatory factor 5. When TLRs on dendritic cells bind to DNA and RNA released during apoptosis and NETosis, dendritic cells transduce signals and produce cytokines, including soluble B cell activating factor (BAFF), type I interferons, type II interferon, IL-12 and IL-23. Numerous cytokines and growth factors signal through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathways to form a bridge between the innate and adaptive immune systems, resulting in T cell activation, B cell activation and autoantibody production. This signalling is of particular interest as a target for the treatment of SLE. Cytokines that link the innate and adaptive immune systems, such as type I interferons, IL-12 and IL-23, as well as those that activate T cell–B cell interaction, such as IL-21, IL-6 and IL-4, are potential targets of JAK inhibitors in SLE. BAFF-R, BAFF receptor; BCR, B cell receptor; FcR, Fc receptor; MHC, major histocompatibility complex; NET, neutrophil extracellular trap; TCR, T cell receptor.

differentiating into autoantibody-producing cells in response to IL-21 and other cytokines. In addition, B cells produce various cytokines, such as IL-6 (REFS[65,66]). Therefore, B cells have a central role in humoral immunity and autoimmune diseases, and therapies targeting B cells are expected to be effective for the treatment of SLE. However, many bDMARDs targeting B cells, such as the anti-CD20 antibody rituximab and the anti-CD22 antibody epratuzumab, have seemed promising, but have not yielded favourable results[67].

GWAS have resulted in identification of the genes encoding IL-1 receptor-associated kinase 1, interferon regulatory factor 5, Toll-like receptor (TLR) 7, TYK2 and STAT4 as disease-susceptibility genes for SLE[64]. In addition, overproduction of interferons and the concomitant overexpression of interferon-induced genes (known as the 'interferon signature') is a canonical feature of SLE and other autoimmune diseases. Expression of these molecules is high in cells of the innate immune system, including dendritic cells[65]. TLRs are highly expressed in dendritic cells in patients with SLE, and their contribution to aberrant cell death, including neutrophil death through formation of neutrophil extracellular traps (NETs), induces the production of cytokines and chemokines, which has an important role in triggering subsequent loss of immune tolerance[65] (FIG. 4). These cytokines, which are produced by the innate immune system, include soluble B cell activating factor (BAFF), type I interferons, type II interferon, type III interferons and IL-12 and/or IL-23, which in turn induce the differentiation and activation of T cells, and class switching and differentiation of B cells to autoantibody-producing cells in the adaptive immune system. Thus, these cytokines link the innate and adaptive immune systems and are of particular interest as targets for treatment[66,67]. Notably, in patients with SLE, serum levels of soluble BAFF and IFNα are positively associated with disease activity, which is also associated with critical organ disorders, such as lupus nephritis and neuropsychiatric SLE.

Belimumab, an anti-BAFF antibody, was the first approved biologic for the treatment of SLE and is also approved for lupus nephritis[68]. Anifrolumab, a monoclonal antibody to type I interferon receptor, was recently approved for patients with moderate to severe SLE in the USA, Japan and the EU on the basis of results from two phase III trials, TULIP1 and TULIP2 (REFS[69,70]).

Many biologics are under development for SLE and lupus nephritis. However, because B cells are activated and antibody production function is enhanced in SLE, administration of large exogenous molecules such as biologics might actually result in the production of anti-drug antibodies.

The use of JAK inhibitors in SLE is currently being assessed (FIG. 4). Cytokines that bridge the innate and adaptive immune systems, such as type I interferons, IL-12 and IL-23, as well as those that activate T cell–B cell interaction, such as IL-21, IL-6 and IL-4, are likely targets of JAK inhibitors in SLE[71]. Results from a pilot phase Ib/IIa trial showed that the immunological response to tofacitinib in SLE is modulated by *STAT4* risk allele rs7574865[T], which is associated with severe SLE manifestations[72]. In those with SLE who carry the *STAT4* risk allele, tofacitinib is associated with low expression of interferon-response genes and reduction in proportions of low-density granulocytes and neutrophil NETosis, whereas in those without the *STAT4* risk allele, tofacitinib is otherwise associated with low concentrations of activation and checkpoint markers, such as CD103, CXCR3, inducible costimulatory molecule (ICOS) and programmed cell death protein 1 (PD1), in multiple T cell subsets[71,72]. In a phase IIb clinical trial of baricitinib in patients with active SLE exhibiting skin and joint symptoms despite standard care, more patients in the baricitinib (4 mg) group achieved resolution of joint or skin symptoms at week 24 (according to SLE Disease Activity Index 2000 criteria) than in the placebo group. In addition to meeting this primary end point, the baricitinib treatment also achieved a response according to the SLE Responder Index criteria[73]. The phase III trials BRAVE I and II, in which the efficacy of baricitinib in SLE is under evaluation, are currently ongoing (NCT03616912 and NCT03616964). In addition, brepocitinib, an inhibitor of JAK1 and TYK2, is currently the subject of a phase II clinical trial for SLE (NCT03845517).

JAK inhibition in other diseases

Although ulcerative colitis and Crohn's disease differ in their clinical signs and pathological features, these IBDs share gut microbial abnormalities that are involved in immune disorders. Biologic agents that target TNF, IL-12, IL-23 and gut-selective integrins have beneficial effects in the treatment of IBD, but these agents are not effective for all patients[74].

According to results from GWAS, IBD is associated with SNPs in *JAK2*, *STAT3*, *TYK2* and *IL23R*[75]. Crohn's disease shares about 30% of its genetic polymorphisms with ulcerative colitis, including the variants in *IL23R*. Several cytokines, including IL-5, IL-6, IL-7, IL-12, IL-13, IL-15, IL-17, IL-18, IL-21, IL-22, IL-23, IL-27, IL-32, IL-33 and IFNγ, have important roles in the pathogenesis of IBD. Among them, IFNγ, IL-6 and IL-7 are more involved in Crohn's disease, which is associated predominantly with T_H1 cell and T_H17 cell immune responses, whereas patients with ulcerative colitis have elevated IL-5, IL-13, IL-15 and IL-33, consistent with a T_H2 cell-based response. These cytokines function through the JAK–STAT pathway and involve all members of the JAK family, so JAK inhibitors have potential for the treatment of IBD[76–79].

Tofacitinib is approved for the treatment of adults with moderately to severely active ulcerative colitis. In three phase III studies, patients with moderate to severe ulcerative colitis who had not responded to conventional therapy or biologics were treated with tofacitinib (10 mg twice a day) and had a higher rate of clinical remission, clinical response and mucosal healing at week 8 than the placebo group. In addition, the groups of patients who received tofacitinib 5 mg or 10 mg in two divided doses as maintenance therapy for ulcerative colitis had higher frequencies of remission at week 54 than the placebo group[80]. However, clinical trials of tofacitinib for Crohn's disease have been disappointing, with no differences in response or remission at various doses compared with placebo[81]. By contrast, the selective JAK1 inhibitors filgotinib and upadacitinib increased remission rates in patients with moderate to severe Crohn's disease in phase II trials, and larger phase III trials for ulcerative colitis are currently underway (NCT03653026 and NCT02914522). Phase II clinical trials with an inhibitor of TYK2 and JAK1, brepocitinib (PF-06700841), for ulcerative colitis (NCT02958865) and Crohn's disease (NCT03395184) are complete. In addition, several clinical trials of retretinib, a JAK3 inhibitor, are ongoing for Crohn's disease (NCT03395184), ulcerative colitis (NCT02958865) and RA (NCT02969044).

Beyond arthritis and IBD, JAK inhibitors are being studied in other autoimmune, inflammatory and allergic diseases including non-infectious uveitis, giant cell arteritis, systemic sclerosis, Sjögren syndrome and dermatomyositis (TABLE 1). In patients with atopic dermatitis, both baricitinib and upadacitinib effectively achieve rapid improvement of clinical activity compared with placebo[82,83]. Baricitinib has been approved for treatment of atopic dermatitis in Europe[84]. Upadacitinib has superior efficacy in atopic dermatitis to dupilumab (a monoclonal antibody targeting IL-4 and IL-13), but it is also associated with higher rates of serious infection, including one death owing to influenza[83]. Evidence for therapeutic efficacy of JAK inhibitors has also been demonstrated in conditions such as alopecia areata, vitiligo and palmoplantar pustulosis[85,86]. In a phase II trial for treatment of alopecia areata, ritlecitinib (a JAK3 inhibitor) and brepocitinib showed marked efficacy and good tolerability after 24 weeks of treatment[87].

An unanticipated role for JAK inhibitors is their use in treatment of COVID-19, to attenuate the dysregulated production and action of pro-inflammatory cytokines, including IL-2, IL-6, IL-12, IFNγ and GM-CSF, in the COVID-19-associated cytokine storm. Extreme elevation of cytokine concentrations is associated with pulmonary and endothelial disease, myocardial damage and mortality[88]. Baricitinib differs from other JAK inhibitors in that it also inhibits AP2-associated protein kinase 1, a pivotal regulator of clathrin-dependent endocytosis, and thus could inhibit viral entry into target cells[89]. In clinical trials, the combination of baricitinib plus remdesivir was superior to remdesivir monotherapy for both improvement in oxygenation and reduction in select inflammatory markers in patients with COVID-19

pneumonia receiving supplemental oxygen, high-flow oxygen or non-invasive ventilation[88,90]. The Adaptive COVID-19 Treatment Trial head-to-head comparison of baricitinib and dexamethasone for treatment of severe COVID-19 was terminated prematurely because early results met pre-defined futility criteria, indicating that it was unlikely that continuation of the study would demonstrate a difference between the two treatment arms[91]. Another industry-sponsored trial involving addition of baricitinib to the combination of remdesivir and dexamethasone for treatment of severe COVID-19 did not meet its primary end point of a composite outcome of progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death, but a reduction in death by 38.2% was observed in those receiving baricitinib[92]. Thus, baricitinib received Emergency Use Authorization for treatment of severe COVID-19 in concomitant use with remdesivir by the FDA in November 2020, and then as monotherapy in July 2021 (REF.[93]). Baricitinib was also approved in Japan[94] and identified as one of the promising candidate therapeutics in Europe[95]. Clinical trials involving several JAK inhibitors in the treatment of COVID-19 are ongoing, and should provide valuable information on the usefulness of these agents. In addition to current indications, the question arises as to whether JAK inhibitors could have roles in the treatment of sepsis and acute respiratory distress syndrome.

Safety concerns with JAK inhibition

Until warnings from the FDA were published in 2021 (REF.[96]), the consensus was that the short-term and long-term safety of JAK inhibitors were comparable with those of bDMARDs. As potent immunosuppressive agents, the incidence rates of infections, including opportunistic infections, are comparable with those for bDMARDs, with the exception of the rate of herpes zoster infections, which is slightly higher for JAK inhibitors[97,98]. Analyses from randomized controlled trials of tofacitinib and baricitinib have suggested a possible dose-dependent pattern of infection risk[99,100]. Studies on the long-term safety of tofacitinib with follow-up of up to 9.5 years identified no changes over time in incidence rates of infection, opportunistic infection, serious infection, malignancy, thrombosis or cardiovascular disorders[101]. In an integrated safety analysis of five phase III trials, upadacitinib had comparable short-term and long-term safety with methotrexate and adalimumab, except for a higher risk of herpes zoster and of creatine phosphokinase elevation with upadacitinib than with adalimumab[98,102]. JAK inhibitors are also associated with potentially serious effects, including malignancy, major adverse cardiovascular events (MACEs) and venous thromboembolic events[103]. The ORAL-Surveillance study (NCT02092467) compared the safety of tofacitinib and TNF inhibitors. The results of the study have not yet been published, but the preliminary data are available on the sponsor's website[104] and in the trial register (NCT02092467). The initial preliminary result in 2019 demonstrated an association with the risk of venous thromboembolism and death in patients taking tofacitinib 10 mg twice-daily dosage, but not 5 mg twice-daily dosage, prompting an FDA warning in relation to high-dose tofacitnib[105]. However, later results show a higher incidence of MACEs and malignancies excluding non-melanoma skin cancer in patients with RA treated with either 5 mg or 10 mg twice-daily dosage of tofacitinib than in patients treated with a TNF inhibitor[96]. In response to this study, the FDA released an updated boxed warning in September 2021 regarding the increased risk of death, MACEs, malignancies and thrombosis with JAK inhibitors compared with TNF inhibitors[96]. It also limits all approved uses to certain patients who have not responded to or cannot tolerate one or more TNF blockers. Although this study only compared tofacitinib with adalimumab, the FDA was concerned about a JAK-inhibitor class effect, and the warning was extended to two other JAK inhibitors approved in the USA for treatment of inflammatory diseases, baricitinib and upadacitinib. Whether the use of inhibitors with different JAK subtype selectivity or the use of JAK inhibitors in different diseases would improve cardiovascular and carcinogenic risk clearly warrants further investigation. Additionally, in clinical scenarios where TNF inhibitors have failed or not been appropriate, the choice between other biologics and JAK inhibitors is unclear.

Some of the adverse events associated with JAK inhibitors are predicted by mechanisms related to the blockade of cytokines that use JAK–STAT for signalling, which could explain the risk of serious and/or opportunistic infections such as herpes zoster[106]. However, the occurrence of thromboembolism, although relatively rare, is an unexpected and unexplained event[104,106]. Whether this event involves activation of the coagulation–fibrinolysis system or of platelets and endothelial cells is not yet known. Thus, although the use of JAK inhibitors is convenient because of their oral administration, it should be carefully considered[12]. Adequate screening should be performed for factors such as infection, cardiovascular disorders, thrombosis and malignancy. JAK inhibitors should be administered by physicians who are able to provide systemic management of adverse events. Contraindications to the use of JAK inhibitors are related to pharmacokinetic and pharmacodynamic profiles and adverse events, and include: severe active infection (acute or chronic), including latent tuberculosis and opportunistic infections with the apparent exception of COVID-19; active malignancy; severe organ damage (including severe hepatic or renal disease); pregnancy and lactation; and history of venous thromboembolism. The safety and efficacy of JAK inhibitors in children have been assessed in some indications. Tofacitinib is currently approved for treatment of polyarticular JIA in the USA[107], and is being studied in systemic JIA (NCT03000439). Ruxolitinib (an inhibitor of JAK1 and JAK2) is approved for treatment of both acute and chronic graft-versus-host disease in patients >12 years old[108]. In general, JAK inhibitors are not recommended for use in combination with bDMARDs or potent immunosuppressants such as cyclosporine and tacrolimus, because these combinations might overly suppress the immune system and unacceptably increase the risk of infection and lymphoma. Finally, appropriately and

regularly planned monitoring during treatment should be performed for known risks including infection, cardiovascular disorders, thrombosis and malignancy. Long-term safety studies regarding the development of infection and malignancy (such as lymphoma) need to be conducted.

Conclusions

JAK inhibitors exert immunomodulatory effects on a wide range of highly heterogeneous diseases by inhibiting STAT-mediated signalling pathways of numerous cytokines. Thus, mechanism-based therapies targeting several cytokines and their signalling have brought a paradigm shift in the treatment strategy for refractory systemic autoimmune diseases. The success of JAK inhibitors has facilitated research on intracellular signal transduction in immune cells and its relevance to pathological processes, as well as the development of inhibitors of targets including spleen tyrosine kinase, Bruton's tyrosine kinase and IL-1 receptor-associated kinase 4, which are undergoing clinical trials[109,110]. Notably, some JAK inhibitors also have activity against Tec family tyrosine kinases (ritlecitinib) and spleen tyrosine kinase (gusacitinib)[111,112]. However, the top research priority in this field should be to improve therapeutic strategies, including strategies to maintain a balanced efficacy and safety profile, as well as thorough implementation of screening at treatment initiation, and monitoring during treatment. Furthermore, mechanism-based targeted therapies such as JAK inhibitors could ultimately enable either complete withdrawal or avoidance of glucocorticoid use in some autoimmune diseases. In many of these conditions, intensive and appropriate induction therapies are prerequisites for the achievement of disease remission and to sustain remission without damage to organs including joints and spine. After sustained remission, drug-free remission and even cure in the later stages of treatment might become possible, following appropriate and rigorous clinical trials. However, factors that act to inhibit the transition from remission to cure could exist, not only in the immune system but also in mesenchymal, intestinal, nerve and metabolic systems[113]. JAK inhibitors target multiple cytokines, growth factors and endocrine factors, so could have the potential to regulate any active factor inhibiting the transition to cure. Elucidation of such factors and approaches to regulate them could be an important strategy in addressing the challenges and unmet needs in the management of autoimmune diseases.

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This review documents future perspectives on pathological relevance and treatment to achieve "cure" of rheumatoid arthritis.

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Treat-to-target in systemic lupus erythematosus: advancing towards its implementation

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Abstract | The treat-to-target (T2T) concept has improved outcomes for patients with diabetes, hypertension and rheumatoid arthritis. This therapeutic strategy involves choosing a well-defined, relevant target, taking therapeutic steps, evaluating whether the target has been achieved, and taking action if it has not. The T2T principle has been embraced by systemic lupus erythematosus (SLE) experts, but measurable and achievable outcomes, and therapeutic options, are needed to make this approach possible in practice. Considerable evidence has been generated regarding meaningful 'state' outcomes for SLE. Low disease activity has been defined and studied, and the most aspirational goal, remission, has been defined by the Definition of Remission in SLE task force. By contrast, current therapeutic options in SLE are limited, and more effective and safer therapies are urgently needed. Fortunately, clinical trial activity in SLE has been unprecedented, and encouraging results have been seen for novel therapies, including biologic and small-molecule agents. Thus, with the expected advent of such treatments, it is likely that sufficiently diverse therapies for SLE will be available in the foreseeable future, allowing the routine implementation of T2T approaches in the care of patients with SLE.

Treat-to-target (T2T) is a therapeutic approach in which adjustments in treatment are made at set intervals in order to achieve a well-defined, clinically relevant target[1]. The concept of T2T has been widely used in the treatment of common chronic diseases such as diabetes, hypertension, hyperuricaemia and hyperlipidaemia, using specific quantitative parameters as targets (glycated haemoglobin, blood pressure, uric acid and cholesterol levels, respectively). The choice of targets is evidence based and supported by recommendations from national and/or international taskforces, and in these diseases, large randomized clinical trials have demonstrated that the T2T strategy yields superior results compared with standard care[2,3]. In rheumatology, in contrast to the above-mentioned chronic conditions, the aim of therapy is often the simultaneous normalization of a number of parameters represented in a combined score[1,4]. Thus, the implementation of T2T for rheumatic diseases is much more complex, as the target is not a single parameter but a score combining multiple clinical and laboratory changes that, in turn, serve as surrogates of disease activity. The use of a multifactor score represents a potential confounding factor in implementing a T2T strategy, especially in the treatment of chronic conditions, in which disease damage could be irreversible; consequently, even patients with a good clinical response might be wrongly classified as not responding well to the treatment plan[5].

The T2T concept in rheumatology was first investigated in the treatment of rheumatoid arthritis (RA). The first randomized controlled prospective study to investigate T2T (or, as it was then called, 'tight control') was the Tight Control in RA (TICORA) trial, which targeted a reduction in disease activity score by means of monthly assessments, and therapy adjustments were mandatory if the target had not been achieved. In this trial, T2T achieved a better response to therapy, higher remission rates and less radiographic damage than standard care[6]. Subsequent studies established the efficacy of T2T in RA[7–9] by demonstrating an improvement in patients' physical function, better health-related quality of life (HR-QoL) and limited radiographic damage[10,11], and T2T is now firmly established in the EULAR treatment recommendations for RA[12,13]. Furthermore, the benefits of a T2T approach have now been demonstrated in other rheumatological diseases, such as psoriatic arthritis and gout[14,15].

In the case of more complex disorders, such as systemic lupus erythematosus (SLE), the T2T approach has not been formally compared with standard care in clinical trials but the principle has been embraced by experts on theoretical grounds[16]. In 2014, an international task force

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Key points

- The treat-to-target (T2T) therapeutic strategy consists of four key steps: establish a relevant individualized target, take steps to achieve it, monitor the target achievement, and adjust the therapy if the target is not achieved.
- Validation of the Lupus Low Disease Activity State (LLDAS) definition of low disease activity and recent consensus on the final DORIS definition of remission in systemic lupus erythematosus (SLE) have provided feasible treatment targets for the adoption of a T2T strategy in SLE.
- With the advent of novel therapeutics for SLE, including biologics and small molecules, T2T for SLE will become a clinical reality in the coming years.
- The use of LLDAS and DORIS definitions in clinical trials for novel therapeutics could provide robust, discriminatory outcome measures.
- Trials comparing the active attainment of LLDAS or DORIS remission as end points in a T2T approach with a conventional management approach are still needed.

formulated recommendations on implementing a T2T approach in SLE and also indicated further work that was needed to achieve this goal[17]. In general, it is clear that to make T2T possible in practice, at least two objectives must be achieved: establishing practical, achievable outcome measures and developing therapeutic options that can realistically allow these targets to be achieved. Despite limited headway early on, substantial progress has been made in the past decade in achieving both objectives in SLE. Considerable evidence has been obtained regarding outcomes based on a clinically meaningful disease activity state for SLE. Low disease activity has been defined and studied based on the Lupus Low Disease Activity State (LLDAS)[18], and remission, the ultimate goal of treatment, has been defined by the Definition of Remission in SLE (DORIS) task force[19] (BOX 1). In parallel, although current therapeutic options are limited and more effective, safer therapies are urgently needed, the growth in clinical trials in SLE has been unprecedented and encouraging results have been seen with a number of novel therapies, including biologics and small-molecule agents.

Box 1 | **Definitions of SLE targets for remission and low disease activity**

Remission has been endorsed as the long-term target to achieve in systemic lupus erythematosus (SLE), and Low Lupus Disease Activity State (LLDAS) might represent a suitable intermediate target, at least in the medium term.

DORIS definition:

- Clinical SLE Disease Activity Index (cSLEDAI) = 0
- Physician's global activity (PGA) (scale 0–3) score <0.5
- Irrespective of serology
- The patient may be on antimalarial, low-dose glucocorticoids (prednisolone <5 mg daily) and/or stable immunosuppressive drugs including biologics

LLDAS definition:

- SLEDAI 2000 (SLEDAI-2K) score ≤4, with no activity in major organ systems (including renal, central nervous system, cardiopulmonary, vasculitis and fever)[18] and no haemolytic anaemia or gastrointestinal activity
- No new features of lupus disease activity (according to SLEDAI-2K) compared with the previous assessment
- SELENA SLEDAI-PGA (scale 0–3) score ≤1
- Current prednisolone (or equivalent) dose ≤7.5 mg daily
- Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents

DORIS, Definition of Remission in SLE.

In this Review, we discuss the progress that has been made in identifying measurable and achievable outcomes and in developing therapeutic options in SLE. We describe how better outcome measures and the expected advent of new effective treatments are likely to provide sufficiently diverse SLE treatments in the foreseeable future to allow the routine implementation of T2T approaches in the care of patients with non-renal SLE.

T2T strategy for SLE

The 2014 T2T in SLE task force recommended remission as the long-term goal of therapy, though recognizing that because remission might not be achievable in many patients with SLE, it was also important to establish safe intermediate targets for lupus disease activity[17]. The 2019 update of the EULAR recommendations for the management of SLE endorses the use of T2T; it specifically states that the ultimate goal of therapy should be to achieve remission without any signs of disease activity, thereby minimizing comorbidities and drug toxicity, ensuring long-term survival, preventing damage accrual and optimizing HR-QoL[20]. In contrast to medical disciplines in which the T2T strategy is well established and widely implemented, such as in cardiology, the implementation of T2T in SLE requires the target to be approached differently, through reasonably close monitoring (every 3–6 months) of disease activity, response to treatment and damage (both disease- and drug-related), coupled with therapy adjustments and optimization, which, unlike T2T in other diseases, are anticipated in the definition of the targets. Although data or consensus regarding the time interval in which a target should or must be achieved are lacking, cohort studies showed that failure to achieve LLDAS at 6 months after treatment initiation is an independent predictor of early damage[21,22]; therefore, a 6-monthly interval has been adopted for monitoring disease activity in the overall T2T strategy for SLE. Furthermore, the decision to include optimal treatment doses in the definition of the targets might be motivated by the fact that managing the clinical manifestations of SLE, as in the vast majority of systemic autoimmune diseases, frequently relies on the use of glucocorticoids that could contribute to damage accrual over time. Depending on the nature and severity of these manifestations, treatment might include: hydroxychloroquine, which is recommended for all patients with SLE provided there are no contraindications, as it not only reduces disease activity but also has multiple other beneficial effects[23]; immunosuppressive agents, including alkylating drugs, selective inhibitors of purine and/or pyrimidine synthesis, inosine monophosphate dehydrogenase inhibitors (IMPDH) and calcineurin inhibitors[20,24]; and glucocorticoids, the use of which is a subject of debate regarding optimal dosing and appropriate use to prevent unwanted adverse effects, as they have adverse effects and are clearly associated with damage accrual[25]. However, a detailed description of these agents is beyond the scope of this Review. Importantly, the treatment approach based on a T2T strategy in the recommendations formulated by the T2T in SLE task force, includes the goal of completely withdrawing glucocorticoids, which might be accompanied

by a higher use of immunosuppressive and/or biologic therapies. Although different strategies for treating SLE have been proposed[26–28], they are all versions of a T2T approach and invariably involve four major sequential steps (FIG. 1): establishment of a clinically relevant target, frequent therapy adjustments to meet the target, close monitoring of disease activity and optimization of the therapeutic strategy to maintain the target. Furthermore, decision-making regarding therapy adjustments should be based on assessment of disease activity, the physician's judgement, the risk/benefit ratio of the treatment plan, comorbidities, and the patients' view of their disease, in a shared decision-making process.

Despite a strong theoretical basis and expert opinion advocating a T2T strategy in SLE, T2T has yet not been assessed in patients with SLE, and the appropriate medication changes to undertake when the target is not met have not been clarified. Furthermore, implementing T2T in clinical practice has some disadvantages. First, T2T is likely to involve more frequent therapy changes than standard care, which patients might find less desirable, potentially diminishing their trust in the physician (if the change is not explained sufficiently well) or encouraging non-compliance. Second, there is a potential risk of discontinuing a moderately successful therapy because the target has not been achieved, whereas the alternative treatment that is then started proves ineffective. Third, given the limited number of drugs approved for treatment of SLE, the available therapeutic options might be rapidly exhausted with a T2T approach. Fourth, implementing T2T might require a step-wise search for treatments that can achieve the target, which would inevitably lead to more expensive therapies.

Low disease activity and remission. In SLE, the ultimate goal is remission (that is, the absence of any disease activity), ideally without the need for maintenance immunosuppressive or glucocorticoid therapy and with no detectable serological activity[17]. Based on the premise that remission is difficult to achieve in the majority of patients with SLE, the LLDAS definition was developed by the Asia-Pacific Lupus Collaboration (APLC) in 2016 (REF.[18]) (BOX 1). In a case-based construct validity study[29] of the LLDAS definition, an experts' perception of disease activity was not dissimilar to the criteria-driven definition of LLDAS, with an overall agreement between expert opinion and the operational definition of LLDAS approaching 80%. The LLDAS definition was more stringent than expert opinion, with the majority of disagreement observed for patients who did not meet the criteria for LLDAS but were assigned as having a low disease activity state or being in remission by experts[29]. Furthermore, a prospective validation study demonstrated that attainment of LLDAS at any time point and maintenance of this state for at least 50% of the observation period was associated with significant reductions in flares (hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.35–0.48; $P<0.0001$) and damage accrual (HR 0.54, 95% CI 0.42–0.70; $P<0.0001$) across the entire observation period compared with patients who spent less than 50% of the observation period in LLDAS[30]. The attainment of LLDAS is also associated with better HR-QoL[31], further supporting the validity of this definition. Although the LLDAS has been shown to be attainable in many patients with SLE, some important factors, such as ethnicity, educational level and damage score, seem to influence LLDAS attainability; as do active musculoskeletal and cutaneous manifestations of SLE[32]. Furthermore, the time to attain LLDAS was longer for African American patients with SLE than for those of other ethnicities[33].

Multiple ad hoc definitions of remission have been proposed, attesting to the substantial interest in the establishment of a generally agreed-upon definition. In 2017, the European DORIS[19] task force presented a blueprint for a definition of remission in SLE, recommending (for reasons of face validity) that such a definition should be based on an accepted disease activity index supplemented with the physician's global assessment (PGA). Several important questions were identified for further investigation. In 2021, the taskforce reported its final recommendations, revealing that consensus was

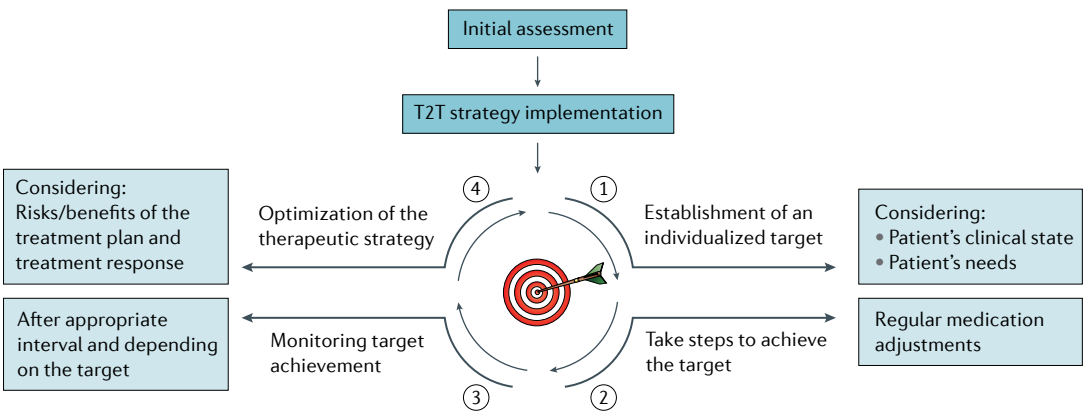

Fig. 1 | **Treat-to-target therapeutic strategy for treatment of systemic lupus erythematosus.** The proposed treat-to-target (T2T) therapeutic strategy can be summarized in four key sequential steps: first, establish a relevant individualized target; second, take steps to achieve that target; third, monitor if the target has been achieved after an appropriate interval; and fourth, adjust the therapy if the target is not attained. Decision-making regarding therapy adjustments should be based on the assessment of the disease, the physician's judgement, the risk/benefit ratio of the treatment plan and the patients' view of their own disease[26–28].

achieved on the eight key statements formulated in the 2017 report, as well as agreeing on a final definition of remission in SLE[34] (BOX 1).

When comparing the DORIS definition of remission and the LLDAS definition of low disease activity, the main differences are found in the disease activity indices and the therapy allowed. For DORIS remission, the Clinical SLE Disease Activity Index (cSLEDAI) is measured and no activity (cSLEDAI = 0) is allowed, whereas for LLDAS as a target, disease activity measured on the SLEDAI index allows scores of up to 4 points (with restrictions specified in BOX 1). The 0–3-point PGA is included in both target definitions, with an allowed maximum score of 1 for LLDAS and less than 0.5 for DORIS. A maximum glucocorticoid dose of ≤5 mg prednisolone (or equivalent) daily is allowed in the DORIS definition, whereas LLDAS allows a higher dose (≤7.5 mg daily). Both definitions permit stable maintenance doses of immunosuppressive drugs, including biologic agents.

The frequency of attaining DORIS remission and LLDAS was compared with a treating physician's judgement of remission in a cohort of 233 patients with SLE. This study found that more patients were in physician-perceived remission than in DORIS remission (31.7% in physician-perceived remission did not achieve DORIS remission)[35]. Remarkably, the discordance was caused in large part by the physician indicating that the patient was in remission while simultaneously giving them a PGA score >0.5; anti-double-stranded (ds)DNA antibody positivity also led to some divergence. In this study, the physician's definition of remission was not manifestly affected by patient-reported outcomes, with the treating physicians' judgement being based mostly on organ-threatening disease manifestations and the disease's physical effects. Thus, physicians seemed to accept a certain level of disease activity without the need for therapeutic escalation. Further prospective data are necessary to gain a better understanding of the relationship between DORIS, LLDAS and physicians' judgement, to enable optimal use of the two definitions in the overall T2T strategy.

LLDAS and DORIS as outcomes. With the establishment of these two targets and their definitions, several cohort and registry studies have investigated the long-term effects of achieving them, including on long-term survival, prevention of organ damage and optimization of HR-QoL. LLDAS was associated with a significant reduction in cumulative organ damage, as demonstrated in the Asia–Pacific collaborative study, in which patients who spent >50% of observation time in LLDAS had a significant reduction in cumulative organ damage and were significantly less likely to have ≥1 increase in the SLICC/ACR Damage Index (relative risk 0.47, 95% CI 0.28–0.79, $P = 0.005$)[18]. Subsequent studies demonstrated the validity of LLDAS as an achievable target in the T2T strategy, with a clear reduction in disease flares and damage accumulation in the Hopkins Lupus Cohort[33,36]. Similarly, several observational studies in different international cohorts (TABLE 1) showed that DORIS remission (or remission defined in similar ways) was associated with a reduction in damage accumulation and better HR-QoL[36–46]. In addition, in a prospective cohort study in patients with SLE from the Asia–Pacific Lupus Collaboration, less-stringent remission definitions might be insufficiently distinct from LLDAS to substantially affect outcome measures[47]. Nevertheless, the attainment of remission (according to the DORIS definition, disregarding serological activity) was associated with considerable reductions in damage accrual and disease flares. In turn, LLDAS was more attainable than any remission definition and provided a similar magnitude of protection from damage accrual and disease flares[47]. Consequently, the attainment of DORIS remission or LLDAS seems to be a pertinent target with a clear long-term benefit in outcome measures.

A programme for the standardized evaluation of patients treated by a T2T approach was reported[48]. Patients in a rheumatology outpatient clinic in the Netherlands were seen in consultation and assessed for different parameters, namely disease activity according to SLEDAI[49], damage accrual reported by the SLICC Damage Index[50], HR-QoL according to the SF-36 and functional status measured by the Health Assessment Questionnaire[51]. In addition, short-term and long-term adverse effects of the drugs used, as well as the personal needs and preferences of the patients, were taken into account when deciding on medication adjustment after the standardized evaluation, consisting of dosage initiation, up-titration and de-escalation, or even stopping the medication. Patient satisfaction with the reported T2T approach was high (average rating of eight (range 5–10 on a scale of 0–10)) and provided the basis of feasibility for implementing a T2T strategy. Further studies are needed to determine the clinical impact of such a strategy but the progress made in creating a standardized strategy represents an important step forward in the establishment of T2T in SLE. The upcoming LUPUS-BEST randomized trial is designed to assess whether implementation of a T2T strategy in clinical care minimizes damage accrual and improves HR-QoL in patients with SLE[52]. The trial design consists of a three-arm, cluster-randomized approach, in which study centres are randomly assigned 1:1:1 to standard care, T2T with remission as the target, or T2T with LLDAS as the target, with 424 patients in each arm. Comparison of DORIS remission and LLDAS will allow identification of the target with the best benefit/risk ratio concerning attainability, adverse events and damage. The trial also emphasizes the need for shared decision-making when applying the T2T strategy, proposing that this approach will strengthen patient autonomy and improve both patient satisfaction and HR-QoL.

LLDAS and DORIS remission have been also analysed in datasets from randomized controlled trials (RCTs) of novel biologic agents for SLE treatment (TABLE 2), including belimumab, atacicept, anifrolumab and baricitinib, to validate these definitions as outcome measures in future RCTs. In brief, LLDAS could discriminate responders from non-responders in the pivotal phase III BLISS-52 (REF.[53]) and BLISS-76 (REF.[54]) trials of belimumab in SLE and was a more stringent outcome measure than the SLE Responder Index 4 (SRI-4)[55]. Furthermore, post hoc analysis of these two RCTs to identify predictors

Table 1 | **Association of remission scores with various outcome measures in observational studies in SLE**

Study	Definition of remission	Number of patients	Association with measured outcomes	Refs
Padua cohort	cSLEDAI = 0	293 224	Significant reduction in damage accrual (OR 0.044, 95% CI 0.012–0.159; $P < 0.001$) in patients in ≥5 years in remission	37,38
GLADEL cohort	DORIS definition[a]	1,350 1,341	Reduced risk of new damage accrual (HR 0.60, 95% CI 0.43–0.85; $P = 0.0042$) and severe damage accrual (HR 0.32, 95% CI 0.15–0.68; $P = 0.0033$) in patients in remission Decreased risk of hospitalization in patients in remission (HR 0.46, 95% CI 0.29–0.72; $P = 0.001$)	39,40
Almenara cohort	DORIS definition[a]	308 281 243	Decreased risk of hospitalization in patients in remission (HR 0.445, 95% CI 0.274–0.725; $P = 0.001$) Lower risk of damage accrual for patients in remission (HR 0.586, 95% CI 0.368–0.933; $P = 0.024$) Remission predicted better HR-QoL in different domains of the LupusQoL score	41–43
Hopkins Lupus cohort	DORIS remission (clinical remission on treatment)	1,356	50% decrease in damage accumulation in patients in remission (RR 0.54; $P < 0.0001$)	36,44
Amsterdam cohort	Various definitions: Complete remission Clinical remission off glucocorticoids Clinical remission on glucocorticoids	183 154	Lower risk of damage accumulation for patients in prolonged remission (OR 0.52, 95% CI 0.28–0.99; $P = 0.046$) Higher HR-QoL in patients in either form of remission	36,45
Chinese cohort	DORIS definition[a]	796	Diminished damage accrual on SDI in patients with remission for ≥5 years compared with those without remission (0.17 ± 0.53 versus 0.67 ± 1.10; $P < 0.001$) Significantly better HR-QoL on SF-36 and LupusPRO in patients with remission for ≥5 years than in those without remission (80.4 ± 14.9 versus 71.7 ± 17.5; $P < 0.001$)	46

cSLEDAI, Clinical SLE Disease Activity Index; DORIS, Definition of Remission in SLE; HR, hazard ratio; HR-QoL, health-related quality of life; OR, odds ratio; RR, risk ratio; SLE, systemic lupus erythematosus. [a]Based on SLEDAI = 0, disregarding serology and allowing some treatment.

of clinical remission (defined as cSLEDAI-2K = 0) and LLDAS attainment after belimumab treatment suggests that belimumab in combination with standard treatment might allow attainment of LLDAS in patients with SLE with limited or no organ damage prior to treatment initiation and patients positive for anti-dsDNA antibodies and on low doses of glucocorticoids (≤7.5 mg daily) might be more likely to achieve clinical remission[56]. Although attainment of DORIS remission was generally infrequent in BLISS-52 and BLISS-76, durable remission on therapy could discriminate patients who received belimumab from those who received placebo[57]. Conversely, in a post hoc analysis of the phase IIb ADRESS II trial of atacicept in SLE, low disease activity (defined as SLEDAI-2K ≤2), LLDAS and DORIS remission were attainable in patients with highly active disease at baseline and discriminated between treatment with atacicept (150 mg) and placebo at week 24, despite being more stringent than SRI-4 or SRI-6 end points[58]. Furthermore, post hoc analysis of the phase IIb MUSE trial of anifrolumab[59], a monoclonal antibody against type I interferon receptor (IFNR1; also known as INFAR), further supports the clinical validation of LLDAS as a meaningful SLE outcome measure, showing that anifrolumab-treated patients were 2–3-fold more likely to attain LLDAS at week 52 compared with those receiving placebo. LLDAS has also been evaluated in a prospective way as a secondary outcome measure in a phase II trial of baricitinib, in which a greater proportion of patients attained LLDAS with baricitinib (4 mg) than with placebo at week 24 ($P = 0.0391$), supporting the findings for the primary end point (resolution of arthritis or rash by SLEDAI-2K), as well as other important general measures of disease activity, such as SRI-4 (REF.[60]). These findings support the inclusion of LLDAS and DORIS remission as measures of treatment response in future phase II and III trials of novel SLE therapies, adding complementary information to other standard outcomes. Of note, a T2T approach to treatment of lupus nephritis (LN), a common manifestation of SLE, is also being investigated (BOX 2).

Novel SLE treatments facilitating T2T

Advances in the understanding of SLE pathogenesis have provided important data on potential targets of novel biologic and small-molecule therapies (summarized in TABLE 3), resulting in targeted therapy becoming a promising option for T2T, especially for those patients who do not respond to conventional treatments.

Agents that target B cells. To date, the anti-B lymphocyte stimulator (BLyS; also known as BAFF and TNFSF13B) antibody belimumab is the only monoclonal antibody

approved for the treatment of non-renal SLE, based on four successful trials[53,54,61,62]. Belimumab was also approved for LN treatment, as an addition to standard therapy, based on significantly improved renal responses compared with standard therapy alone in the BLISS-LN trial[63]. In addition, rituximab (an antibody against the B cell surface marker CD20) is also included in the EULAR recommendations[20] as an off-label treatment option for severe, refractory renal and non-renal SLE, despite rituximab showing no statistically significant difference in primary or secondary end points compared with placebo in the EXPLORER[64] and LUNAR[65] trials. Off-label use of rituximab is rare (estimated in 0.5–1.5% of all patients with SLE in Europe) and limited to specialized, tertiary care centres and patients for whom all reasonable conventional options have been exhausted[66]. In addition, obinutuzumab (a new generation anti-CD20 antibody) showed a good safety profile and sustained benefit (a greater modified CRR in patients with class III/IV LN receiving obinutuzumab and standard therapies than with placebo and standard therapies) in the NOBILITY trial[67]. Based on these encouraging results, further investigation is ongoing in the phase III REGENCY trial (NCT04221477)[68].

As belimumab and rituximab, the only biologic drugs currently available for the treatment of SLE, target different B cell signalling pathways, combining these agents (anti-BLyS and anti-CD20 antibodies) is an exciting idea, considering that a secondary increase in BLyS production after B cell depletion with rituximab could favour the re-emergence of autoreactive B cells[69]. Several phase II trials have assessed this therapeutic approach. A phase II proof-of-concept study (15 patients with SLE, including 12 (80%) with LN) investigated the long-term feasibility of combining rituximab and belimumab, showing a potential clinical benefit with this combination: 67% (10/15) of patients achieved LLDAS during the 2 years of follow-up; 9 patients showed a renal response (CRR in 8/9 patients); and depletion of $CD20^+$ B cells was higher in responders than in non-responders[70]. Furthermore, the combination showed a good safety profile and was well tolerated during the 2 years of follow-up, even allowing the discontinuation of treatment with mycophenolate mofetil in responders. The phase IIb Belimumab after B cell depletion in SLE (BEAT-LUPUS) trial[71] showed a significant reduction in anti-dsDNA IgG antibody levels at 52 weeks ($P<0.001$) and a prolonged time to severe flare in patients treated with belimumab after B cell depletion with rituximab, compared with placebo; these results further support the development of this combination as a novel therapeutic strategy. No major safety issues were raised in these studies, leading to this combination being further studied in the ongoing phase III BLISS-BELIEVE trial (NCT03312907), which is aimed at establishing the efficacy of combined rituximab and belimumab compared with standard treatment[72].

Table 2 | **LLDAS and DORIS validation as outcome measures in post hoc analyses of RCTs**

Study	Outcome measure	Datasets	Effect of post hoc implementation
Oon et al.[55]	LLDAS	BLISS-52 (REF.[53]) BLISS-76 (REF.[54])	Patients who achieved a SRI-4 response also attained LLDAS at week 52 on 10 mg/kg belimumab (17.0% in BLISS-52 and 19.3% in BLISS-76) Attainment of LLDAS at week 52 was higher for 10 mg/kg belimumab compared with placebo in BLISS-52 (12.5% versus 5.8%, OR 2.32; $P=0.02$) and BLISS-76 (14.4% versus 7.8%, OR 1.98; $P=0.04$)
Parodis et al.[56]	LLDAS and clinical remission (cSLEDAI-2K = 0)	BLISS-52 (REF.[53]) BLISS-76 (REF.[54])	SDI >1 prior to initiation of belimumab treatment associated with reduced probability of achieving LLDAS (OR 0.46, 95% CI 0.27–0.77; $P=0.004$) Mucocutaneous damage associated with a reduced probability of achieving clinical remission (OR 0.33, 95% CI 0.12–0.89; $P=0.028$) Anti-dsDNA-positive patients more likely to achieve clinical remission and limited glucocorticoid use (OR 1.74, 95% CI 1.03–2.94; $P=0.040$)
Parodis et al.[57]	DORIS remission	BLISS-52 (REF.[53]) BLISS-76 (REF.[54])	Clinical SLEDAI-2K = 0 definition of remission had a higher rate of remission compared with BILAG D/E: 9 (26.5%) versus 1 (2.9%) of 34 participants in off-therapy category
Morand et al.[58]	LDA, LLDAS and DORIS remission	ADDRESS II[98]	T2T end points were significantly more stringent than SRI-4 and SRI-6 response ($P<0.0001$) LLDAS attainment increased 5-fold in patients treated with 150 mg atacicept compared with placebo (OR 5.03, 95% CI 1.32–19.06; $P=0.018$)
Morand et al.[59]	LLDAS	MUSE[82]	Anifrolumab was associated with more patients who met LLDAS criteria versus placebo (OR versus placebo; 300 mg: $P<0.001$; 1,000 mg: $P=0.046$) LLDAS attainment at week 52 was associated with SRI-4 and BICLA response ($P<0.001$)

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CI, confidence interval; cSLEDAI, Clinical SLE Disease Activity Index; dsDNA, double-stranded DNA; DORIS, Definition of Remission in SLE; LDA, low disease activity; LLDAS, Lupus Low Disease Activity State; OR, odds ratio; RCT, randomized controlled trial; SDI, SLICC Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity index 2000; SRI-4, SLE Responder Index 4; SRI-6, SLE Responder Index 6; T2T, treat-to-target.

Box 2 | **A T2T strategy for lupus nephritis treatment**

Lupus nephritis (LN) is a common and potentially severe manifestation of SLE. Up to 40% of patients with SLE develop LN and despite treatment, LN results in end-stage kidney disease (ESKD) in 10% of these patients[122,123]. Several features of this manifestation influence the decision to use a treat-to-target (T2T) strategy in this patient population. The current treatment strategy for LN involves an initial phase (induction) of intensive treatment with immunosuppressive agents in combination with glucocorticoids, which is aimed at minimizing early glomerular damage and preserving long-term function. Induction is followed by a subsequent maintenance phase of continued immunosuppressive treatment, aimed at achieving a complete renal response and preventing renal flares[63,64]. Induction and maintenance can involve the use of two different immunosuppressive agents, such as cyclophosphamide followed by azathioprine, or a single drug, such as mycophenolate mofetil. The limitations of this two-phase approach include the lack of complete efficacy and possible treatment-related toxicity owing in particular to the use of high doses of glucocorticoids and their well-established contribution to long-term damage in SLE[25]. Suggestions to improve efficacy, reduce toxicity or both have included the use of combined immunosuppressive ('multitarget') therapy and reducing the dosages of concomitant glucocorticoids[124–127].

In contrast to other SLE manifestations, the management of LN is based predominantly on laboratory measures (for example, proteinuria, erythrocyturia and serum creatinine), making it fairly straightforward to establish the target in a T2T approach, although challenges remain. The ultimate therapeutic goal is complete renal remission (CRR), which is usually defined as a low level of proteinuria, normal or stable renal function and, in some studies, an inactive urinary sediment[128,129]. Consensus is still lacking on the ideal target level for proteinuria, but <0.7 g daily has been described as the best positive individual predictor of long-term renal outcomes[130,131]. Furthermore, the use of clinical parameters to differentiate between renal damage and ongoing disease activity in patients with persistent urinary abnormalities remains challenging without a renal biopsy[132]. In addition, current therapeutic options for LN are limited, and a tight-control treatment strategy, such as T2T, with aggressive immunosuppressive therapies raises safety concerns, given the prevalence of infectious complications among patients with LN[133]. However, the approval of two new treatments for LN, belimumab and voclosporin, ongoing work to create and validate better CRR measures, and the remarkable clinical trial activity for the development of novel biologic agents are likely to boost the T2T approach to LN.

Other B cell approaches targeting the inhibition of BLyS and APRIL (a proliferation-inducing ligand) have been explored, some with less favourable results, whereas promising new therapies are still being explored in phase II and III clinical trials (TABLE 3).

Agents that target co-stimulation. Another interesting approach to inhibiting B cell autoimmunity in SLE is blocking cell-surface costimulatory molecules, based on the premise that B cell activation requires co-stimulation by T cells and antigen-presenting cells via different signalling pathways, namely, CD40–CD40 ligand (CD40L), cytotoxic T lymphocyte antigen 4 (CTLA4) and CD28–CD80/CD86[73].

To date, there are no approved co-stimulation-inhibitory therapies for the treatment of SLE. However, treatment with dapirolizumab pegol[74], a polyethylene glycol-conjugated (PEGylated) Fab′ fragment that targets CD40L, produced consistent improvements in disease activity in a phase IIb study, suggesting that this antibody has clinical potential. A larger, phase III trial of dapirolizumab pegol is currently ongoing (NCT04294667)[75]. Of note, this study employs LLDAS attainment in ≥50% of patients as one of the secondary end points, further enhancing the validation of this T2T end point and the benefits of the T2T approach in the development of novel biologic agents.

Agents that target cytokines. A pipeline of other novel agents is being developed to target pro-inflammatory cytokines and chemokines, intracellular signalling pathways and the proteasome. As various cytokines are involved in the dysregulated immune response in SLE pathogenesis[76], interest is growing in blockade of these molecules using agents approved for other diseases. Some of these approaches have been unsuccessful in clinical trials, including the IL-6 antagonists sirukumab and tocilizumab[77,78], as well as ustekinumab, a monoclonal antibody against the common component (p40) of the IL-12 and IL-23 receptor[79,80]. Conversely, anifrolumab has been approved by the FDA for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy[81], based on the primary end point being achieved and anifrolumab demonstrating efficacy and a good safety profile in the phase II MUSE trial[82]. Although the primary end point was not met in the subsequent phase III TULIP-1 trial[83], anifrolumab showed significant benefit in several key secondary outcomes, including a British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response. In the phase III TULIP-2 trial, a significantly higher proportion of patients achieved the primary end point of a BICLA response at week 52 (47.8% with anifrolumab versus 31.5% with placebo, $P = 0.001$)[84]. This is the first regulatory approval of an agent of this type, and the only new treatment approved for SLE in more than 10 years. Furthermore, anifrolumab has received a temporary use authorization by the French National Agency for the Safety of Medicines and Health Products, indicated as an additional background treatment in adult patients with SLE whose disease is inadequately controlled despite optimal treatment with currently available biotherapies or who are intolerant of these therapies[85].

The inhibition of the 20 S subunit of the proteasome by bortezomib also constitutes a new therapeutic option for SLE, based on the depletion of autoreactive memory plasma cells. In a small ($n = 14$) randomized trial, a higher proportion of patients on bortezomib had an SRI response than of those on placebo but the drug was associated with many adverse reactions[86]. In a more recent uncontrolled study, 12 Swedish patients with severe SLE manifestations unresponsive to conventional immunosuppressive agents were treated with bortezomib and showed favourable therapeutic effects, with acceptable tolerability; mild adverse events were observed in half of the patients[87]. Further clinical trials are still needed to confirm its efficacy and safety profile.

Small-molecule agents that target intracellular signalling. Small-molecule inhibitors of intracellular signalling pathways are currently of great interest with regard to SLE given their effectiveness in other rheumatic diseases. The Janus kinase (JAK) inhibitor baricitinib is used in the treatment of RA[88] and was investigated as a potential SLE treatment in a 24-week phase II trial (NCT02708095)[59]: baricitinib produced a significant improvement in disease activity in patients whose disease was not adequately controlled by standard care therapy, a greater proportion of patients attained LLDAS at 24 weeks with baricitinib than with placebo ($P = 0.0391$),

Table 3 | **Novel therapies in phase II and phase III clinical trials for the treatment of SLE and LN**

Agent	Mechanism of action	Completed trial phase	T2T used?	Current development phase	Status	Refs
Agents targeting B cells						
Belimumab	Anti-BLyS mAb	Phase III[a]	Yes, LLDAS as end point[70]	Phase IV — on the market	Approved for use in non-renal and renal SLE as add-on therapy Ongoing phase IV for efficacy, safety and tolerability Ongoing phase III study in combination with rituximab[61]	53,54,61–63,70–72
Blisibimod	BLyS inhibitor	Phase III	No	Not reported	Development stopped owing to failure to meet SRI-6 response as primary end point	99
Tabalumab	Anti-BLyS mAb	Phase III	No	Not reported	Development stopped owing to lack of significant effects	100
Atacicept	BLyS and-APRIL inhibitor	Phase IIb Phase II/III[a]	No	Not reported	Evidence of efficacy in patients with HDA Phase II/III in patients with active LN terminated owing to severe infectious complications	98,101,102
Telitacicept	BLyS and APRIL inhibitor	Phase II	No	Phase III	Phase II showed significant SRI-4 response compared with placebo Ongoing phase III study	103,104
Rituximab	Anti-CD20 mAb	Phase III	Yes, LLDAS as end point[70]	Phase III	Primary end points not reached 'Off-label' recommendation for the treatment of severe, refractory renal and non-renal SLE Ongoing phase III study in combination with belimumab[105]	20,64–66,70–72,105
Obinutuzumab	Anti-CD20 mAb	Phase II[a]	No	Phase III[a]	Phase II showed greater modified CRR than with placebo at week 52 and good safety profile Ongoing phase III study	67,68
Ocrelizumab	Anti-CD20 mAb	Phase III	No	Not reported	Development stopped owing to safety concerns and increased risk of adverse events	106,107
Epratuzumab	Anti-CD22 mAb	Phase III	No	Not reported	Development stopped owing to failure to show a significant difference in the primary outcome	108
Agents targeting co-stimulation						
Abatacept	Inhibitor of CD28–CD80/CD86 co-stimulation	Phase IIb Phase II/III[a]	No	Not reported	Failed to achieve primary end points in non-renal SLE and LN	109–111
Dapirolizumab pegol	Anti-CD40L mAb	Phase II	Yes, LLDAS as end point[75]	Phase III	Phase II trial showed disease activity reduction, but primary end point was not met Ongoing phase III study	74,75
Antibodies targeting cytokines and intracellular signalling						
Sirukumab	Anti-IL-6 mAb	Phase II	No	Not reported	Development stopped owing to failure to achieve primary end point	77
Tocilizumab	Anti-IL-6 mAb	Phase II	No	Not reported	Development stopped owing to unfavourable safety profile	78
Ustekinumab	Anti-IL12/23 mAb	Phase III	No	Not reported	Phase III study discontinued owing to lack of efficacy	79,80
Secukinumab	Anti-IL-17A mAb	Not reported	No	Phase III[a]	Ongoing phase III trial in patients with active LN	112
Guselkumab	Anti-IL-23 mAb	Not reported	No	Phase II[a]	Ongoing phase II trial in patients with active LN	113
Anifrolumab	Anti-IFNR1 mAb	Phase III Phase II[a]	No	Not reported	Second phase III trial (TULIP-2) met the primary end point of SRI-4 response TULIP-LN trial failed to meet primary end point, although IR was associated with numeric improvements across clinical end points compared with placebo	81–85,114
BIIB059	Anti-BDCA2 mAb	Phase II	No	Phase III	Phase II trial showed dose-related efficacy Ongoing phase III study	115–117
Bortezomib	Proteasome inhibitor	Not reported	No	Not reported	Trial stopped owing to lack of safety	86,87

Table 3 (cont.) | **Novel therapies in phase II and phase III clinical trials for the treatment of SLE and LN**

Agent	Mechanism of action	Completed trial phase	T2T used?	Current development phase	Status	Refs
Small-molecule agents targeting intracellular signalling						
Baricitinib	JAK1 and JAK2 inhibitor	Phase II	Yes, LLDAS as end point	Phase III	Phase II trial showed significant SRI-4 and LLDAS response compared with placebo Ongoing phase III studies	60,88–91
Tofacitinib	JAK1, JAK2 and JAK3 inhibitor	Phase Ib/IIa	No	Not reported	Adequate safety profile Ongoing phase II study	118–120
Fenebrutinib	BTK inhibitor	Phase II	No	Not reported	Failed to achieve primary end point of SRI-4	121
Voclosporin	Calcineurin inhibitor	Phase II[a] Phase III[a]	No	Phase III[a]	First oral therapy approved for patients with active LN AURA-LV trial showed superior renal response rates with voclosporin + MMF compared with glucocorticoids + MMF AURORA-1 trial showed better renal response rates and proteinuria suppression with SoC + voclosporin than with SoC alone Ongoing second phase III study (AURORA-2)	95–97

APRIL, a proliferation-inducing ligand; BDCA2, blood dendritic cell antigen 2; BLyS, B lymphocyte stimulator; BTK, Bruton's tyrosine kinase; CD40L, CD40 ligand; CRR, complete renal remission; HDA, high disease activity; IFNR1, interferon alpha/beta receptor 1; IR, intensive regimen; JAK, Janus kinase; LLDAS, Lupus Low Disease Activity State; LN, lupus nephritis; mAb, monoclonal antibody; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus; SoC, standard of care; SRI-4, SLE Responder Index 4. [a]Study in lupus nephritis.

and the safety profile was consistent with that in other studies. This trial provided the foundation for several ongoing phase III trials (NCT03843125, NCT03616964 and NCT03616912)[89–91], which, notably, all include the percentage of participants achieving LLDAS as one of the secondary outcomes. In addition, other strategies targeting the INFR1 signalling pathway components tyrosine kinase 2 (TYK2), and Bruton's tyrosine kinase (BTK; a key mediator of B cell receptor signalling), are currently being studied as potential therapies for SLE[92–94].

Blocking T cell activation through the inhibition of the calcium/calmodulin-dependent phosphatase calcineurin has long been used in SLE with agents such as cyclosporin A and tacrolimus. A novel calcineurin inhibitor, voclosporin, was approved by the FDA in January 2021 for the treatment of patients with active LN, in combination with standard therapy. Approval was based on the AURA-LV and AURORA 1 trials, in which the proportion of patients achieving CRR was significantly higher ($P<0.0001$) with add-on voclosporin than with placebo (40.8% versus 22.5%; OR 2.65, 95% CI 1.64–4.27)[95,96]. A second phase III extension study (AURORA 2) is currently ongoing to assess the long-term efficacy and safety of voclosporin in patients with LN who previously completed AURORA 1 (REF.[97]). The approval of voclosporin expands the number of therapeutic options for LN, contributing to the feasibility of a T2T approach for this lupus manifestation.

Impact of T2T end points on future RCTs of novel agents. A large number of phase II and III RCTs in SLE were 'failures' (that is, they did not meet their primary end points), and while this might have been due to lack of efficacy of the drug in some cases, it is likely that pitfalls in clinical trial design (such as unsuitable target populations and ill-defined targets and outcome measures) contributed to at least some of these failures. Replacing the traditional approach to clinical trial design, which is typically based on a single randomization followed by landmark assessments of efficacy, with a T2T-based trial design, might be an interesting strategy. Progress in the establishment of a T2T strategy, the achievement of international consensus on the definitions for LLDAS and DORIS remission in SLE, and the concomitant rise of validation studies for these T2T end points emerge as an opportunity for optimizing clinical trial design in SLE and overcoming the above-mentioned challenges.

Based on the traditional parallel design for clinical trials, different scenarios could be proposed (FIG. 2), taking into account a careful selection of the study population, which should be sufficiently large to generate the power to achieve significance when a true effect is present. One approach, which could be designated as a 'new drug versus placebo' study (FIG. 2a), involves implementing the T2T strategy in both drug and placebo arms; the T2T protocol is flexible, with frequent adjustments of therapy dosing, and LLDAS or DORIS remission could be the (primary) outcomes. This study design could help to potentially demonstrate the efficacy of the new drug, although implementation is only possible once targeted therapy is better understood and established. One disadvantage of this design is that the T2T strategy results in the arms 'converging' in terms of outcomes, as was seen in the iconic BeSt T2T trial[11] in RA. Alternatively, standard care and T2T strategies could be compared, in a parallel trial design in which the new drug is used in both arms (FIG. 2b) when the target is not met with other treatments. Such a design might potentially demonstrate the efficacy of the new drug as well provide data about the potential efficacy and superiority of the T2T strategy. A third trial design involves implementation of T2T in both arms but inclusion of the new drug in only one of the arms (FIG. 2c), although the decision of whether to use the new drug is based on the clinical situation.

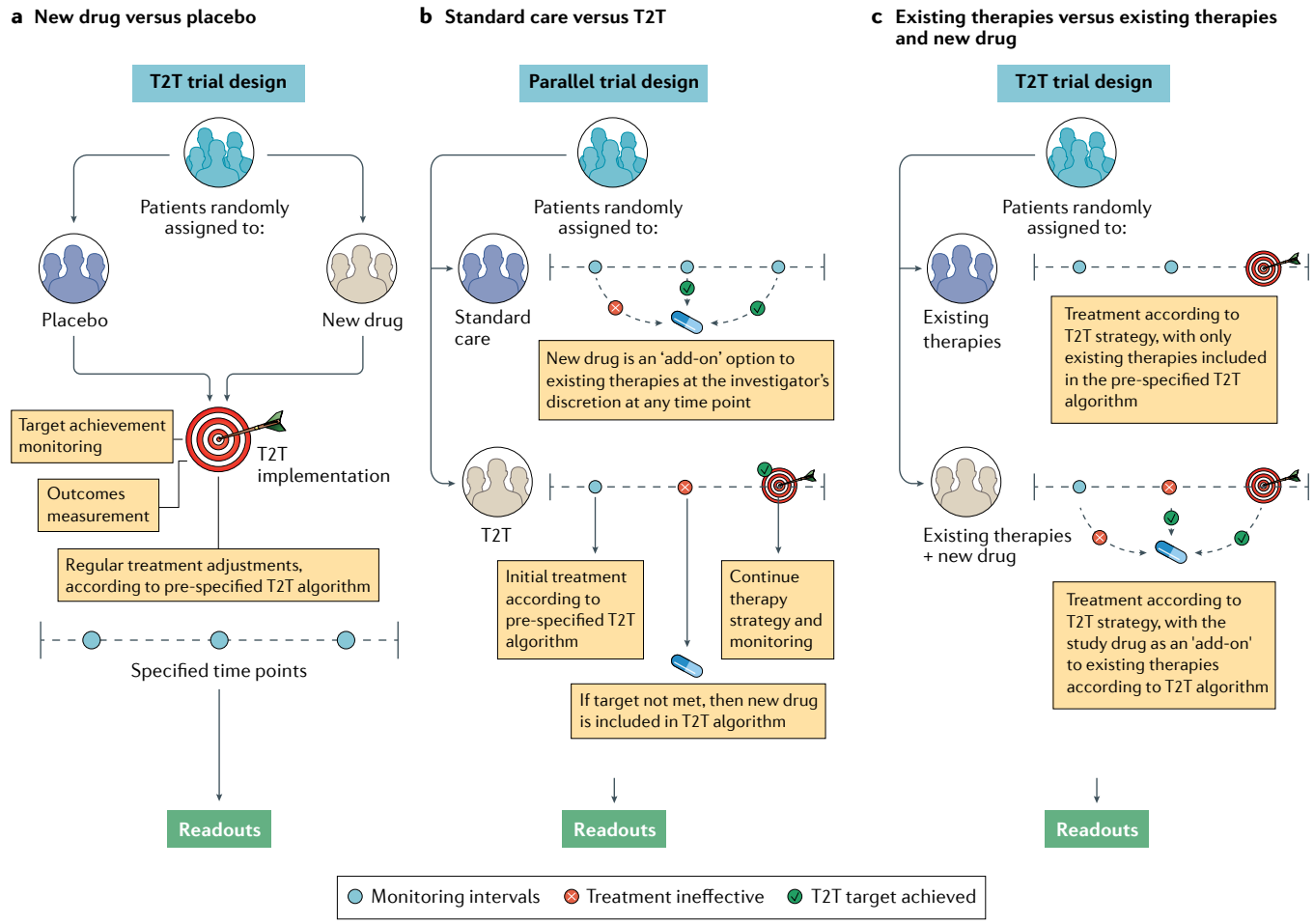

Fig. 2 | **Proposed designs of T2T-based randomized controlled trials of novel therapies in SLE.** The schematic depicts three approaches for the design of treat-to-target (T2T)-based clinical trials, which could aid in the discovery of novel therapeutic agents for systemic lupus erythematosus (SLE). **a** | T2T-based trial design comparing a new drug with placebo, in which the new drug is administered according to a T2T protocol, therapy dosage adjustments are frequent, and time in Lupus Low Disease Activity State (LLDAS) or Definition of Remission in SLE (DORIS) remission could be used as outcomes. **b** | Parallel trial design in which the T2T approach is compared with the traditional treatment approach, referred to here as standard care. In this study type, if the target is not met, the novel therapeutic agent is added to the T2T algorithm in the T2T arm or to the traditional treatment arm at the investigator's discretion at any point in the trial. **c** | T2T-based trial design comparing existing therapies with combined existing therapies and the new drug. In this study design, both treatment arms adhere to a T2T approach. Alternatively, instead of patients, the sites can be randomized (that is, a cluster-randomized trial).

This design allows the efficacy of the new drug as well as its role in the overall treatment to be determined. Of note, these trial designs might also attenuate the problem of exposure to high doses of glucocorticoids during the trial, which complicates interpretation of trial results.

Conclusions

The implementation of a T2T strategy for SLE is becoming a clinical reality. On the one hand, there is now international consensus on two useful clinical targets, LLDAS and DORIS remission, the impact of which on long-term disease outcomes is being progressively validated with very promising trial results. On the other hand, positive trial results with several new therapeutic options for SLE justify the hope that more and more effective treatments for SLE will be available in everyday clinical practice. These two developments will make T2T feasible in routine patient care, leading to better outcomes for patients with SLE. Although remission is conceptually the more desirable goal, as stated in the T2T consensus statement of 2014, it should also be recognized that, for the majority of SLE patients, LLDAS may be a more feasible target to achieve than remission. It is our opinion that remission should be the goal in newly diagnosed patients. By contrast, based on the current therapeutic possibilities, it may indeed be more realistic to target LLDAS in many patients with established disease. However, we are optimistic that the possibility of remission will increasingly become a more realistic target, and that in the future LLDAS might instead be seen as an intermediate goal. We hope that, as more drugs for SLE are approved, information about their efficacy will become available, either from new trials or from observational studies, with at least the hope that some of the new therapies will eliminate the need for extensive maintenance therapies, especially glucocorticoids.

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The role of neutrophils in rheumatic disease-associated vascular inflammation

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Abstract | Vascular pathologies underpin and intertwine autoimmune rheumatic diseases and cardiovascular conditions, and atherosclerosis is increasingly recognized as the leading cause of morbidity in conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis and antineutrophil cytoplasmic antibody-associated vasculitis. Neutrophils, important cells in the innate immune system, exert their functional effects in tissues via a variety of mechanisms, including the generation of neutrophil extracellular traps and the production of reactive oxygen species. Neutrophils have been implicated in the pathogenesis of several rheumatic diseases, and can also intimately interact with the vascular system, either through modulating endothelial barriers at the blood–vessel interface, or through associations with platelets. Emerging data suggest that neutrophils also have an important role maintaining homeostasis in individual organs and can protect the vascular system. Furthermore, studies using high-dimensional omics technologies have advanced our understanding of neutrophil diversity, and immature neutrophils are receiving new attention in rheumatic diseases including SLE and systemic vasculitis. Developments in genomic, imaging and organoid technologies are beginning to enable more in-depth investigations into the pathophysiology of vascular inflammation in rheumatic diseases, making now a good time to re-examine the full scope of roles of neutrophils in these processes.

Neutrophils are essential components of the innate immune system. In humans, an estimated 10^{11} neutrophils are generated daily, as neutrophils have the shortest lifespan among immune cells[1]. In contrast to the conventional view of neutrophils as terminally differentiated professional phagocytes that engulf microbes, a body of research from the past two decades has gradually revealed the essential immune-regulatory roles of neutrophils in both health and disease that result from their plasticity and diversity[2]. In particular, neutrophils have emerged as important effector cells in vascular disorders.

Systemic vascular inflammation is the major clinical manifestation of all types of systemic vasculitis, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which mainly affects small vessels, medium-vessel vasculitis and large-vessel vasculitis (LVV). Systemic vasculitis is a term that encompasses a group of autoimmune disorders characterized by inflammation of blood vessels that results in end-organ damage and, in untreated individuals, death. The term AAV covers granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA[3]. In AAV, ANCA-induced excessive neutrophil activation causes damage to small vessels, leading to systemic inflammatory responses and the production of more ANCAs[4]. The term LVV covers giant cell arteritis (GCA) and Takayasu arteritis. Vision loss resulting from vascular narrowing or occlusion of the ophthalmic artery is the most important morbidity in GCA, whereas Takayasu arteritis has more prominent aortic and cardiopulmonary involvement, leading to a mortality rate higher than that in the general population[5]. Vascular inflammation is also a common occurrence in systemic lupus erythematosus (SLE)[6] and rheumatoid arthritis (RA)[7]. Consequently, cardiovascular complications are closely associated with rheumatic diseases.

In this Review, we discuss the emerging roles of neutrophils in rheumatic disease-associated vascular inflammation. We begin by briefly covering the origins of neutrophil diversity in the vascular system, essential neutrophil effector functions and current understanding of the interactions between neutrophils, platelets and endothelial cells, with an emphasis on implications for vascular inflammation. It was not possible to provide a comprehensive analysis of all inflammatory rheumatic diseases in which neutrophils have a role in this Review, so the main discussion focuses on the cellular and molecular mechanisms that underlie

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Key points

- Neutrophils are heterogeneous and have diversified phenotypes and functions, such as reactive oxygen species-producing immature neutrophils and neutrophil extracellular trap-producing mature neutrophils.
- Neutrophils participate in the progression of disease from onset to chronic inflammation affecting multiple organs and tissues in rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus and vasculitis.
- Vascular inflammation in rheumatic diseases is associated with cardiovascular complications, such as atherosclerosis, which are a leading cause of morbidity and mortality.
- Neutrophils, both mature and immature, have an essential role in initial endothelial activation and dysfunction associated with vascular inflammation and atherosclerosis.
- Immune complexes in rheumatic diseases with well-defined autoantibodies excessively activate neutrophils to induce endothelial damage.

neutrophil-mediated vascular inflammation in AAV, LVV, RA and SLE. To conclude, we provide an overview of therapeutic targeting of neutrophils to treat various rheumatic diseases and how new technologies could be introduced to further our understanding of the role of neutrophils in vascular inflammation.

Neutrophil biology and function

Neutrophils exert their conventional antimicrobial activities through the release of cytotoxic products such as reactive oxygen species (ROS), neutrophil extracellular traps (NETs) and pore-forming molecules[8]. These effector activities can cause tissue damage if poorly controlled. Moreover, as important regulatory myeloid cells, neutrophils also orchestrate immune homeostasis, both systemically via the circulation[9] and locally in the tissue[10]. Under the control of distinct transcriptional networks, neutrophils can be reprogrammed to adapt to the local environment in organs such as the lungs and to protect the vascular system[11]. In this section, we provide an overview of neutrophil heterogeneity and effector functions, and their relevance for vascular inflammation.

Neutrophil heterogeneity. Neutrophils develop and mature in the bone marrow under the tight control of transcription factor networks in health[11] and during inflammation[12]. Neutrophils circulate in the blood in a terminally differentiated mature form, patrol into the tissue and extravasate into various organs to maintain tissue homeostasis[10]. The majority of circulating neutrophils do not encounter any pathogens during their lifetime and are recruited back to the bone marrow, spleen, lung or liver to be destroyed by macrophages[13]. A delicate balance between neutrophil turnover and replenishment is essential for the well-being of the host to avoid any excessive toxic activities. Systemic infections, such as sepsis, can trigger the premature release of large numbers of neutrophils to compensate for those lost in a short time frame combating the disseminated systemic infection[14]. Similarly, in disease states, the process of mature neutrophil release can be altered by the influence of cytokines and growth factors produced at the sites of inflammation, leading to the release of abnormal immature neutrophils into the circulation and tissues. These immature neutrophils can be detected in the blood of patients with autoimmune diseases or cancer[15], and studies have suggested a role for these neutrophils in autoimmune disease[16] and have highlighted context-specific diversity in neutrophil identity, plasticity and function[17].

Neutrophil populations with distinct phenotypes and functions have been reported in chronic inflammatory conditions such as RA, vasculitis, SLE, HIV infection and cancer[2]. Neutrophil heterogeneity can simply stem from physical changes in different pathological settings. For example, low-density neutrophils (LDNs), which have a similar density to mononuclear cells and are enriched in peripheral blood mononuclear cells obtained by density gradient centrifugation, are found in blood from patients with inflammatory conditions but are usually absent in health. Increased numbers of LDNs have been reported in SLE[18–20], RA[18,21], AAV[22] and GCA[23]. In GCA[23], AAV[24] and SLE[25], LDNs are composed of both mature $CD10^{hi}$ and immature $CD10^{lo}$ neutrophils. In GCA, increased numbers of immature $CD10^{lo}$ but not mature $CD10^{hi}$ LDNs correlate with disease progression[23], whereas in AAV and SLE, mature $CD10^{hi}$ LDNs are associated with measures of disease activity such as ANCA titre[24] or the Systemic Lupus Collaborating Clinics–ACR damage index score[25].

Neutrophil effector functions. When neutrophils encounter pathogens, they undergo a respiratory burst to produce a large amount of ROS to kill the invading microorganisms (BOX 1). This process intimately depends on the assembly of the NOX2 NADPH oxidase complex[26]. Prolonged and excessive activation of neutrophils by inflammatory stimuli, such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and TNF, can also lead to ROS production and thus expose neighbouring cells to high concentrations of neutrophil oxidants, causing cytotoxicity and deleterious tissue damage[26]. In fact, the extracellular release of ROS is a major source of potentially harmful neutrophil oxidants in autoimmune diseases[27]. If not removed efficiently, oxidants from superoxide, H_2O_2 and hypochlorous acid and their derivatives can modify proteins, DNA and lipids, thereby resulting in irreversible changes in cellular structure and metabolism, often coupled with the activation of signalling pathways that exacerbate inflammatory responses[28,29].

The importance of ROS production in autoimmune diseases is further supported by results from genetic studies. For example, several independent genome-wide association studies have revealed polymorphisms in genes encoding various NOX2 components in patients with SLE[30–33]. Neutrophils from patients with SLE who have a single nucleotide polymorphism in *NCF1*, which encodes one cytosolic subunit of NOX2, produce lower amounts of ROS[34]. Moreover, lower ROS production by these neutrophils seems to correlate with SLE severity[35]. The intriguing roles of low ROS production in triggering autoimmunity requires further investigation and might, for example, be linked to the increase in type I interferon signalling noted in both ROS-deficient mice and in patients with chronic granulomatous disease, which is associated with the development of autoantibodies and

an increased incidence of SLE and other autoimmune conditions[36,37].

Release of NETs is another potent microbiocidal mechanism employed by neutrophils to combat pathogens (BOX 2). However, if NETs are excessively produced and not removed in a timely manner, they can lead to a breakdown of self-tolerance and chronic inflammation[38]. Accumulating evidence on the presence of NETs in tissues from patients and animals with experimental models of disease indicates a pathological role for NET formation in conditions including sepsis[39] and autoimmune diseases[40]. In SLE[41,42] and RA[43], immune complexes containing autoantibodies and self-antigens are potent NET inducers. In AAV, binding of ANCAs to specific self-antigens presented on activated neutrophil surfaces induces excessive NET formation[44,45], forming a vicious cycle of inflammation. Cholesterol crystals are also capable of inducing NET release, as occurs in atherosclerotic plaques[46].

The presence of numerous granules with distinct sizes and contents is a unique feature of neutrophils. Extracellular release of granular proteins, termed degranulation, is another important defence mechanism that neutrophils possess to control infection. Neutrophil granules contain potent antimicrobial proteins such as myeloperoxidase (MPO), cathepsin G, neutrophil elastase, proteinase 3 (PR3), pentraxin 3, lysozymes, defensins and matrix metalloproteinases (MMPs), which can all cause tissue damage if not removed completely after infection or inflammation is resolved[47,48]. Pro-inflammatory stimuli such as chemokines, cytokines and complement fragments can induce neutrophil degranulation via G protein-coupled receptors, Fcγ receptors or complement receptor 3 (REF.[49]). Increased neutrophil degranulation has been documented in sepsis[50], SLE[25,51] and AAV[52,53]. In fact, neutrophil degranulation is hypothesized to increase the percentage of membrane-bound $PR3^+$ neutrophils[54,55], which are particularly associated with an increased risk of the onset and relapse of GPA[56,57].

Box 1 | **Reactive oxygen species generation**

Upon infection, neutrophils undergo a respiratory burst and produce large amounts of reactive oxygen species (ROS) to kill invading microorganisms. The NOX2 NADPH oxidase complex is an important molecular apparatus for the production of ROS, a process that is tightly controlled. In response to invading microorganisms, neutrophils assemble the NOX2 complex so that a respiratory burst can take place. Recognition of immune complexes by Fcγ receptors, activation of complement receptors bound to opsonized particles, and recognition of the bacterial f-Met-Leu-Phe peptide by its cognate receptor (as well as pro-inflammatory cytokines and lipid mediators) can cause NOX2 to be assembled at either the internal or external cell membrane, resulting in oxygen being reduced by a single electron to form superoxide[26]. Depending on the NOX2 assembly site, superoxide can either be released into the extracellular space or into internal vesicles such as phagosomes. When NOX2 is activated at the plasma membrane, superoxide is dismutated into oxygen and hydrogen peroxide (H_2O_2) by extracellular superoxide dismutase. NOX2 activation at the cellular membrane often causes the release of myeloperoxidase (MPO) from primary granules. In the presence of H_2O_2, MPO converts chloride into hypochlorous acid, a potent secondary oxidant that can efficiently kill microorganisms at the site of infection. In phagosomes engulfed with microorganisms such as bacteria and fungi, activated NOX2 and primary granules fuse with the phagosome membrane to create a narrow space in which superoxide is quickly catalysed to H_2O_2 by MPO. Abundant MPOs then use H_2O_2 to catalyse chloride conversion to hypochlorous acid which, together with proteases from the granules, kills the engulfed microorganism. Hypochlorous acid is the most potent and characteristic antimicrobial oxidant produced by neutrophils[177].

Interactions with platelets. Platelets have a central role in haemostasis, blood coagulation and wound healing[58]. Activated platelets release stored coagulation factors to form blood clots to prevent pathogens from spreading and to promote wound healing. Platelet growth factors are simultaneously secreted to activate more platelets, thereby amplifying the haemostasis response. Beyond these classic roles in blood coagulation, platelets also orchestrate inflammatory responses via interaction with neutrophils, particularly in vascular pathologies[59]. Platelets can initiate inflammatory responses via pattern recognition receptors such as Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns or danger-associated molecular patterns (DAMPs)[59]. For example, activated platelets can induce NET release in sepsis via TLR4 (REF.[60]) and can recruit neutrophils in sterile inflammation[61]. In thrombosis, NETs facilitate the formation of cell aggregates of platelets and erythrocytes by binding to plasma proteins including fibrinogen, fibronectin and von Willebrand factor to stabilize clot formation[62]. This process is particularly important following plaque rupture in atherosclerosis.

Both neutrophils and platelets can secrete cytokines and chemokines and modulate the expression of cell adhesion molecules on their cell surfaces to reciprocally recruit and activate each other at the vascular endothelium. Activated platelets express P-selectin, the receptor for neutrophil-expressed P-selectin glycoprotein ligand 1, by which they directly engage neutrophils. In addition, platelet-expressed CD42b contributes to neutrophil and platelet interaction, leading to thrombosis formation[62].

Interactions with endothelial cells. Neutrophil recruitment and transmigration through the endothelium to clear pathogens that have invaded tissues often results in vascular inflammation. Dynamic interactions between neutrophils and endothelial cells are vital for pathogen clearance. The cellular and molecular mechanisms underlying neutrophil trafficking from blood to the site of infection have been extensively studied using intravital imaging technologies[63,64]. On the basis of data mainly obtained from mouse models of infection, neutrophil trafficking can be divided into separate steps, in which endothelial cells and neutrophils actively change and modulate their surface proteins, cellular structures and signalling pathways to safeguard neutrophil perivascular migration[63,65,66]. A detailed discussion of the molecular events governing each step is beyond the scope of this Review, and these events have been reviewed elsewhere[63,64]. In sterile inflammation, mechanical trauma, ischaemia and environmental insults can induce vascular inflammation[67]. Notably, DAMPs are recognized by innate immune cells at the injured tissue, and cause the release of cytokines and chemokines that prepare endothelial cells and neutrophils to interact and for the final transmigration of neutrophils into the affected tissues for tissue repair. Not surprisingly, molecular mechanisms of neutrophil trafficking similar to those

Box 2 | **Neutrophil extracellular trap formation**

Since its discovery as an antibacterial host response nearly two decades ago, neutrophil extracellular trap (NET) release has been a focal point of neutrophil research in both health and disease[139]. In addition to bacteria, viruses[178,179], fungi[180] and parasites[181] can also induce NET release. NETs are web-like structures made of externalized DNA and proteins. Nuclear DNA serves as the NET scaffold to hold antimicrobial proteins, including histones, neutrophil elastase, myeloperoxidase (MPO), calprotectin, cathelicidins, defensins and proteinase 3 (REF.[182]). If dysregulated, this potent microbiocidal machinery can lead to a breakdown of self-tolerance and chronic inflammation.

NETs can be released by both viable and lytic neutrophils, depending on the type and strength of the stimulus. Cytolytic NET formation (sometimes termed NETosis) often results from persistent infection (enabling large pathogens to be directly engulfed), sustained immune signalling activation by phorbol 12-myristate 13-acetate (PMA) and ionomycin, and immune complex–Fcγ receptor ligation[182]. NET formation requires reactive oxygen species (ROS) generation for chromatin decondensation. Stimuli such as PMA and fungal hyphae can activate the NOX2 NADPH oxidase complex to oxidize MPO[183]. Oxidized MPO frees neutrophil elastase to translocate to the nucleus and proteolytically process histones. Subsequently, MPO further unpacks chromatin to form NET–DNA scaffolds[184]. By contrast, ionomycin and immune complexes can trigger mitochondrial ROS generation independently of NOX2 during NET formation[42].

Peptidylarginine deiminase 4 (PAD4) is an enzyme reported to participate in chromatin decondensation in NET formation by citrullinating histones[185]. PAD4 synergizes with neutrophil elastase in histone modification and is required for NET formation in response to the majority of NET-inducing stimuli and agents, with the exception of cholesterol crystals[46] and viral infections[186]. PAD4 can also interact directly with subunits of NOX2. Calcium influx induced by ionomycin, but not by PMA stimulation, induces PAD4 dissociation from NOX2 and reduces ROS generation[187], which might be the mechanism underlying NOX2-independent NET formation in response to ionomycin.

that occur during infection have been found in several animal models of sterile inflammation[66,68].

Neutrophils in vascular inflammation

Vascular pathologies are widely reported in rheumatic diseases, and vascular inflammation mediated by neutrophils has an essential part in these rheumatic disease-associated cardiovascular complications. In this section, we outline the role of neutrophils in vascular inflammation in AAV, LVV, RA and SLE, and propose a unifying model that links vascular inflammation to cardiovascular disease.

ANCA-associated vasculitis. ANCAs recognize and bind to MPO and PR3 expressed by neutrophils, and are the most reliable biomarkers for AAV diagnosis[4]. Although the precise mechanisms underlying ANCA generation are unclear, neutrophils seem to be the main targets of autoimmunity in AAV. The current working model of pathogenesis was formed on the basis of discoveries from both animal models and patients with AAV, and involves several steps[69]. First, genetic predisposition, infection and environmental factors contribute to ANCA generation. Pro-inflammatory mediators such as TNF, IL-1β and complement protein C5a prime circulating neutrophils to express MPO or PR3 on their cell surface, which are recognized by ANCAs. Simultaneously, FcγR on neutrophils binds to the Fc portion of ANCAs to fully activate neutrophils, leading to ROS generation and degranulation, which damages vascular endothelial cells. In turn, more neutrophils are then recruited to the site of vascular injury. Activated neutrophils also form NETs, which expose and present yet more MPO and PR3 autoantigens to ANCAs, resulting in an amplifying cycle of detrimental inflammatory responses. ANCA-induced NET formation can reportedly also induce endothelial leakage that can be abolished by NET removal by DNase[70]. However, the paradigm of a perpetuating ANCA–NET–ANCA axis in AAV has been challenged by the finding that ANCA-independent NET formation can occur in neutrophils from patients with AAV both ex vivo[71] and in vitro[72]. These contradictory observations could have resulted from the sensitivity of the NET quantification methods used in the studies. Notably, NET quantification has mostly been performed on neutrophils from healthy individuals under different ex vivo stimulations that might not replicate the in vivo inflammatory environment in patients with AAV. Therefore, it is likely that NET production can be induced by ANCA-dependent and ANCA-independent mechanisms in different AAV disease states depending on the degree of inflammatory response.

ANCAs also participate in vascular inflammation via activation of the alternative complement pathway to release the strong neutrophil chemoattractant C5a[4,69]. Neutrophils primed by C5a in the presence of ANCAs further induce NET release, which reciprocally triggers C5a generation to recruit and activate more neutrophils. The ANCA–C5a axis, which couples neutrophil activation, NETs and the complement pathway presents another arm of important molecular mechanism in AAV pathogenesis.

In addition to ANCAs, autoantibodies that recognize total NETs, termed anti-NET antibodies, have been reported in patients with AAV[73,74]. Interestingly, the presence of anti-NET antibodies might inhibit NET degradation in some patients[73,74]. Anti-NET antibodies have not been reported in patients with SLE or RA and, at present, the possibility that there will be an overlap between anti-NET antibodies and ANCA, or between anti-NET antibodies and antinuclear antibodies (ANAs) in SLE or autoantibodies such as anti-citrullinated protein antibodies (ACPAs) or anti-carbamylated protein antibodies in RA cannot be excluded. However, it is appealing to note that a potential new molecular mechanism might exist in parallel with deficiency in DNase-I to account for the impaired NET degradation ability that occurs in autoimmune rheumatic diseases.

The essential role of neutrophils in AAV pathogenesis is further strengthened by a study in which whole-blood transcriptomic analysis was performed in a large cohort of children with small-vessel to medium-vessel vasculitis, which demonstrated that neutrophil degranulation and $CD4^+$ T cell activation could be used to define different disease endotypes independently of the presence of ANCAs[75]. The discovery of these molecular signatures in children, whose young age mean that they are generally exposed to fewer environmental factors than adults, could offer genetic cues for disease onset or relapse in AAV.

Cardiovascular diseases are currently the most common cause of mortality in patients with AAV[76]. A 2018 meta-analysis revealed that patients with AAV have a cardiovascular risk that is increased by 65% compared with that in the general population[77]. Myocardial infarction and stroke are the most commonly reported

cardiovascular events in AAV[77], despite the fact that mainly small vessels are affected in the disease, and accelerated atherosclerosis has been reported in GPA[78]. The endothelial activation and injury that occurs in AAV could also serve as the initial step towards establishing atherosclerosis. However, whether the mechanisms of ANCA-induced neutrophil dysfunction in small-vessel inflammation will also work on larger arteries remains an open question that requires comprehensive research in both human studies and mouse models. Preliminary results of a profile of inflammatory molecular signatures in patients with systemic vasculitis have revealed an increased plasma concentration of tissue factor pathway inhibitor 1 (TFP1) in newly diagnosed patients with GPA compared with the concentration in healthy individuals (L.W. and I.A.U., unpublished observations). As endothelial cells are the primary cells that express TFP1 (REF.[79]), it will be useful to establish if increased TFP1 expression during endothelial cell activation causes long-term cardiovascular complications.

Large-vessel vasculitis. Inflammation of blood vessels is a unifying feature of all forms of systemic vasculitis. Autoantibodies in LVV have been sought after for a long time in an effort to improve the precision of diagnosis and to understand the molecular pathogenesis of these conditions. Anti-endothelial cell antibodies (AECAs) have been reported in Takayasu arteritis for two decades[80,81]. However, only in 2020 were two self-antigens from endothelial cells identified, and AECAs specific for these antigens were shown to be present in up to one-third of patients with Takayasu arteritis[82]. Although the diagnostic value of these specific AECAs in Takayasu arteritis will need to be confirmed in larger, multicentre cohorts of patients, the presence of AECA strongly suggests widespread vascular endothelial cell activation and damage that could underlie disease progress. Considering the intimate interaction between neutrophils and endothelial cells, it is tempting to speculate that neutrophils might have an important role in causing the endothelial cell damage that leads to the generation of AECAs in Takayasu arteritis. In GCA, a wide range of autoantibodies, including ANCA[83], anti-ferritin antibodies[84], anti-phospholipid antibodies[85] and anticardiolipin antibodies[86] have been reported. However, these studies were limited by their small patient sample sizes and lack of appropriate controls.

In the absence of well-established animal models of LVV, the precise cellular and molecular events initiating and shaping LVV remain elusive compared with AAV. In GCA, a circulating AnxA1^{hi}CD62L^{lo}CD11b^{lo} neutrophil subset with T cell-suppressive properties has been identified that seems to emerge in response to treatment with glucocorticoids[87]. The peripheral blood of patients with GCA has a predominant monocyte and neutrophil profile compared with that of healthy individuals that remains consistent throughout treatment with glucocorticoids[88], suggesting disturbed neutrophil development throughout the disease course. An increased neutrophil-to-lymphocyte ratio has also been reported in patients with active GCA independently of glucocorticoid treatment in a large cohort of patients with newly diagnosed GCA, which is likely to be an outcome of chronic inflammation[89]. These findings might explain the presence of immature CD10^{lo} LDNs in patients with newly diagnosed GCA[23]. Functionally, immature CD10^{lo} LDNs can generate ROS and promote endothelial leakage but lack the machinery to produce NETs[23]. Immature CD10^{lo} LDNs have a prolonged lifespan and enhanced association with platelets, and have been found primarily in the lumen of inflamed temporal artery tissue samples from patients with GCA[23]. Interestingly, NETs (that are likely to be produced by mature neutrophils) have been found in temporal artery tissue samples from patients with GCA, primarily in the adventitia of the vessel wall and in close proximity to the microvasculature of the large vessel, where they co-localize with the pro-inflammatory cytokines IL-6 and IL-17A[90]. More research is needed to dissect the contribution of different neutrophil subsets to vascular inflammation in GCA on the basis of their distinct functions and spatial distribution.

Furthermore, longitudinal whole-blood transcriptome data in both GCA and Takayasu arteritis have demonstrated an activated IL-1 signalling pathway that might underlie the high relapse rate in patients with LVV following glucocorticoid treatment[91]. Whether or not increased IL-1 signalling will effect neutrophil functions, including recruitment to and interaction with endothelial cells, in LVV merits further investigation.

Results from two large cohort studies suggest that a substantial increase in cardiovascular risk exists in patients with GCA compared with matched controls[92] at a degree comparable with the risk in patients with AAV[93]. Although patients with Takayasu arteritis have a higher risk of aortic aneurysm than those with GCA, contradictory results have been published for the degree of risk in patients with GCA, with some studies finding a risk up to 17-fold greater than in healthy individuals[94] and others finding a much smaller risk (approximately twofold to fourfold)[95]. The direct link between neutrophils and aortic aneurysm has yet to be established. However, inflammatory mechanisms have been suggested to underlie the development of thoracic aortic aneurysm on the basis of a high neutrophil and lymphocyte ratio in the patients[96]. Furthermore, in a mouse model of disease, a decreased incidence of thoracic aortic aneurysm was associated with a reduction in the number of neutrophils that had infiltrated the vessels[97].

Rheumatoid arthritis. Neutrophils participate in nearly every stage in RA development, from disease onset to established systemic chronic inflammation, which affects not only the synovial joints but also the skin, lungs and the vasculature[98]. RA is often associated with the presence of autoantibodies such as rheumatoid factor, ACPAs and anti-carbamylated protein antibodies[99]. Neutrophils are the most abundant cells in the synovial fluid[100,101] in RA. Neutrophils are thought to act as a source of autoantigens before clinical onset of RA by externalizing citrullinated proteins[43,102] and carbamylated proteins on NETs[103]. At disease onset, neutrophils infiltrate the synovium and initiate inflammation.

By producing pro-inflammatory cytokines and chemokines, neutrophils recruit monocytes, macrophages, T cells, B cells and more neutrophils into the synovial joints, which progress to a state of sustained inflammation[98,104]. Neutrophils also produce growth factors that support the proliferation of autoreactive B cells and contribute to further autoantibody generation[105]. In addition, RA-associated autoantibodies can trigger NET formation in both circulating and synovial fluid neutrophils, which in turn produce more autoantigens and cause tissue damage via release of ROS and toxic enzymes[43].

Vascular pathologies are common comorbidities of RA and range from rare rheumatic vasculitis[106] to more common atherosclerotic lesions[7]. The increased risk of atherosclerosis contributes to higher cardiovascular mortality in patients with RA than in matched non-RA population controls or healthy individuals[107]. Vascular endothelial dysfunction is also greater in patients with RA than in healthy individuals[108]. In RA, both clinical studies and basic research in mouse models of disease have contributed to mapping the inflammatory circuits that connect innate and adaptive immunity in the joints. However, an immunological understanding of the high prevalence of cardiovascular conditions such as atherosclerosis in RA is lacking, and chronic inflammation is generally considered to underlie atherosclerotic lesion formation in RA, in addition to genetic and environmental factors. Central to both rheumatic synovitis and atherosclerosis is the activation and dysfunction of vascular endothelium in the synovial joints[109] and arteries[110]. It is plausible to hypothesize that, in RA, neutrophils have roles similar to those in vascular inflammation in AAV. Neutrophils interact intimately with synovial endothelium via activation of the complement pathway to elicit joint inflammation[68]. Amounts of cell-free nucleosomes, a by-product of NETs, can be used to identify patients with RA who have early atherosclerosis with a high degree of specificity[111]. Furthermore, in vitro endothelial activation and prothrombotic profiles induced by neutrophil supernatant treated with serum from patients with RA can be abolished by DNase treatment. MPO–histone complexes, which are formed during NOX-independent NET formation, are present in RA and can also activate endothelial cells[112]. Furthermore, supernatants from neutrophils cultured with sera from patients with RA being treated with either infliximab or tocilizumab could reduce the inflammatory profiles of endothelial cells, including the over-expression of adhesion molecules, prothrombotic and pro-inflammatory mediators[111]. These studies, together with the discoveries that infliximab and tocilizumab can directly inhibit NET formation in vitro, possibly via inhibiting TNF and/or IL-6 signalling pathways in neutrophil activation[111,113], indicate that neutrophils are important immune cells linking endothelial dysfunction with the development of atherosclerosis in RA.

Systemic lupus erythematosus. In SLE, uncontrolled activation of both the adaptive and innate immune systems by autoantibodies such as ANAs induces systemic inflammation and results in organ damage. Dysregulated B cell and T cell responses are well documented in SLE, and macrophages incapable of disposing of apoptotic cellular debris have been reported to be a major source of nuclear antigens[114]. Type I interferons, such as IFNα, are produced by plasmacytoid dendritic cells (pDCs) after TLR ligation with immune complexes[115–117] and are a prominent feature in SLE. For example, in children with SLE, anti-ribonucleoprotein (RNP) antibodies can induce NET release, which in turn triggers the production of type I interferons by pDCs[118]. A genomic study found predominant neutrophil-specific and interferon-induced gene signatures in the peripheral blood of patients with SLE, and that enrichment of neutrophil transcripts was associated with disease activity[119]. In particular, the gradual enrichment of a neutrophil gene signature in whole-blood transcriptomes from a large cohort of patients with SLE who had been studied longitudinally was suggested to lead to nephritis[119]. An in-depth analysis of transcriptomic datasets from multi-cohort independent studies of SLE published up to 2019 further confirmed a core interferon-stimulated gene signature and increased neutrophil-mediated transcriptional activities across disease subsets and cell types in SLE that are distinct from other inflammatory conditions[120].

Neutrophils have essential roles in disease initiation and propagation in SLE[121]. Neutrophils activated by anti-RNP antibody-containing immune complexes have an increased propensity to release NETs in the tissues, which serve as an additional source of immunogenic nucleic acids that sustain inflammation[41,42,122,123]. Components of NETs, such as DNA strands embedded with antimicrobial enzymes, procoagulant proteins and complement factors, result in direct tissue damage and indirectly lead to local thrombosis, which exacerbates tissue damage[123,124]. In particular, LDNs in SLE have increased mitochondrial ROS production which promotes the spontaneous formation of NETs enriched in oxidized mitochondrial DNA[42]. Oxidized DNA is more immunogenic than conventional, unoxidized DNA and has a greater ability to induce IFNα production by pDCs[42,125].

Vascular inflammation is one of the most prevalent clinical manifestations of SLE, involving nearly all sizes of vessels[126]. SLE is also associated with an increased risk of cardiovascular disease[6]. In a study in 40 patients with SLE and 50 age-matched individuals, about one-third of patients with SLE developed carotid atherosclerosis during a 5-year follow-up period, a figure that was eight times greater than that in the age-matched individuals[127]. A dysfunctional endothelium is likely to be a prelude to developing overt atherosclerosis and other cardiovascular complications in SLE[128].

Through the enhanced production of type I interferons by pDCs, neutrophils can indirectly impair the differentiation capacity of endothelial progenitor cells and disrupt endothelium renewal upon vascular injury in SLE[129]. NETs in SLE promote vascular leakage[19], endothelial-to-mesenchymal transition[130] and induce endothelial cell apoptosis[123]. Furthermore, circulating MPO–DNA complexes in the plasma of patients with SLE correlates positively with the presence of

endothelial microparticles, strengthening the strong link between NETs and endothelial injury in SLE[131]. Bulk and single-cell transcriptomic analysis of neutrophil populations from patients with SLE have revealed the highest expression of interferon-stimulated genes to be in CD10^{hi} LDNs, the number of which also correlates positively with arterial wall inflammation, possibly via increased NET formation[25]. The number of LDNs is also positively associated with cardiovascular risk and vascular pathology in patients with SLE[132]. LDNs potentially accelerate SLE-associated atherosclerotic complications by oxidizing HDL via spontaneous NET formation[133]. MMP9 on NETs from LDNs induces endothelial cell apoptosis by activating endothelial MMP2 (REF.[134]). Moreover, LDNs from patients with SLE were retained in the microvasculature in vitro in a microfluidic microvasculature mimetic, despite the fact that they did not exhibit increased adherence to endothelial cells in 2D assays[135].

Neutrophil-mediated vascular inflammation. Mounting evidence strongly suggests a central role for neutrophils in initiating and shaping vascular inflammation. We propose that a three-stage model of neutrophil-mediated vascular inflammation could underpin rheumatic disease-associated cardiovascular complications and atherosclerosis (FIG. 1a).

The first stage involves immune-mediated activation of both neutrophils and endothelial cells. In AAV, SLE and RA, infection, drugs and environmental factors in genetically predisposed individuals promote inflammatory responses, pathogenic autoantibody production and the formation of immune complexes. Pro-inflammatory stimuli such as TNF, IL-1 and GM-CSF prime neutrophils and activate and upregulate adhesion molecules on both neutrophils and endothelial cells[136]. Primed neutrophils are recruited to endothelium, at sites where immune complexes have been deposited in the extracellular matrix[137]. Via recognition through FcγRs and other

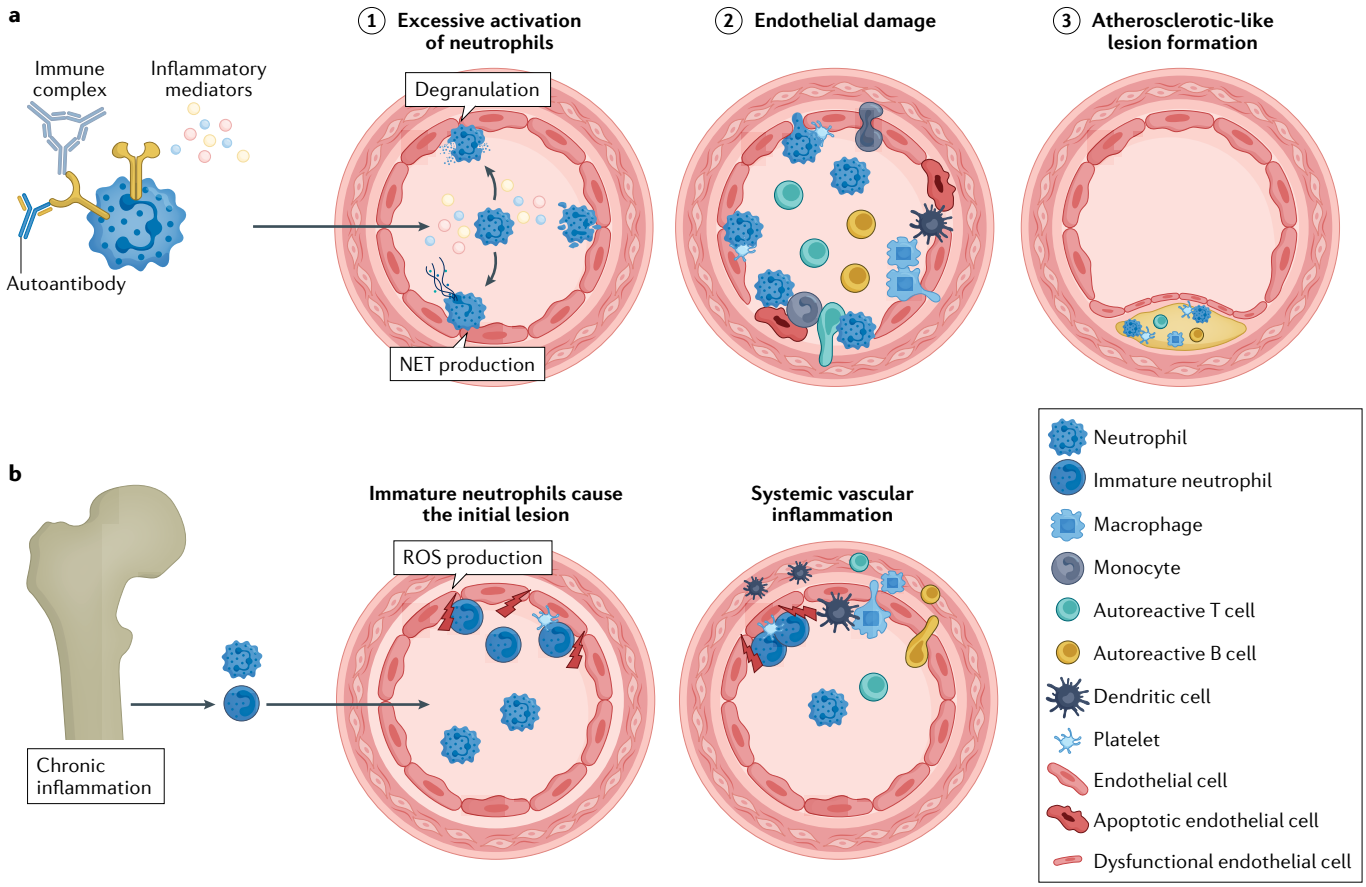

Fig. 1 | **Proposed model of neutrophil-mediated vascular inflammation.** **a** | Immune-mediated activation of neutrophils and endothelium. Immune complexes formed between autoantibodies and self-antigens in antineutrophil cytoplasmic antibody-induced vasculitis, rheumatoid arthritis and systemic lupus erythematosus activate primed neutrophils in the presence of pro-inflammatory mediators such as TNF, IL-1 and granulocyte–macrophage colony-stimulating factor. Immune complex-activated neutrophils produce reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) and undergo degranulation to cause initial endothelial leakage and apoptosis (1). Sustained local endothelial inflammation and failure to repair endothelial damage (2) gradually lead to the formation of atherosclerotic like lesions (3), which could serve as a basis for increased cardiovascular disease risk in these rheumatic diseases. **b** | Role of immature neutrophils in large-vessel vasculitis initiation and cardiovascular conditions. Chronic inflammation causes the release of immature neutrophils into the circulation. Immature neutrophils generate large amounts of ROS that break down vascular endothelial integrity, increase endothelial permeability and elicit initial lesion formation. Having a prolonged lifespan compared with mature neutrophils and increased retention in the vessel walls, ROS-generating immature neutrophils eventually lead to the establishment of systemic vascular inflammation by recruiting more neutrophils and other immune cells, including macrophages, T cells and B cells, via the initial endothelial lesions.

Box 3 | **Neutrophil-mediated inflammation in atherosclerosis**

Atherothrombosis is the leading cause of cardiovascular death in the world. Myocardial infarction and stroke often result from the rupture of atherosclerotic plaques and subsequent thrombosis[188]. Atherosclerosis has long been viewed as a lipid storage disease; however, inflammation also underlies the pathogenesis of atherosclerosis and involves both innate and adaptive immunity[188]. In particular, it has been suggested that neutrophils have essential roles in atherosclerotic plaque development and thrombosis[182,188]. Endothelium, activated by inflammatory stimuli such as TNF and IL-1β, can recruit neutrophils that release neutrophil extracellular traps (NETs), which are highly toxic to endothelial cells[189,190]. Injured endothelium recruits monocytes and macrophages to ingest lipoprotein and cholesterol aggregates, which gradually build up a plaque[191]. Cholesterol crystals can trigger spontaneous NET release, which was found to lead to the production of IL-1β by macrophages in a mouse model of atherosclerosis[46]. Disabling NET formation by knocking out neutrophil elastase substantially reduced atherosclerotic lesion formation in the mice[46]. NETs can also directly stimulate macrophages to secrete pro-inflammatory cytokines and chemokines such as IL-1β, CCL2, CXCL1 and CXCL2 in vitro[192]. In a mouse model of diabetes, glycolysis and inflammasome pathways were enriched in macrophages isolated from NET-rich plaque areas compared with those in NET-poor regions[193]. Additionally, both the number and degree of the inflammatory response in macrophages within atherosclerotic lesions could be reduced by treatment with DNase-I[193] or by knocking out peptidylarginine deaminase 4 (REF.[192]). Taken together, the interactions between neutrophils and macrophages linked by NET production could have a considerable role in plaque development during atherosclerosis.

Upon plaque rupture, primed circulating neutrophils are recruited to the site of endothelial injury along with activated platelets. The formation of neutrophil and platelet cell aggregates on the endothelium induces thrombosis[193]. Furthermore, activated platelets induce NET release to precipitate thrombus formation[194]. Following plaque rupture, NETs contribute to thrombogenic events in three ways[195]: first, NETs form a scaffold that stabilizes clots; second, histones exposed on NETs are strong activators and recruiters of platelets, which amplify thrombogenic events; and third, components of NETs such as tissue factor can further mediate thrombosis.

unknown receptors, immune complexes activate neutrophils to unleash a wide spectrum of effector functions: ROS production, phagocytosis, degranulation and NET formation. These potent effector functions cause initial endothelial damage, such as apoptosis and leakage. New evidence suggests that immature neutrophils can also contribute to the initiation of endothelial layer damage. In LVV specifically, retention of ROS-producing $CD10^-$ immature neutrophils, potentially assisted by platelets, might elicit the initial arterial endothelial insult[23]. However, this mechanism might also extend to other rheumatic diseases in which LDNs, and specifically $CD10^-$ LDNs, are detected in the circulation[23] (FIG. 1b).

Neutrophils participate directly in various stages of atherosclerosis, from initial endothelial activation and dysfunction, through to plaque formation and thrombosis formation resulting from plaque rupture (BOX 3). The initial process of endothelial activation and damage in atherosclerosis is similar to that in rheumatic disease-associated vascular inflammation. The inflammatory environment in the vessel promotes neutrophil and endothelial cell activation and interactions[64]. In the absence of immune complexes and other known activating signals, how neutrophils are activated to produce NETs and perform other effector functions remains unknown. However, it has been suggested that metabolic disturbances, such as hypercholesterolaemia and hyperglycaemia, might be involved[138]. Preliminary observations from a small cohort of patients with cardiovascular disease have revealed increased numbers of immature neutrophils in LDNs (L.W. and I.A.U., unpublished observations). The presence of immature neutrophils in cardiovascular diseases could offer a direction for further investigation, as the release of immature neutrophils might damage vascular endothelium in a similar manner to that hypothesized in GCA.

In the second stage, the initial insult progresses to sustained damage owing to a failure to resolve and repair the initial endothelial lesion. In contrast to infection-induced vascular inflammation, which usually resolves rapidly following pathogen removal and tissue repair, autoimmune sterile inflammation is sustained by the constant and excessive activation of neutrophils and failure to remove neutrophil debris from the site of inflammation as a result of DNase deficiency and overloading of macrophages. Digestion of the DNA backbone of NETs by DNases has long been known to disrupt NET formation[139,140]. Interestingly, in vivo data from mice deficient in DNase have established the role of DNases in NET removal to prevent vascular occlusion[141]. In SLE, a subset of patients has been identified who have impaired NET removal owing to defects in DNase-mediated degradation mechanisms[142]. The unresolved local inflammation at the vascular endothelium recruits more neutrophils to the initial lesion site, leading to the generation and externalization of more NETs, ROS and cytotoxic proteins. NETs expose self-antigens, leading to increased autoantibody production that amplifies the inflammatory responses and the recruitment of macrophages, autoreactive T cells and B cells to the site of inflammation. Platelets also contribute to heighten inflammatory responses and endothelial damage by interacting with neutrophils and releasing pro-thrombotic factors (BOX 3). In atherosclerosis, neutrophils seem to co-localize with endothelial cells that express TLR2, signalling via which promotes endothelial cell apoptosis[138].

In the third stage, the formation of a pro-inflammatory feedback loop can lead to chronic vascular inflammation, which could eventually result in the breakdown of the endothelium and the formation of an irreversible lesion, such as the granulomatous inflammation that occurs in AAV and the atherosclerotic-like lesions found in SLE and RA.

Therapies targeting neutrophils

Despite the considerable progress that has been made in understanding the pathophysiology of autoimmune diseases, blanket suppression of excessive inflammation using non-specific immunosuppressive agents remains the gold standard treatment for many autoimmune rheumatic diseases. For example, glucocorticoids are widely used to treat SLE, AAV and LVV[143]. Biologic agents that target specific aspects of the immune system have had a positive effect on the quality of life of patients with rheumatic diseases and have become an important part of routine treatment for some diseases. Several biologic agents and small-molecule inhibitors that affect neutrophils have either been approved or are currently in development (TABLE 1).

In AAV, avacopan, an antagonist to the C5a receptor expressed on neutrophils, has demonstrated promising

Table 1 | **Neutrophil-targeting drugs in development for rheumatic diseases**

Agent	Molecular target	Neutrophil mechanism targeted	Indication	Stage of development	Refs
Avacopan	Complement protein C5a receptor	Activation and recruitment	AAV	FDA-approved	144,145
Tofacitinib	Janus kinases	Low-density neutrophils and NET formation	SLE	Phase Ib/IIa	147
Otilimab	GM-CSF	Survival and migration	Rheumatoid arthritis	Phase IIa/b	149
Mavrilimumab	GM-CSF receptor	Survival and migration	Giant cell arteritis	Phase II	150
Cl-amidine	Peptidylarginine deaminases	NETs	SLE and atherosclerosis	Preclinical	153,154
AR-447	p38 MAPK	Reactive oxygen species production and degranulation	AAV	Preclinical	156

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; GM-CSF, granulocyte–macrophage colony-stimulating factor; MAPK, mitogen-activated protein kinase; NET, neutrophil extracellular trap; SLE, systemic lupus erythematosus.

results in a phase III trial compared with tapered glucocorticoid therapy in achieving remission. Superior remission was achieved at 52 weeks with avacopan, suggesting that remission could be achieved without glucocorticoids, which would reduce glucocorticoid-related toxicity in patients[144]. In July 2021, the FDA approved the use of avacopan for the treatment of AAV[145]. Inhibition of molecules in the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling pathways has the potential to block multiple pro-inflammatory cytokines and has been extensively explored over the past few years for the treatment of RA and SLE. Two small-molecule inhibitors of JAKs, tofacitinib and baricitinib, have been approved and marketed to treat active RA[146]. Notably, in a phase Ia/IIb clinical trial in 30 patients with SLE, tofacitinib reduced the numbers of LDNs, the type I interferon gene signature and NET formation; tofacitinib also reduced disease activity and improved vascular function[147]. Inhibiting GM-CSF, a chemokine that promotes neutrophil generation and survival, might also reduce ROS and NET production[148]. Successful phase IIb clinical trials have been reported in the past 2 years investigating the use of otilimab, an anti-GM-CSF monoclonal antibody, for treating RA[149], and promising preliminary data have been reported for the use of mavrilimumab, an anti-GM-CSF receptor antibody, for treating GCA[150].

Blocking NETs specifically would have obvious advantages over pan-neutrophil inhibition. Specific PAD4 inhibitors such as GSK199 have been developed[150] and shown to halt arthritis in mice with collagen-induced arthritis[151,152]. Moreover, global inhibition of PADs using Cl-amidine protected vascular integrity in a mouse model of lupus[153] and reduced atherosclerotic burden and thrombotic risk in a mouse model of atherosclerosis[154]. Although no clinical trials have been reported for PAD4 inhibitors in rheumatic diseases or cardiovascular conditions, the potential of inhibiting PAD4 to reduce the increased cardiovascular risk associated with RA, SLE and vasculitis deserves further exploration and validation. In addition to targeting NETs, oxidative stress management could offer new avenues for complementary therapeutics in rheumatology[155]. In a mouse model of AAV, inhibition of p38 mitogen-activated protein kinase could prevent neutrophil respiratory bursts, and thus prevent neutrophil activation by MPO ANCAs and PR3 ANCAs[156]. Direct inhibition of MPO to block oxidant production has also been reported to ameliorate joint inflammation in mouse models of arthritis[155]. However, the complexity of ROS systems and their role in controlling infections and in regulating other immune cells has slowed progress in targeting disease-specific oxidative stress.

Looking further ahead, targeting specific neutrophil effector functions using nanoparticles is a novel area in modulating neutrophil-mediated inflammatory responses and associated diseases[157,158]. Nanoparticles coupled with sialic acid chains have been developed that can reduce neutrophil ROS production and NET release[159], and clinical trials of nanoparticles coupled with anti-inflammatory drugs have demonstrated a reduction in the number and size of plaques or prevented plaque rupture in atherosclerosis[160]. Nanoparticles can also be engineered to possess catalytic functions that mimic natural enzymes. These so-called nanozymes have more stable kinetics than natural enzymes and can be delivered in a site-specific manner. For example, nanozymes that function like hydrogen peroxide scavengers and catalase could effectively prevent vascular inflammation and promote tissue healing in several mouse models of inflammatory disease[161]. These results could lay a foundation for the development of similar ROS scavenger nanozymes to directly inhibit ROS production in specific neutrophil subsets, which would overcome the potential hazard of completely blocking neutrophils that are essential in fighting infection. The detailed characterization of neutrophil subsets in diseases such as SLE and GCA would enable nanozymes to be specifically designed and delivered to the precise pathological neutrophils to suppress their deleterious functions, including ROS production.

Future directions

In vitro vascular models. Basic research using animal models has been instrumental in elucidating the role of neutrophils in health and diseases such as AAV, RA and SLE. However, mouse neutrophils are considerably different from their human counterparts[162]. In addition,

mouse models of disease often fail to reproduce the entire disease progress from initiation to manifestations, which usually take years to develop in humans. Therefore, there is a recognized limit to translating findings obtained from basic research in model systems into human diseases. Moreover, for conditions such as GCA and Takayasu arteritis, the lack of well-established and practical animal models has delayed understanding their pathogenetic mechanisms compared with progress in other rheumatic diseases. Improved in vitro models and systems are therefore clearly needed to help translate findings from mice to humans.

A 3D microvascular mimetic has been developed to enable the study of neutrophil and endothelial cell interactions[135]. Using this technique, an extended retention time of LDNs in the vasculature has been revealed, which could enable them to damage endothelial cells in SLE. The successful development of 3D vessel-on-a-chip models[163] and vascular organoids[164,165] heralds a new direction in experimental design and modelling that should help reveal the role of neutrophils in breaking down the endothelial barrier, leading to established vascular inflammation. Currently, these 3D vessel culture systems and vascular organoids are not attuned to rheumatic disease-associated vascular inflammation. 3D microvessels-on-a-chip can be generated by using appropriate and relevant primary endothelial cell lines. Various vascular disease settings can therefore be mimicked by co-culturing these cells with neutrophils and other types of immune cells. Grafting of vascular organoids to human lung and kidney organoids will help researchers dissect the precise cellular mechanisms of how neutrophils contribute to development of vascular inflammation in SLE and AAV.

Post-multi-omics era: single-cell spatial transcriptomics. Omics technologies, including genomic, transcriptomic, epigenomic and metabolomic platforms, have changed the landscape of nearly every aspect of medical research. These technical advances have enabled exciting breakthroughs in the cellular and molecular understanding of several rheumatic diseases, but have yet to advance our understanding of the role of neutrophils. In LVV, transcriptomic studies have been directly concentrated on T cells[166] rather than neutrophils. In RA, transcriptomic studies have provided a comprehensive map of cellular and signalling networks that will serve as a strong foundation to identify therapeutic targets for patients who do not respond well to disease-modifying drugs[167,168]. Although neutrophils have not been identified in studies conducted so far, tissue processing involving freeze–thaw cycles might have contributed to their disappearance or lack of abundancy. Similarly, in tissue transcriptomic studies in SLE, neutrophils were largely absent from kidney tissue in patients with active nephritis[169,170]. Again, the freezing process that is often involved in tissue preparation might be important, contributing to missing neutrophil populations or their reduced abundance.

A major disadvantage of omics technologies is the lack of spatial information they provide on the cells extracted and isolated from the tissues. Single-cell spatial transcriptomics could be one of the best approaches to overcoming these problems. Spatial transcriptomics enables the simultaneous visualization and quantification of gene expression data at specific locations in tissues[171]. Measurement of the transcriptome of a cell at its physiological or pathological position would undoubtedly offer unprecedented information about the molecular networks that are active in precise microenvironments. In the context of vascular inflammation, dissecting these networks in inflamed vessels at the single-cell spatial level would give new insights into the molecular mechanisms controlling neutrophil effector function and communication with endothelial cells and other immune cells at various stages of inflammation. Although published spatial transcriptomic data are yet to emerge, we anticipate that exciting discoveries in rheumatology research using this cutting-edge technology will be generated soon.

Multiplex imaging. Neutrophils fulfil their effector functions and immune-regulatory roles in the tissues and organs they are recruited to. Vascular inflammation involves not only neutrophils and other immune cells, but also endothelial and muscle cells. Classic histology and immunohistochemistry techniques provide important information on the biological structure of affected tissues and the presence and spatial distribution of specific immune cells during inflammation. However, these traditional techniques are often limited by the numbers and types of cells that can be recognized differentially by the available dyes or fluorochromes. The development of multiplex imaging platforms has revolutionized the ability to simultaneously detect multiple cell types in the same tissue[172]. Multiplex imaging technologies, including multiplex immunofluorescence assays[173], multiplexed ion beam imaging[174] and imaging mass cytometry[175], have already been widely applied in cancer and autoimmunity. Though based on different chemical and physical mechanisms, these platforms offer unprecedented resolution to spatially map cellular composition directly in a complex biological structure and can be used to identify unique cellular markers of prognosis[176]. Therefore, the time seems right for these technologies to be applied to vascular pathologies specifically to investigate neutrophil diversity in the tissues, neutrophil–endothelial interactions and neutrophil crosstalk with other immune cells to reveal the mechanisms involved in neutrophil-mediated endothelial injury.

Conclusions

The view of neutrophils as short-lived foot soldiers that exist just to clear infection is now outdated. Neutrophil diversity and plasticity underlie their regulatory roles in maintaining a balanced and functional immune system. Physiologically, neutrophils protect the vascular system and are essential in tissue haemostasis. Dysfunctional neutrophils participate in a variety of immune-mediated diseases, including sepsis and autoimmune diseases, and vascular inflammation links infection, autoimmune rheumatic diseases and cardiovascular complications. Some of the universal mechanisms of how neutrophils interact with endothelium to infiltrate the extravascular

space have been uncovered. Various disease-dependent neutrophil subsets and populations have been discovered, particularly in the blood. Will different neutrophil populations interact with the endothelium differently? How will the endothelium influence neutrophil subsets to function differently as they leave vessels and infiltrate tissues? Novel technologies including multiplexed imaging and spatial transcriptomics should help address these questions and could lead to the discovery or enhancement of neutrophil-specific therapeutic targets.

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Erosive hand osteoarthritis: latest findings and outlook

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Abstract | Osteoarthritis (OA) most commonly affects knee joints, and the next most commonly affected sites are the hands and hips. Three distinct hand OA phenotypes have been described: erosive hand OA (EHOA), nodal hand OA — also known as non-erosive hand OA (non-EHOA) — and first carpometacarpal joint OA. EHOA predominantly affects women and is the most aggressive form of hand OA, characterized by a severe clinical onset and progression, leading to joint damage, disability and reduction of quality of life. Clinical signs of inflammation associated with EHOA include the acute onset of pain, swelling and redness. Moreover, EHOA is characterized by radiographic features such as central erosion, saw-tooth and gull-wing lesions and, rarely, ankylosis. The aim of this Review is to report the latest findings on epidemiology, clinical features, pathology and aetiopathogenesis, biomarkers, imaging modalities and treatments for EHOA. The ongoing development of new hand OA classification criteria should facilitate standardization between studies.

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Osteoarthritis (OA) is one of the major causes of disability globally[1], and as life expectancy improves, increasing incidence of OA is expected to place a great burden on society and on health-care systems[2]. OA is a complex and multifactorial joint disease that affects all articular tissues[3,4]. The knee is the joint that is most commonly affected, followed by the hands and hips[5]. Estimates of hand OA prevalence vary according to the definition used (radiographic or symptomatic) and according to sex, age and geographical location of the study population[6]. Notably, the prevalence worldwide of symptomatic hand OA is lower (3–16%) than that of radiographic hand OA (21–92%)[6].

Definition of hand OA is challenging as it can be classified according to radiographic results, symptoms or clinical features. Radiographic hand OA is characterized by abnormal findings on radiographs, such as joint-space narrowing (JSN), osteophytes, subchondral cyst formation and subchondral sclerosis. Symptomatic hand OA is characterized by clinical symptoms such as pain, aching or stiffness in the setting of typical structural changes[6]. The three distinct hand OA phenotypes are erosive hand OA (EHOA), non-EHOA (also known as nodal hand OA) and first carpometacarpal joint (CMCJ) OA[6,7]. Non-EHOA mostly affects the distal interphalangeal joints (DIPJs), followed by the thumb CMCJs and the proximal interphalangeal joints (PIPJs). The hallmark of non-EHOA is the formation of nodes: Heberden's nodes at DIPJs and Bouchard's nodes at PIPJs. The nodes are bony enlargements of the joints that can be accompanied by synovial inflammation and soft-tissue swelling of the affected region[6]. Compared with healthy individuals, OA of the first CMCJ is characterized by reduced range of motion in thumb abduction, decreased combined thumb abduction and index-finger extension strength, and increased pain sensitivity[6]. EHOA is an aggressive form of hand OA that is characterized by inflammation and erosion of the DIPJs and PIPJs[8]. Clinical definition of hand OA relies on the 1990 ACR classification criteria, which are based on clinical symptoms (pain, aching or stiffness) and at least three of the following signs on physical examination: hard-tissue enlargement of two or more of 10 selected joints; fewer than three swollen metacarpophalangeal joints; hard-tissue enlargement of two or more DIPJs; and deformity of at least one of the ten selected joints (second and third PIPJs and DIPJs and first CMCJ in both hands)[9]. The ACR classification criteria are quite subjective, do not take into account structural features of disease and were developed before the complexity of hand OA clinical phenotypes was appreciated. Better classification criteria are needed to facilitate meaningful research on OA pathogenesis and treatments, and thereby move the field forward. Notably, the EULAR taskforce for evidence-based recommendations on hand OA diagnosis ranked the development of new classification criteria for all hand OA phenotypes as a top research priority, and an international group of experts has undertaken their formulation[10]. According to EULAR, and unlike other forms of hand OA, EHOA is characterized by a severe inflammatory

Key points

- Erosive hand osteoarthritis (EHOA) is a severe form of hand OA, and evidence suggests that it is characterized by genetic predisposition involving *HLA*, *IL1B* and *SERPINA1* genes.
- The radiological hallmark of EHOA is central erosion of the joint, and both radiography and ultrasonography are useful tools for the detection of EHOA.
- Serological and synovial-fluid biomarkers such as soluble IL-2 receptor and myeloperoxidase are identifiable in EHOA, confirming the role of inflammation in this aggressive form.
- EHOA biomarkers that are useful in clinical practice have not yet been identified.
- EHOA is characterized by the presence of signs of inflammation, which correlates with symptoms and the appearance of bone erosions.
- Currently, no specific treatments are available to slow disease progression in EHOA.

clinical phenotype associated with distinct radiographic features[11,12].

In this Review, we focus on the latest findings for EHOA pertaining to epidemiology, risk factors, clinical and imaging features, molecular mechanisms, genetic predispositions, biomarkers and current therapies. Furthermore, we hope to draw attention to this aggressive form of hand OA, to incentivize researchers to carry out clinical and basic research studies.

The history of EHOA

The term 'erosive osteoarthritis' was first coined in 1966 to reflect hand-joint findings of prominent cartilage destruction, central erosion and osteophyte formation in DIPJs and PIPJs[13]. Six patients with IPJ OA displayed similarities with previously described instances of acute inflammatory episodes, with eventual ankylosis in some IPJs[14]. In the 1970s, analysis of 170 patients with inflammatory OA of the small joints of the hands characterized by abrupt, painful, polyarticular onset enabled definition of the pathology of this condition in greater detail[15,16]. Currently, no consensus exists on whether EHOA is a distinct nosological entity from non-EHOA. A hypothesis published in 1995 indicated that EHOA might be a progression of non-EHOA[17,18]. EHOA has similar radiographic characteristics to both moderate-to-severe and severe non-EHOA, with a pattern of joint involvement that includes a greater prevalence of OA in DIPs than in PIPJs, suggesting that EHOA is a severe form of hand OA, rather than a distinct entity[19]. A 2016 report presented evidence that EHOA is characterized by more synovitis, pain and disease progression than non-EHOA, but that radiographic progression does not correlate with the identification of synovitis by MRI or ultrasonography[20]. However, further evidence demonstrated that the presence of synovial inflammation is associated with the appearance of new bone erosions[21,22]. The debate is ongoing with regard to the definition of EHOA. We support the hypothesis that EHOA is a separate entity from non-EHOA, owing to the particular clinical, serological and radiological features and progression pattern that distinguish EHOA from non-EHOA[23]. EHOA has an abrupt onset and a worse clinical outcome than non-EHOA. The diagnostic hallmark of EHOA is central erosion on radiographs, in association with typical features that will be described in the following section[8]. EHOA is also characterized by the presence of clinical and radiological signs of inflammation, as demonstrated in several studies by the use of ultrasonography and MRI[24–28]. In particular, synovial inflammation in EHOA correlates with symptoms and with the appearance of new bone erosions[21,22]. However, synovial inflammation can decrease over time during the natural course of the disease, which might explain the lack of efficacy of conventional synthetic and biological DMARDs that target synovial inflammation[20,21]. Studies of histology, genetic predisposition and biomarkers have produced interesting insights into EHOA molecular mechanics and pathogenesis[29,30]. Results from genetic-predisposition studies have demonstrated that some *HLA* alleles and *IL1B* single-nucleotide polymorphisms are associated with the development of EHOA[31,32], consistent with involvement of the innate immune system and inflammation. In addition, serological and synovial-fluid biomarkers such as soluble IL-2 receptor and myeloperoxidase[32,33] are identifiable in EHOA (FIG. 1), confirming the role of inflammation in this pathological condition.

Epidemiology and clinical features

Epidemiological studies of EHOA are scarce, given the lack of clearly defined diagnostic criteria. Furthermore, there are obvious discrepancies between results from older studies, in which EHOA was considered to be a rare inflammatory condition, and those of more recent studies, in which EHOA was deemed a more common disease (TABLE 1). Notably, the use of a variety of EHOA radiographic scoring systems might explain the differences in prevalence estimates among studies. Prevalence of radiographic hand OA (estimated at 21% in the USA and 92% in Japan) is greater than that of symptomatic hand OA (3% in Iran and China and 16% in the USA)[6]. In addition to the use of a variety of radiographic scoring systems, and the evaluation of either symptomatic or radiographic EHOA, other factors might also influence estimates of EHOA. Many epidemiological studies take place in individual countries, and their study populations can vary considerably in genetic profiles and demographic characteristics. The estimated prevalence of EHOA in the Netherlands (defined by erosion of one or more IPJs on radiography) is about 2.8%[34], but the prevalence is considerably higher (between 10.2% and 25%) in individuals with symptomatic OA[34,35]. In the UK, the estimated prevalence of EHOA is 14.9% in patients affected by hand OA[36], and 4.8% in individuals with symptomatic limb-joint OA[37]. In a study conducted in northern Italy, among 640 individuals (data on comorbidities unavailable), 31.2% suffered from hand OA and 8.5% had EHOA (identified by erosion in at least one IPJ on radiography)[38], whereas in a cross-sectional study in Belgium, among 270 patients with hand OA, 167 (61.9%) had EHOA[39].

In a 2013 study involving 1,076 patients with symptoms typical of hand OA, an EHOA prevalence of 7.4% was reported, using a definition of one or more eroded (E) or remodelled (R) phase in IPJs, according to the Verbruggen–Veys Anatomical Phase Progression Score (which is described later in the review, in the section on 'Radiography')[40]. In another analysis of the same 1,076

Osteophytes
Bone spurs that grow along bone–joint margins.

Subchondral cyst
Fluid-filled sac occurring in subchondral bone.

Subchondral sclerosis
Hardening of the bone just below the cartilage surface.

Ankylosis
Fusion of the joint.

Paraesthesia
Abnormal skin sensation (such as numbness or a burning feeling).

symptomatic individuals, the prevalence was 22.5% for thumb base OA, 7.6% for nodal IPJ OA and 5.5% for non-nodal IPJ OA (as defined in the paper), 15.2% for generalized hand OA and 4.8% for EHOA, diagnosed by E or R phase (Verbruggen–Veys score) in two or more IPJs across either hand[41]. The differences between the prevalence estimates reflect the number of erosions considered in each analysis (one or more). Although the involvement of first CMCJ in OA is recognized to have a mechanical pathogenesis, an evaluation of erosive changes in the same cohort found erosive disease (at least one E or R phase) in any first CMCJ in 2.2% of patients, with only 0.5% having erosive changes in both IPJs and first CMCJs[42].

EHOA predominantly affects women, as indicated by results from the 2011 Framingham Osteoarthritis study, in which the age-standardized prevalence of EHOA was much higher in women (9.9%) than in men (3.3%)[43], and from a study conducted on 141 patients (89.3% female) affected by EHOA diagnosed by at least two erosions in IPJs, and as corroborated in the literature[12,41] (FIG. 1). In terms of the development of incident EHOA, in a cohort of 3,365 participants from the Osteoarthritis Initiative, who had or were at risk of knee OA, but did not have EHOA at baseline, 86 patients (2.6%) developed EHOA over a 48-month period[44].

Clinical signs of inflammation in EHOA include the acute onset of pain, swelling and redness (FIG. 2a). Joint inflammation is associated with the subsequent development of osteophytes[45], and functional limitation of IPJs as well as recurrent and persistent interphalangeal involvement are observed in most patients. Moreover, individuals affected by EHOA can exhibit paraesthesia in the fingertips during the night[13]. In patients with EHOA, DIPJs can be more commonly affected than PIPJs, whereas metacarpophalangeal joints and thumb base joints are generally not affected[43]. In a study of 3,430 individuals from the general population, erosions were found in 96 patients, and among those with EHOA, erosions were predominantly in DIPJs, although erosions of first CMCJs were also observed in 30% of these individuals, and 46% of them had two or more erosions[34]. Notably, EHOA differs from non-EHOA for its polyarticular involvement and persistent clinical signs of inflammation that can last for many years[8], albeit with a steady symptom reduction over time[20,25]. By contrast, in non-EHOA, IPJ involvement can develop one joint at a time in an additive manner[45]. The development of chronic nodular deformities of

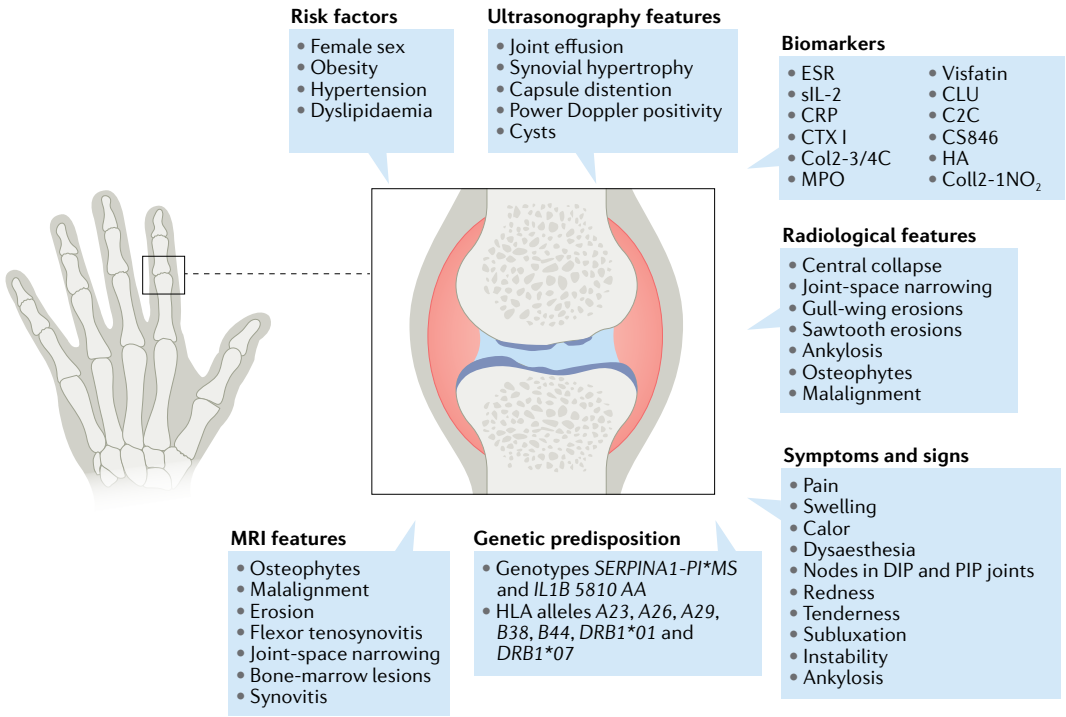

Fig. 1 | **Features of erosive hand osteoarthritis.** Erosive hand osteoarthritis (EHOA) risk factors, symptoms and signs, radiological features, genetic predisposition and biomarkers are shown. Female sex, obesity, hypertension and dyslipidaemia are risk factors for EHOA. A potential association between metabolic syndrome and EHOA is still under debate. The main symptoms and signs of EHOA are pain, redness, swelling, calor and dysaesthesia in the IPJs. Further clinical features of EHOA include the presence of nodes in the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints, redness, tenderness, subluxation, instability and ankyloses. The radiological signs of EHOA are subchondral-bone central collapse, joint-space narrowing, osteophytes, malalignment, cysts, ankyloses and gull-wing and sawtooth erosions. In addition, the presence of synovitis, joint effusion, flexor synovitis, bone-marrow lesions, capsule distension and power Doppler signals can be detected by MRI and/or ultrasonography. Several genes are linked to predisposition to EHOA. Several EHOA biomarkers have been suggested, but none has yet been validated. Potential biomarkers include erythrocyte sedimentation rate (ESR), soluble IL-2 receptor (sIL-2), C-reactive protein (CRP), C-telopeptide of type I collagen (CTX I), collagenase cleavage neoepitope (Col2–3/4C), myeloperoxidase (MPO), vistafin, clusterin (CLU), type II collagen cleavage product (C2C), aggrecan epitope (CS846), hyaluronic acid (HA) and nitrated Coll2-1 (Coll2-1NO_2).

Table 1 | **Representation of erosive hand osteoarthritis in study populations**

Study	Study population	Patients with EHOA (*n*)	Percentage of study population with EHOA	Percentage of hand OA population with EHOA	Ref.
Pattrick et al. (1989)	119 white participants, 67 affected by hand OA	10	8.4%	14.9%	36
Cobby et al. (1990)	500 consecutive patients with symptomatic limb joint OA	24	4.8%	ND	37
Haugen et al. (2011)	Framingham OA Study (2,301 participants)	ND	9.9% in women; 3.3% in men (adjusted for age)	4.6% in women; 0% in men (radiographic hand OA)	43
Kwok et al. (2011)	3,430 participants, 1,916 with radiographic hand OA, 371 with symptomatic hand OA	96 (one or more interphalangeal erosion), 44 (two or more erosions), 29 (erosions of first CMCJs)	2.8%	5.0% (radiographic hand OA), 10.2% (symptomatic hand OA)	34
Wittoek et al. (2012)	270 patients with hand OA	167	61.9%	61.9%	39
Kwok et al. (2013)	1,076 participants with hand symptoms, 798 symptomatic hand OA	80 (one or more erosive or remodelled DIPJ, PIPJ or first IPJ	7.4%	10.0% (symptomatic radiographic hand OA)	40
Kwok et al. (2014)	1,076 participants with hand symptoms	98 (EHOA in one or more IPJs, first CMCJs or both), 24 (one or more erosions in any first CMCJ), six (in IPJs and first CMCJ)	9.1% (EHOA in one or more IPJs, first CMCJs or both), 2.2% (one or more erosion of first CMCJ), 0.5% (in IPJs and first CMCJ)	ND	42
Cavasin et al. (2004)	640 participants; 200 with hand OA	17	2.7%	8.5%	38
Bijsterbosch et al. (2010)	192 white sibling pairs (Genetics, Arthrosis and Progression study population) with symptomatic OA at multiple sites in the hands or in two or more of the following joint sites: knee, hip or spine; 236 with hand OA	42	10.9%	16%	35
Marshall et al. (2013)	6,306 from the general population, including 1,076 with hand symptoms	52 patients among the 1,076 (eroded or remodelled phase in two or more interphalangeal joints (rays 2–5) across either hand	1% of 6,306 from the general population	4.8% of 1,076 patients	41

CMCJ, carpometacarpal joint; DIPJ, distal interphalangeal joint; EHOA, erosive hand osteoarthritis; IPJ, interphalangeal joint; ND, no data; OA, osteoarthritis; PIPJ, proximal interphalangeal joint.

IPJs (Heberden's and Bouchard's nodes) can present with a variable course in EHOA, and is similar to that in non-EHOA except for a faster progression (FIG. 2b). Particular deformities of EHOA are instability and, rarely, ankylosis of IPJs[8]. The most frequently involved fingers are the second and third, often symmetrically, followed by the fourth and fifth. No consensus exists on whether the involvement of the trapezio-metacarpal joint (previously described in at least one third of patients) should be considered characteristic of EHOA[14]. Large joints such as hip, shoulder, foot and lumbar spine (inter-apophyseal joints) are rarely involved[46–49].

Clinical ramifications of EHOA

The main predictors of functional impairment in EHOA are female sex (post-menopausal women are predominantly affected) and number of affected joints on radiography[13]. Similarly, a major determinant of pain is the number of joints presenting erosion: involvement of two or more joints is associated with a fivefold higher likelihood of pain than in non-EHOA[34]. Overall, patients with EHOA have a greater clinical burden of pain than those with non-EHOA or inflammatory arthritis of the hands, even after correction for potential confounders[20,39,50]. Levels of pain and disability in EHOA are comparable with those in patients with rheumatoid arthritis (RA)[39]. However, 60% of patients with EHOA have no pain, which is consistent with evidence demonstrating a reduction of inflammation over time[20,25]. The most commonly used scores to measure joint pain and function in EHOA are the visual analogue scale for pain, the Australian/Canadian Hand OA Index (AUSCAN) pain and function subscales, and the Functional Index for Hand OA for function[51].

JSN and the presence of erosions and osteophytes in EHOA correlate with symptom duration, AUSCAN scores, pain and active joints (characterized by tenderness, redness and swelling). Severe radiographic damage is associated with high AUSCAN scores and evolution to ankylosis at PIPJs[52]. Although some evidence indicates that inflammation and pain at rest in EHOA joints are comparable with those in non-EHOA, patients with EHOA present with more aesthetic damage and functional impairment[53]. A health-assessment questionnaire completed by 245 patients with EHOA revealed substantial deficits in all physical and mental domains of health-related quality of life in relation to the general population. Overall, physical-health scores were worse than mental-health scores. Predictors of health-related quality of life included gender, race, insurance coverage, disease severity and comorbidities[54]. These findings suggest that EHOA causes greater pain and dysfunction than non-EHOA, with a considerable effect on patients' quality of life.

Pathology and aetiopathogenesis

Although many studies have examined the pathology of OA in large joints, tissue samples from late-stage EHOA have rarely been investigated, with the notable exception of two pioneering studies from the 1960s[14,55]. A histological analysis of tissue samples obtained from patients with end-stage EHOA who underwent IPJ-replacement surgery revealed complete erosion of the cartilage with sclerosis, remodelling of the exposed bone and focal fibrocartilaginous resurfacing[56]. Radiography demonstrated large-to-moderate central erosions, with a pseudo-widening appearance in one of the two patients. Both patients had large osteophytes and severe JSN with bone-to-bone contact, subchondral bone sclerosis, degenerative pseudocysts and malalignment. Histologically, the researchers observed osteoclast activity with resorptive lacunae in the bone surrounded by degenerative fibromyxoid pseudocysts[56]. Synovial-membrane analysis revealed non-specific mild hypertrophy and slightly cellular fibromyxoid stroma without fibrinous exudate, lining-cell-layer proliferation, interstitial mast cells and perivascular/interstitial lymphoplasmacytic inflammation[56]. Similar histological features were described previously in cartilage and bone samples from large joints (such as hip and knee) affected by OA, in which a severe loss of cartilage matrix can occur, resulting in erosion and denudation of the unmineralized hyaline cartilage[57]. Subchondral-bone remodelling results in sclerosis and cyst formation, and bone-plate microfracture occurs with attempted repair of fibrocartilage[57]. By contrast, synovial inflammation in knee OA is characterized not only by hypertrophy but also by overgrowth of the lining-cell layer and perivascular and/or inflammatory infiltrate[58]. This difference might be the result of the late stage at which EHOA samples were collected, as these features might be a characteristic of an earlier, acute stage of EHOA.

For both EHOA and non-EHOA, the aetiopathogenesis is not yet known. The limited access to EHOA and non-EHOA joint tissues and the absence of animal models has hampered studies of disease mechanisms. Therefore, our current understanding of the aetiopathogenesis of EHOA and non-EHOA is mainly based on the study of genetic risk factors and serum and imaging biomarkers.

Genetic predisposition. The currently accumulated evidence does not enable determination of the roles of genetic predisposition in EHOA, as many studies of hand OA do not separate patients by disease subtype. In general, the genetic component is an important predisposing factor in hand OA, as identified in 1941 in a study in which Heberden's nodes were three times more common in sisters of women with hand OA than in women in the general population[59]. Notably, monozygotic twins have a higher correlation of OA prevalence than dizygotic twins[60]. However, the hereditary pattern of OA in general is complex and does not follow a simple model of Mendelian inheritance[61]. The development of hand OA is modulated by many genes with small effects, and by gene–environment interaction[62]. Mutations in genes involved in the production of aggrecan and human homeostatic iron regulator protein are associated with

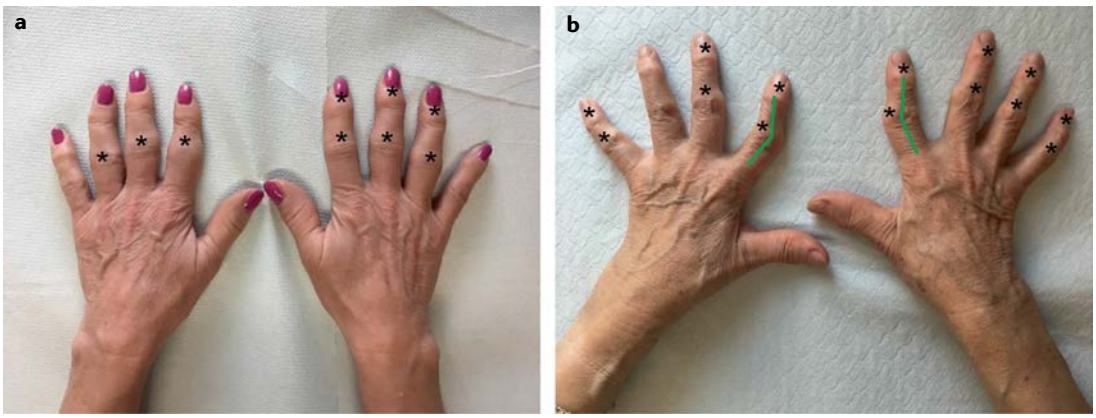

Fig. 2 | **Clinical features of erosive hand osteoarthritis. a** | Early-phase erosive hand osteoarthritis (EHOA), demonstrating soft swelling (marked by asterisks) of the proximal and distal interphalangeal joints. **b** | Late-phase EHOA, demonstrating deformity and bony enlargement (nodes) of proximal and distal interphalangeal joints (marked by asterisks) and subluxation at the proximal interphalangeal joint levels (highlighted by the green lines).

hand OA, but information on the relative involvement in EHOA and in non-EHOA is not available[63,64]. Polymorphisms of *TNF*, *ASPN*, *CILP*, *A2BP1*, *COG5* and *HFE* are also associated with hand OA[62,65–69]. Of particular interest is the study of genetic markers on chromosome 6 in regions corresponding to class I and class II major histocompatibility complex genes. One of the first studies on HLA-associated phenotypes was published in 1989 (REF.[70]); the *HLA-A1-B8* haplotype was more common in individuals with hand OA than in reference populations, and the presence of the *SERPINA1-PI*MS* genotype (*SERPINA1* encodes α1-antitrypsin) was more common in patients with EHOA than in those with non-EHOA[70] (Supplementary Table 1). Notably, patients with EHOA also had greater radiographic scores than those with non-EHOA; thus, it cannot be excluded that the *SERPINA1-PI*MS* genotype is related to severe joint damage[70]. In a study conducted in northern Italy, patients were stratified, and HLA alleles with a higher prevalence in patients with EHOA than in those with non-EHOA were *HLA-A23*, *HLA-A26*, *HLA-A29*, *HLA-B38*, *HLA-B44*, *HLA-DRB1*01* and *HLA-DRB1*07* (REF.[32]). The presence of the *HLA-DRB1*07* allele correlated with disease severity[32]. Because the HLA system is involved in immune regulation, these results suggest that immune-system dysregulation is involved in the pathology of EHOA. Notably, EHOA is associated with autoimmune diseases such as chronic autoimmune thyroiditis and Sjögren syndrome[32]. A single-nucleotide polymorphism (*IL1B* 5810G>A) in the genomic region that encodes IL-1β, which is involved in synovial inflammation and cartilage degeneration, might also have a link to EHOA in a white population from the mid-Atlantic region of the USA[31]. Further studies are needed to ascertain any effects of the *IL1B* 5810G>A polymorphism in EHOA.

Risk factors associated with EHOA. Female sex is one of the main risk factors for EHOA, followed by obesity, hypertension and dyslipidaemia[6,34,41,71]. Researchers have identified associations between individual components of metabolic syndrome (but not the syndrome as a whole) and EHOA[72]. Type 2 diabetes mellitus is associated with hand pain in EHOA, but rarely in non-EHOA[73]. Diabetes mellitus is a risk factor for radiographic hand OA progression in individuals with hand OA (particularly EHOA), whereas other factors (such as obesity, hypertension and dyslipidaemia) are not independently or collectively associated with hand OA progression[74,75]. Further studies are needed to ascertain the role of systemic metabolic disturbances in the pathophysiology of EHOA and non-EHOA[74].

Biomarkers of EHOA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurement are common laboratory tests that are performed in assessment of rheumatic disease[76]. Although they are non-specific biomarkers of inflammation, researchers have studied them in relation to EHOA (TABLE 2). Both biomarkers generally show poor sensitivity for EHOA, although a modest elevation of ESR might occur in patients with EHOA (as observed in 14–57% of patients with EHOA in a case-series review)[13]. By contrast, in another study, ESR and CRP were lower in patients with EHOA than in those with non-EHOA[77]. Methods of high-sensitivity CRP measurement might facilitate monitoring of the inflammatory aspects of EHOA[33,78]. Measurements of high-sensitivity CRP and ESR were higher in patients with EHOA than in patients with non-EHOA, but not after adjustment for age, sex and BMI[79]. Concentrations of the soluble IL-2 receptor, which is associated with lymphocytic activity, are higher in individuals with EHOA than in those with non-EHOA or in healthy individuals, suggesting the involvement of the immune system in the pathophysiology of EHOA[71].

Reported concentrations of C-telopeptide of type I collagen (CTX I), a marker of bone resorption, are higher in patients with EHOA than in those with non-EHOA[80], providing evidence of EHOA-associated bone-resorption activity, consistent with the presence of erosions[80]. Among typical biomarkers of cartilage metabolism, serum concentrations of collagenase-cleavage neoepitope Col2–3/4Cshort are higher in both patients with EHOA and those with non-EHOA than in healthy individuals[81]. Col2–3/4Cshort is a marker of collagen degradation, suggesting that cartilage degradation occurs in hand OA[81]. Concentrations of C2C (a marker of type II collagen degradation) are higher, whereas those of the aggrecan epitope CS864 are lower, in patients with EHOA than in healthy individuals[81]. Similarly, higher serum concentrations of hyaluronic acid are present in patients with EHOA than in those with non-EHOA, even after adjusting for age and disease duration, which might indicate that more synovial inflammation and destruction of cartilage occurs in EHOA[82]. Although concentrations of the Coll21–epitope (another marker of type II collagen degradation) do not differ between patients with EHOA and non-EHOA, greater amounts of the nitrated form Coll21–NO_2 occur in EHOA[33], suggesting that EHOA is characterized by high oxidative stress compared with hand OA[33].

Patients with EHOA have higher serum concentrations of myeloperoxidase (a marker of leukocyte function and inflammation) than patients with non-EHOA or healthy individuals[33,83]. Myeloperoxidase is a haem-binding protein that is abundant in neutrophils, which catalyses the conversion of hydrogen peroxide to hypochlorous acid[84]. Although myeloperoxidase seems to be involved in the development of several inflammatory pathological conditions, it remains unknown whether its effects are direct or are mediated by excessive generation of myeloperoxidase-derived oxidants[84]. High concentrations of myeloperoxidase in patients with EHOA suggest a possible association between oxidative stress, inflammation and joint damage. Myeloperoxidase might have potential as a biomarker to discriminate between the forms of hand OA[83].

Among the adipokines, serum concentrations of visfatin are higher in patients with EHOA, and those of resistin are higher in both EHOA and non-EHOA, compared with healthy individuals[85]. No differences were observed regarding adiponectin[85]. Visfatin has pro-inflammatory and immunomodulatory functions, as well as degradative effects on cartilage that are

Table 2 | **Potential biomarkers for erosive hand osteoarthritis**

Biomarker	EHOA and hand OA association	Ref.
ESR	Modest elevation of ESR might occur in patients with EHOA	13
	Reduction of ESR in patients with EHOA, compared with patients with hand OA	77
	Modest elevation of ESR in patients with EHOA	78
	Higher ESR in patients with EHOA compared with patients with non-EHOA, but no differences after adjusting for age, BMI and sex	79
Soluble interleukin-2 receptor concentration	Higher in patients with EHOA	71
C-reactive protein concentration	Lower in patients with EHOA than in patients with hand OA	77
	Higher in patients with EHOA than in patients with hand OA	78
	Higher in patients with EHOA than in patients with hand OA	33
	Higher in patients with EHOA than in patients with hand OA, but no differences after adjusting for age, BMI and sex	79
C-telopeptide of type I collagen concentration	Higher in patients with EHOA than in patients with hand OA	80
Collagenase cleavage neoepitope (Col2–3/4C) concentration	Higher in patients with EHOA and hand OA than in healthy individuals	81
Collagenase cleavage neoepitope (C2C) concentration	Slight increase in patients with EHOA compared with healthy individuals	81
Aggrecan epitope (CS846) concentration	Slight decrease in patients with EHOA compared with healthy individuals	81
Hyaluronic acid concentration	Higher in patients with EHOA than in patients with hand OA	82
Coll21–epitope (HRGYPGLDG) concentration	No difference between patients with EHOA and patients with hand OA	33
Coll21–NO_2 (nitrated form) concentration	Higher in patients with EHOA	33
Myeloperoxidase concentration	Higher in patients with EHOA	33
	Higher in patients with hand OA than in healthy individuals; patients with EHOA have elevated myeloperoxidase compared with patients with hand OA	83
Visfatin concentration	Higher in patients with EHOA than in both patients with hand OA and healthy individuals	85
Resistin concentration	Higher in both patients with EHOA and patients with hand OA than in healthy individuals; no differences between EHOA and hand OA	85
Adiponectin concentration	No differences among patients with EHOA, patients with hand OA and healthy individuals	85
Clusterin concentration	Lower in patients with hand OA than in controls; lower in patients with EHOA than in patients with hand OA	88

EHOA, erosive hand osteoarthritis; ESR, erythrocyte sedimentation rate; OA, osteoarthritis.

mediated through the synthesis of enzymes that target the extracellular matrix[86]. Resistin increases the expression of inflammatory markers and matrix degradative enzymes in chondrocytes[87]. More studies are needed to determine the roles of these adipokines in EHOA.

Serum concentrations of clusterin are lower in patients with hand OA than in healthy individuals and, notably, are even lower in patients with EHOA than in those with non-EHOA[88]. Moreover, clusterin correlates negatively with hand pain[88]. Clusterin is a molecular chaperone that is involved in multiple biological processes. Low expression of clusterin might confer protection against the development of bone erosions[88].

Knee synovial-fluid samples collected from patients with EHOA have notable differences compared with samples from patients with non-EHOA, including higher white blood cell counts and concentrations of inflammatory mediators and metalloproteinases[89]. These results are consistent with previous findings demonstrating the role of inflammation in this subset of patients and, importantly, supporting the possibility that factors released in one joint might circulate systemically and have effects in another joint[89].

Further research will be required to investigate and validate all of the potential biomarkers for EHOA in large cohorts of patients, with appropriate adjustment for confounding factors such as age and BMI.

Imaging modalities for EHOA

Radiography. Radiography can help to distinguish among EHOA, non-EHOA and other types of arthritis (FIG. 3). The radiological abnormalities that are usually observed on hand OA radiographs are JSN, osteophyte formation, subchondral sclerosis and subchondral cyst

formation, whereas the typical hallmarks of EHOA are centrally located subchondral erosions, which can progress into marked bone and cartilage attrition, instability and bony ankylosis[11]. For the definition of EHOA, a single erosive IPJ on a radiograph might be sufficient, although there is no general consensus on this issue among experts. Many studies in the field have used the criterion of a single erosive joint to be sufficient to classify EHOA[8]. In EHOA, erosions occur at the centre of the joint and are associated with JSN. The proximal bone surface often shows a central collapse, leading to the classic gull-wing appearance that is characterized by sclerosis and the presence of osteophytes (FIG. 3a)[8,90]. The saw-tooth appearance (another pattern that is frequently found in patients with EHOA) (FIG. 3b) can lead to ankylosis[8] (FIG. 3c). Whereas the saw-tooth pattern is more prevalent in PIPJs, the gull-wing pattern is a feature of DIPJs[91]. Crumbling erosions, which are less common, are found in PIPJs and are characterized by porosities in the proximal subchondral area, and they can lead to bone fusion, especially in the late phase of the disease[8]. Although marginal erosions that are more typical of RA (FIG. 3d) and psoriatic arthritis (FIG. 3e) can also occur, they are rare in comparison with central erosions[8]. RA is also characterized by ankylosis of PIPJs and metacarpal phalangeal subluxation (FIG. 3d). Features of psoriatic arthritis are marginal erosions with a 'mouse ear' appearance and soft-tissue swelling showing 'sausage digit' presentation (FIG. 3e). Capsule distension, wide erosions and microcrystal deposition (tophus) are key features of gout (FIG. 3f).

Several radiographic scoring systems exist for the evaluation of hand OA. The Kellgren–Lawrence classification system was approved by the World Health

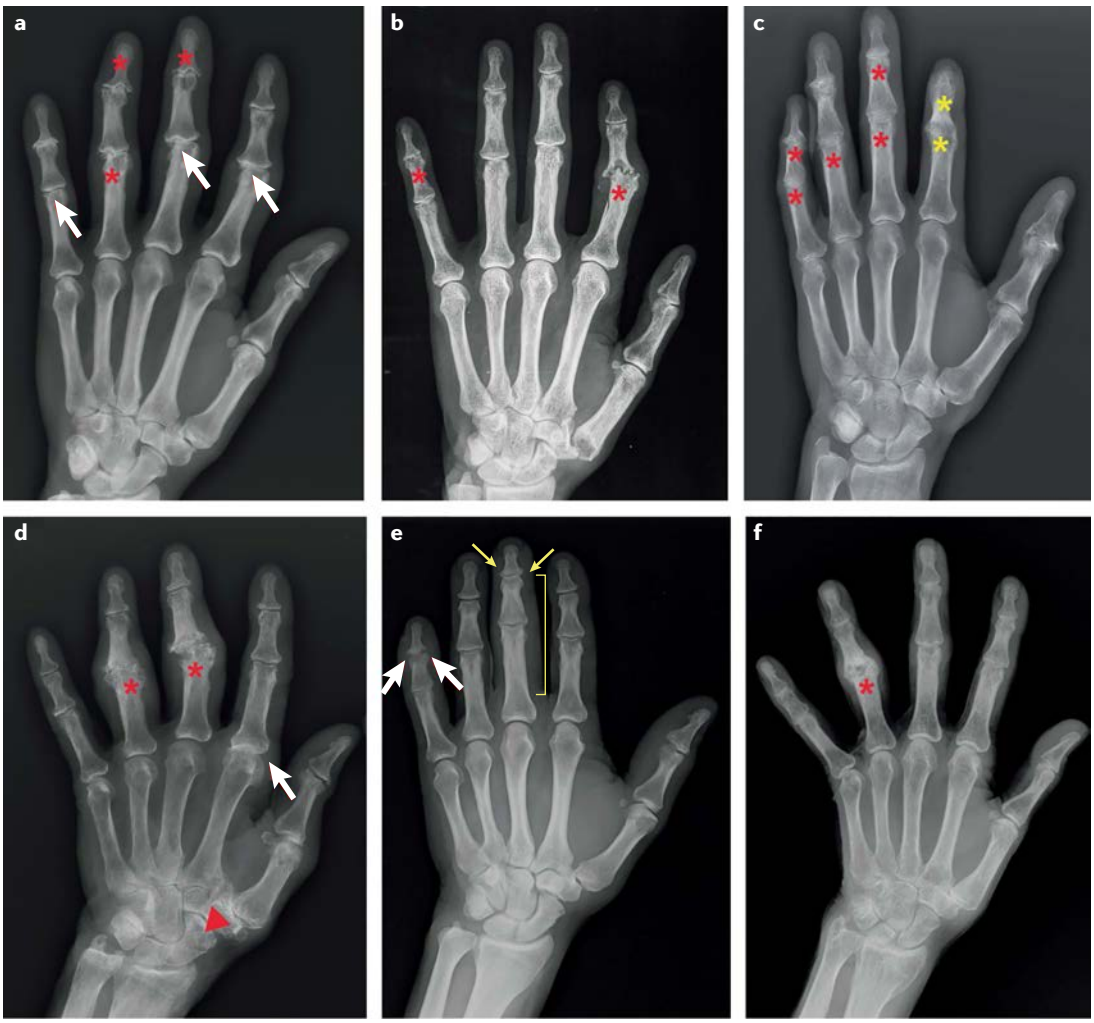

Fig. 3 | **Radiological features of erosive hand osteoarthritis and comparison with other arthritis types. a** | Radiograph of erosive hand osteoarthritis (EHOA), demonstrating 'gull-wing' appearance (red asterisks) and joint-space narrowing (white arrows). **b** | Radiograph of EHOA, demonstrating 'saw-tooth' appearance (red asterisks). **c** | Radiograph of EHOA, demonstrating marked joint-space narrowing (red asterisks) and joint 'fusion' (yellow asterisks). **d** | Radiograph of the hand in rheumatoid arthritis, demonstrating erosions (red asterisks), metacarpal phalangeal subluxation (white arrow) and thumb base osteoarthritis (red arrowhead). **e** | Radiograph of the psoriatic arthritis hand, demonstrating marginal erosions (white arrows), soft-tissue swelling characterized as a 'sausage digit' (yellow bracket) and peripheral erosions with a 'mouse ear' appearance (yellow arrows) in the third distal phalangeal. **f** | Radiograph of the hand in a patient with gout, demonstrating wide interphalangeal erosion with capsule distension (red asterisk) in a tophus.

Organization in 1961 as a valid tool for evaluation of both disease severity and evolution. In this system, typical hand OA lesions such as osteophytes, JSN, sclerosis and subchondral cysts, are assessed globally in PIPJs, DIPJs and CMCJs[92]. The Kallman score, developed in 1989, adds the evaluation of erosive changes including central collapse and joint deformities[93]. The Altman score has undergone several adjustments (the latest in 2007) and takes into account additional manifestations such as malalignment, subluxations and erosions[94–96]. The Verbruggen–Veys score enables evaluation of hand OA disease progression by defining five anatomical phases: the normal ('N phase') joint, non-erosive stationary OA joint ('S phase'), disappeared joint space ('J phase'), erosive lesions ('E phase') and the remodelled ('R phase') joint[17,18]. Further information on these scoring systems is provided in Supplementary Table 2.

Ultrasonography. OA affects both bone and soft tissues, including those that might not be visible on radiographs, and researchers have evaluated the use of advanced imaging techniques such as ultrasonography and MRI for the diagnosis of hand OA. The first extensive ultrasonographic investigation of the distal phalanx was conducted in a cohort that included patients with EHOA[97]. Ultrasonography facilitates detection of erosions, osteophytes, joint effusion, synovial hypertrophy, vascularization, periarticular and peritendinous soft-tissue irregularities and, importantly, provides an assessment of the inflammatory status of the joint[7]. Moreover, ultrasonography enables analysis of the joint along longitudinal and transverse planes to detect small erosions that might not be visible on radiographs[7]. Ultrasonography is a useful, sensitive and specific tool for the detection of central erosions[24] and osteophytes, and it is more sensitive than conventional radiography in patients with EHOA[98]. Although the lack of a standardized scoring system might constitute a limitation to the use of ultrasonography in patients with OA, most investigators measure the following parameters: joint effusion, synovial hypertrophy, JSN, erosions, osteophytes and power Doppler signal[24]. Results from ultrasonographic investigations, as with genetic associations and biomarkers, have highlighted the role of synovial inflammation in the pathogenesis of EHOA[7,99]. Patients with EHOA have higher power Doppler signals than healthy individuals or patients with non-EHOA[100]. Furthermore, the power Doppler signal is the only synovial feature that correlates with cartilage thickness, radiological damage and new bone erosions[100]. The presence of effusion and hypertrophy of the synovial membrane, in addition to a positive power Doppler signal, is more frequent in EHOA than in non-EHOA, in all joints, with and without erosions[25]. Moreover, synovial thickening, effusion and power Doppler signal are all associated with evolving erosion in patients with hand OA, suggesting that synovial inflammation is important in pathogenesis, and is a potential therapeutic target[21].

MRI. In contrast to ultrasonography, MRI enables three-dimensional evaluation of all components of the joint. Moreover, MRI also has an important role in the evaluation of synovial inflammation and bone-marrow lesions (BMLs)[101]. Evidence increasingly supports a correlation between synovial inflammation and OA pain and dysfunction, as well as with bone-marrow injury[102]. Central erosions (the hallmarks of EHOA) can be detected by MRI, in which they are present as areas of subchondral-bone collapse and pressure atrophy, appearing as gull-wing deformities. BMLs can be found in the proximity of erosions, as well as in areas without signs of erosion[27]. Both EHOA and non-EHOA demonstrate synovial-membrane hypertrophy on MRI[7,27], but the former is characterized by a higher prevalence and greater severity of synovitis than non-EHOA (odds ratio 1.85; 95% confidence interval 1.19–2.85 for moderate to severe synovitis)[20]. Several MRI scoring systems exist for assessment of hand OA, as listed in Supplementary Table 3. Few studies have included testing of the ability of MRI to distinguish between EHOA and non-EHOA. The Oslo Hand OA MRI (OHOA–MRI) scoring system is designed to enable description of hand OA MRI characteristics such as osteophytes, JSN, erosions, cysts, malalignment, synovitis, flexor tenosynovitis, BMLs and collateral ligament abnormalities (Supplementary Table 3)[103]. The reliability of OHOA–MRI was corroborated by results from a study of EHOA that associated inflammatory imaging results with an aggressive disease course[99]. MRI enabled the detection of synovitis in 39.8% of 80 joints (with mild synovitis in 80% of the joints), erosions in 51.1% and BMLs in 20.5% of joints on the distal side and 23.9% on the proximal side[99]. The presence of erosions, BMLs and synovitis correlated with the number of tender joints and pain. Synovial inflammation correlated with the presence of erosions, which in turn correlated with pain. The presence of synovitis and BMLs also correlated with clinical symptoms[99]. Other studies have evaluated the MRI features of hand OA, and 24–60% of the cohorts in those studies consisted of patients with EHOA, but subgroup analyses relating to each form are lacking[23,104]. However, results have shown that baseline synovitis, BMLs, JSN, bone damage, osteophytes and malalignment are all associated with the development of EHOA[28,99]. Some of the limitations of the OHOA–MRI scoring system include the time-consuming nature of the assessment of many features and the need to separate the scores relative to the proximal and distal parts of the joint. Furthermore, some features, such as collateral ligament pathology and flexor tenosynovitis, are uncommon, have limited reliability and are not associated with pain[105].

A preliminary Outcome Measures in Rheumatology MRI scoring system for hand osteoarthritis, proposed to overcome the limitations of OHOA–MRI[105,106] (Supplementary Table 3), has good to very good inter-reader correlation for cross-sectional assessment, although its longitudinal reliability (measured at baseline and after 5 years of follow-up) was estimated by analysis of fewer scores, and is not as good[106]. The MRI scoring system for hand osteoarthritis has good responsiveness (with cross-sectional, inter-reader, intra-class correlation coefficients ≥0.74) for all features except synovitis, cysts and BMLs[106]. Results from a study involving 55 patients with EHOA indicate that MRI can detect

Gradient echo MRI sequence
The gradient echo sequence is an excitation sequence for rapid image acquisition.

more erosive lesions than radiography, and that synovitis and BMLs mainly occur in joints with structural damage, but also in joints with concomitant erosion and osteophytes[107]. The use of susceptibility-weighted MRI, a novel gradient echo MRI sequence, could improve the detection of hand erosions by increasing specificity and accuracy[108]. Finally, hybrid imaging techniques such as PET–CT and PET–MRI might enable the simultaneous evaluation of morphological and metabolic changes[101].

Treatments

Currently available treatment options for EHOA and non-EHOA do not prevent or delay disease progression (TABLE 3). Despite considerable efforts, the lack of clear

Table 3 | **Pharmacological treatments that have been tested for use in EHOA**

Treatment	Study design	Treatment duration	Treatment effects	Ref.
Glucocorticoids				
Triamcinolone hexacetonide	Two joints injected with 10 mg of triamcinolone hexacetonide in 15 patients. Second joint injected 2–4 months after first	6–18 months	Injection resulted in reduction of synovitis	113
	Ultrasonography-guided injection in the painful and swollen proximal interphalangeal/first interphalangeal and/or distal interphalangeal joint in 12 patients with EHOA	6 months	Injections were effective in reducing pain and swelling, with improvement in physical function and patient's ability to perform daily tasks, and reduction of joint effusion, synovial hypertrophy and capsule distention	114
Conventional synthetic DMARDs				
Hydroxychloroquine vs clodronate	Group A: 24 patients treated for 24 months with clodronate 300 mg i.v. for 7 days, followed by clodronate 100 mg i.m. for 14 days every 3 months; group B: 14 patients treated with hydroxychloroquine 400 mg daily for 30 days, followed by 200 mg daily for 11 months	24 months	Clodronate is effective in EHOA; hydroxychloroquine seems to be ineffective	118
Hydroxychloroquine	Patients randomized to receive hydroxychloroquine 200–400 mg/day ($n = 75$) or placebo ($n = 78$)	52 weeks	Changes in radiographic scores did not differ significantly; there was no difference in AUSCAN score between the groups	119
Methotrexate	Patients with EHOA ($n = 64$) randomized to either placebo or methotrexate (10 mg per week)	12 months	Treatment not effective in reducing symptoms or pain compared with placebo	120
TNF inhibitors				
Adalimumab	Patients with EHOA ($n = 12$) received adalimumab 40 mg every other week for 12 weeks	12 weeks	No improvement	121
	Double-blind, randomized trial in 60 patients with EHOA, treated with 40 mg of adalimumab or placebo s.c. every 2 weeks over 12 months	12 months	Treatment significantly halted progression of joint damage compared with placebo	123
	Patients with EHOA ($n = 43$) were randomized to adalimumab (40 mg s.c. injections every other week) or placebo for 12 weeks followed by an 8-week washout and then the converse treatment for 12 weeks	12 weeks	No effects were observed on pain, synovitis or bone-marrow lesions in patients with EHOA with MRI-detected synovitis	122
Etanercept	Patients ($n = 90$) were randomized to etanercept 50 mg weekly s.c. for the first 24 weeks, followed by 25 mg weekly for the remainder of the study, or placebo	24 weeks	Etanercept did not relieve pain effectively after 24 weeks in erosive osteoarthritis, although small subgroup analyses showed a signal for effects on subchondral bone in actively inflamed joints	124
Infliximab	Patients with EHOA ($n = 10$) were treated with monthly injections of 0.2 ml of infliximab (0.1 mg/ml)	6–12 months	At 6 months all patients experienced relief from pain in the hand treated with infliximab, becoming significant after 1 year	126
IL-1 inhibitors				
Anakinra	Three patients were enrolled and treated with 100 mg daily s.c. injection of anakinra	12 weeks	Patients had a good response to therapy	127
Lutikizumab	Patients with EHOA ($n = 132$) in phase IIa, placebo-controlled, randomized study treated with 200 mg of lutikizumab or placebo s.c. injection every 2 weeks for 24 weeks (13 injections)	24 weeks	Treatment did not improve pain or imaging outcomes in EHOA compared with placebo at 26 weeks	109

AUSCAN, Australian/Canadian Hand OA Index; EHOA, erosive hand osteoarthritis; i.m., intramuscular; i.v., intravenous; s.c., subcutaneous.

therapeutic targets has hindered the development of new effective therapies[109]. Non-pharmacological treatments for EHOA include patient education, splints and physical therapy for the hand, which are often used in combination with pharmacological treatments such as oral and topical NSAIDs to relieve pain[110–112]. Topical NSAIDs represent the first-line treatment, followed by oral NSAIDs, which are only recommended for short-term use because of adverse effects[111]. The 2018 EULAR recommendations for hand OA indicate that intra-articular injections of glucocorticoids should not generally be used, but can be considered in patients with flares and those with painful IPJs[111]. The first study on glucocorticoids was conducted in 1978, and its results demonstrated association of a triamcinolone hexacetonide injection with reduction of detection of synovitis by physical examination in patients with EHOA[113]. More recently, ultrasonography-guided intra-articular injections of triamcinolone hexacetonide proved to be safe and effective in achieving pain relief and reduction of swelling and joint effusion, capsule distention and synovial-membrane hypertrophy in patients with EHOA[114]. Infrared thermal imaging can help to monitor the efficacy of these intra-articular injections in patients with EHOA[115]. Despite extensive study of the use of intra-articular hyaluronic acid injections in knee OA, data are scarce in relation to its efficacy in EHOA[110].

The 2018 EULAR guidelines and the 2019 ACR–Arthritis Foundation guidelines for the management of hand OA do not recommend the use of conventional synthetic DMARDs (such as methotrexate) or biological DMARDs (such as TNF inhibitors) in EHOA because of lack of efficacy[111,116]. Hydroxychloroquine has demonstrated a lack of efficacy in EHOA[117,118]. According to the results of a large, randomized, double-blind, placebo-controlled, multicentre, investigator-initiated trial (the OA-TREAT study), hydroxychloroquine is no more effective than placebo in terms of AUSCAN scores or radiographic changes over a period of 52 weeks in patients with EHOA[119]. In a study with a small sample size of patients with EHOA who were treated with a low dose of methotrexate (10 mg weekly), it was not found to be more effective than placebo for improvement of pain and function at 12 months[120]. Notably, the researchers in this study used a low-power MRI (0.3 Tesla) and only detected synovitis in 13.3% of the patients treated with methotrexate, which means that the prevalence of synovitis might have been underestimated at baseline, thereby limiting the determination of treatment response[120]. TNF and IL-1β are important cytokines that are involved in synovial inflammation in patients with EHOA[102]. However, many trials focusing on the use of biological DMARDs to target these cytokines in EHOA have yielded poor or mixed results. In a small, open-label study, treatment of patients with EHOA for 3 months with adalimumab, a TNF inhibitor, did not produce an improvement from baseline signs and symptoms[121]. Similarly, in a randomized, double-blind, placebo-controlled, crossover trial, adalimumab did not result in any effects on pain, synovitis or BMLs after 12 weeks[122]. In a double-blind, randomized trial, treatment with adalimumab did not result in improvement in clinical symptoms, but it did halt the progression of joint damage in patients with EHOA[123]. Treatment with etanercept (another TNF inhibitor) resulted in reduction of aberrant subchondral bone change in actively inflamed joints[124]. Reduction in amounts of matrix metalloproteinase-3 in patients with EHOA also occurred on treatment with etanercept[125]. Infliximab (a TNF inhibitor), anakinra (an IL-1 receptor antagonist) and lutikizumab (a dual IL-1α–IL-1β inhibitor) are all associated with partial pain relief in patients with EHOA[109,126,127]. Notably, different outcomes and endpoints were considered in many of these studies, which could account for the discrepancies between the results. When pharmaceutical and non-pharmaceutical treatments fail to achieve pain relief, surgery can also be considered in patients with structural abnormalities and sustained disease progression[111].

Conclusions

EHOA is an inflammatory form of hand OA that is characterized by abrupt onset and worse clinical outcomes than non-EHOA. Evidence supports the hypothesis that EHOA is a separate form of hand OA, because EHOA has particular clinical, serological, radiological and progression features (FIG. 1). A problem that hampers the comparison of data between studies in this field is the lack of clinical-outcome standardization. Updating hand OA classification criteria to address structural change and phenotypic variation would facilitate advancement in this area. Appropriately sized, prospective, longitudinal studies and clinical trials with specific and adequate clinical-outcome measurements are warranted, to further our understanding of EHOA risk factors and disease pathogenesis, and to enable a tailored therapeutic approach.

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