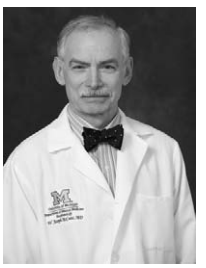
Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

SECTION EDITORS

W. Joseph McCune



Dr W. Joseph McCune MD is Michael and Marcia Klein Professor of Rheumatic Diseases and Director of the Lupus Program at the University of Michigan. Following an Internal Medicine residency at the University of Michigan and a fellowship in Immunology and Rheumatology at Harvard Medical School and the Brigham and Woman's Hospital, Dr McCune has been a member of the faculty at the University of Michigan where he specializes in the epidemiology, diagnosis, and treatment of lupus and systemic vasculitis.

Bryant R. England

Dr Bryant R. England is a clinician-investigator at the University of Nebraska Medical Center and VA Nebraska-Western Iowa Health Care System. He focuses on improving long-term outcomes in patients with rheumatoid arthritis (RA), and conducts clinical and epidemiologic research in RA-associated lung disease, cardiovascular disease, cancer, and multimorbidity using several large observational datasets. He also leads prospective studies in RA-associated lung disease and connective tissue disease-interstitial lung disease. Clinically, Dr England is a rheumatologist focused on the care of patients with inflammatory arthritis and incorporates the use of musculoskeletal ultrasound into the diagnosis and management of rheumatic diseases. He also directs the UNMC Autoimmune Lung Disease Clinic, a multi-specialty clinic that specializes in treating autoimmune lung diseases (e.g. RA-interstitial lung disease and other connective tissue disease-interstitial lung disease). Dr England is actively involved in the American College of Rheumatology and teaches medical students, residents, and fellows in the areas of rheumatology, musculoskeletal ultrasound, and clinical research as well as serving as a research mentor to students, residents, and fellows.

Quinacrine: au Revoir or Adieu? This safe and effective drug should be reintroduced

W. Joseph McCune

The history of the development of antimalarial drugs and their use to treat rheumatic diseases, particularly lupus, is the history of tension between efficacy and toxicity. Extracts from the bark of the Andean Cinchona tree were found to be effective against malaria, and imported from South America into Europe in the 17th century and widely used to treat malaria and other febrile illnesses. There was a high level of interest in this medication as illustrated by offering of a 20,000 Franc prize in France for isolation of its active compounds; the most notable of which turned out to be quinine. It was soon recognized that large doses of quinine were associated with significant toxicities, collectively termed 'chinconism' including flushing, confusion, tinnitus, hearing loss, ataxia tremor, and visual disturbances including blindness [1].

Payne first reported success using quinine to treat cutaneous lupus in 1894 [2], but widespread use of antimalarials for lupus awaited the development of less toxic derivatives. Quinacrine was developed in Germany in the 1920s and later manufactured in the USA during World War II. It was administered to millions of American soldiers in the South Pacific for malaria prophylaxis for several years with no reported retinal toxicity. Chloroquine was developed in 1934 and after its introduction was found to have significant retinal toxicity [3]. In 1945, hydroxychloroquine was synthesized with the hope that it would be a less toxic alternative to chloroquine and have lower risk of retinal toxicity. Subsequent experience over almost a century has confirmed that quinacrine, as monotherapy, is unique among antimalarials for lupus in having no retinal toxicity. It has been widely assumed, although it is less well established, that addition of quinacrine to hydroxychloroquine, and or chloroquine to treat lupus can achieve greater therapeutic efficacy without increasing the risk of retinal toxicity.

Quinacrine was first used for discoid lupus in the 1940s and chloroquine in the 1950s. In 1956, hydroxychloroquine was reported to be effective in discoid lupus with less toxicity than chloroquine at equivalent doses [3]. From this era, when corticosteroids were just being introduced, there are dozens of reports of the efficacy of quinacrine for discoid and systemic lupus [4–7]. Dubois described highly favorable responses to quinacrine [8] and interestingly reported that quinacrine impaired the formation of LE cells *in vitro* [9]. Frances Page in 1951 wrote that 'Quinacrine . . .was used in a case of lupus erythematosus. The result was so dramatic that all cases of lupus erythematosus seen in this hospital. . .have been treated with this drug. . .Eighteen cases have been observed, and only one failed to improve. . . In a few cases all the lesions disappeared within 6 weeks so that it was impossible to distinguish their previous sites' [10].

In 1959, Tye reported the effectiveness of Triquin, a combination of chloroquine, hydroxychloroquine, and quinacrine in the New England Journal of Medicine and Triquin was FDA approved [11]. As a result, quinacrine became FDA approved as an ingredient in Triquin. In 1972, the FDA in a campaign against combination drugs, mandated cessation of sale of Triquin. Since that time quinacrine has been used without FDA approval as monotherapy. Until recently quinacrine could readily be obtained from compounding pharmacies in the USA. Unfortunately, it is now impossible to obtain.

In the ensuing 70 plus years, quinacrine, alone or in combination with hydroxychloroquine or chloroquine has been effectively used for lupus with remarkable safety. Studies in the 1990s by Feldman [12] and Lipsker *et al.* [13] reported response rates on the order of 75% when quinacrine was added to hydroxychloroquine or chloroquine for cutaneous lupus. Toubi [14] reported improvement of the SLEDAI in 5 of 6 patients with systemic lupus treated with combination therapy. In a larger study in 2018, Ugarte [15] reported improvement of the Cutaneous Lupus Erythematosus Disease Area and Severity

University of Michigan Medical School, Ann Arbor, Michigan, USA

Correspondence to W. Joseph McCune, MD, University of Michigan Medical School 300 N Ingalls 7C27 Ann Arbor MI USA 48109.
E-mail: jmccune@med.umich.edu

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Index (CLASI) and SLEDAI in 47 lupus patients when quinacrine was added to their baseline regimens, most of which included hydroxychloroquine. Recent surveys by Mittal [16,17] and colleagues have confirmed widespread and safe use of this compound in academic dermatologic practices.

Quinacrine therefore has a place in the management of systemic lupus as a safe and effective drug that enhances is the effects of antimalarials is with reduced ocular toxicity. The case for quinacrine in lupus management has been elegantly made over the years by Wallace [3,18]. The value of quinacrine in our therapeutic armamentarium can be summarized as follows:

(1) Of the antimalarial drugs quinacrine stands out for alleviating fatigue, and increasing focus and concentration. This may be in part a property of the drug itself rather than its direct effect on lupus. Patients who have had to discontinue quinacrine mourn the loss of its effects on mental focus and alertness.
(2) As monotherapy quinacrine is highly effective and fast acting, particularly for cutaneous disease.
(3) Addition of quinacrine to hydroxychloroquine or chloroquine provides greater drug exposure with less potential ocular toxicity than increasing the dose of either hydroxychloroquine or chloroquine with no infectious risk.
(4) Recent studies have emphasized the marked increase in toxicity of hydroxychloroquine in standard doses when it has been administered for 5 to 10 years [19]. The combination of low doses of quinacrine and hydroxychloroquine could be used for long-term maintenance with reduced risk of retinal toxicity [20].

There is a strong argument for performing a large clinical trial of quinacrine with the goal of reintroducing it as a drug for lupus with FDA approval. This would be a relatively straightforward process, as the drug is easily synthesized, its side effects are well understood, and there is no need for dose ranging. The weight of the evidence suggests that it would prove effective in achieving the endpoint of reduced disease activity. It is also likely to score highly in patient generated measures of improvement and satisfaction. In an era when increasingly complex and costly biologic agents are being tested, it is time to reintroduce this easily manufactured, safe, and effective drug.

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Conflicts of interest

There are no conflicts of interest.

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The use of mycophenolate mofetil area under the curve

Katherine Chakrabarti[a], *David Frame*[b], *Mousa Al Abbas*[c], *and W. Joseph McCune*[a]

Purpose of review
Although mycophenolate mofetil (MMF) has been used successfully to treat a myriad of autoimmune diseases, its complex pharmacokinetics make it difficult to determine the true drug exposure for an individual patient. This review summarizes the body of literature focused on the gold standard measurement of the area under the curve (AUC) of mycophenolic acid (MPA), the active metabolite of MMF.

Recent findings
Fixed dosing of MMF leads to highly variable drug exposure. Retrospective series have reported improved clinical outcomes when a minimum AUC value from 0 to 12 h (AUC_{0-12h}) $\geq$30 mg h/l is achieved. MPA levels are affected by various drug interactions, hypoalbuminemia, and renal insufficiency and the measurement of free rather than total MPA levels is prudent in some situations. A limited number of studies employing prospective dose adjustment of MMF based on AUC_{0-12h} measurements have yielded mixed results.

Summary
Given the wide range of MPA AUC encountered in autoimmune diseases, dose adjustments of MMF based on AUC rather than fixed dosing of MMF should be considered in both clinical practice and clinical trials. Limited sampling strategies have been proposed to improve clinical feasibility of measurements, but a standard is yet to be defined.

Keywords
area under the curve (AUC), mycophenolate mofetil (MMF), pharmacokinetics, rheumatic diseases, therapeutic levels

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is frequently used for both the treatment of autoimmune diseases and prevention of organ rejection posttransplantation. The active metabolite, mycophenolic acid (MPA), was initially discovered in 1893 and over the following century was found to have antibacterial, antifungal, and antiviral properties [1–3]. In the 1980s, MPA was utilized for the treatment of psoriasis, but the high doses required because of its rapid absorption and elimination carried detrimental side effects [4].

Finally, in the mid 1990s, MMF, a compound with superior pharmacokinetics was released on the market, followed several years later by enteric-coated, delayed-release mycophenolate sodium (EC-MPS). Traditional dosing of MMF established in the literature ranges between 1 and 3 g daily but there is substantial variation in its active metabolite, MPA, and the amount of available nonprotein bound fraction. Further understanding of the pharmacokinetics and pharmacodynamics of MMF is required to ensure therapeutic drug effects of this commonly used immunosuppressant are maximized, whereas toxicities are minimized.

PHARMACOKINETICS OF MYCOPHENOLATE MOFETIL

MMF is hydrolyzed to its active metabolite, MPA, by esterases in the stomach, small intestine, blood, liver, and tissues. Approximately 97–99% of MPA

[a]Department of Internal Medicine, Division of Rheumatology, University of Michigan, [b]Department of Clinical Pharmacy, University of Michigan, Ann Arbor, Michigan, USA and [c]Staff Rheumatologist, King Fahad Specialist Hospital, Dammam, Saudi Arabia

Correspondence to W. Joseph McCune, Division of Rheumatology/ Department of Internal Medicine, 300 North Ingalls St., Suite 7C27, Ann Arbor, Michigan 48109-5422, USA. Tel: +734 936 5561; e-mail: jmccune@med.umich.edu

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KEY POINTS

- Current dosing of mycophenolate mofetil is based on standard dosing regimens that do not take into account variable drug metabolism.
- The use of the area under the curve (AUC), rather than troughs or single-time point measurements, allows for the most accurate interpretation of MPA exposure.
- Because only free (unbound) MPA is pharmacologically active, assessment of the AUC of free MPA would theoretically be the optimal measure of drug exposure although this is not currently practical because of expense.
- Identification of a limited sampling strategy to characterize free MPA AUC_{0-12h} would allow clinicians to economically understand exposure to the active component of mycophenolate, potentially improving clinical outcomes and avoiding toxicities.

is protein bound, usually to albumin, whereas the remaining small fraction of free MPA is the pharmacologically active form [5▪▪,6,7].

With oral dosing of MMF, MPA is rapidly absorbed with a peak plasma concentration 1–2 h after administration [6,7]. The EC-MPS, with drug release and absorption primarily in the small intestine, has a later peak concentration occurring 1.5–2.75 h after dosing with reportedly lower gastrointestinal side effects [6,8]. Both MMF and EC-MPS have a half-life ranging from 8 to 16 h [6,9].

MPA is converted to its inactive metabolite, 7–0-MPA glucuronide (MPAG), in the liver and to a lesser extent the intestine and kidney. MPAG, whereas eventually being excreted primarily in the urine, will be secreted into bile. When secreted in the bile, MPAG can undergo deconjugation and conversion by bacterial glucuronidases back to MPA. Enterohepatic recirculation may account for 10–60% of total MPA exposure and may explain the second peak of MPA levels typically seen 4–8 h after oral administration [7].

Studies of the pharmacokinetics of MMF in both transplant and autoimmune diseases have found wide interpatient variation in levels despite stable dosing of MMF. This variation is multifactorial with contributions from differences in enterohepatic circulation and other factors such as hypoalbuminemia, renal impairment, and pharmacogenomics [9,10].

MEASURING LEVELS OF MYCOPHENOLIC ACID AND ITS METABOLITES

Early assays for total MPA levels relied on enzymatic techniques that measured inhibition of the target enzyme, inosine monophosphate dehydrogenase. Subsequently, assays employing high-pressure liquid chromatography (HPLC) and more recently tandem mass spectrometry (MS/MS) have become standard for the assessment of the levels of MPA and its metabolites including MPAG. These assays measure total MPA levels including both free and bound fractions [11,12].

Measurement of the free MPA level, whereas superior in clinical meaning to total level, remains a specialized and expensive technique that cannot be accomplished by many laboratories. For this reason, the focus of understanding MPA exposure has been the determination of the area under the curve (AUC) of total MPA levels.

FREE VS TOTAL MYCOPHENOLIC ACID

In vivo, it is only the free fraction of MPA that can cross cell membranes and exert effects. Free MPA levels are particularly affected by hypoalbuminemia or any drug interaction leading to the displacement of MPA from albumin [5▪▪,13]. If only total MPA levels are measured, variation in free levels can go unnoticed, leading to ineffective dosing or toxicities. Figure 1 shows a comparison of free vs total (free + bound) AUC_{0-2h} measured in patients receiving MMF [5▪▪].

This has been well documented in the transplant literature. In a study of 33 pediatric and adult hematopoietic stem cell transplant patients, the percentage of free MPA ranged from 1 to 5% [14].

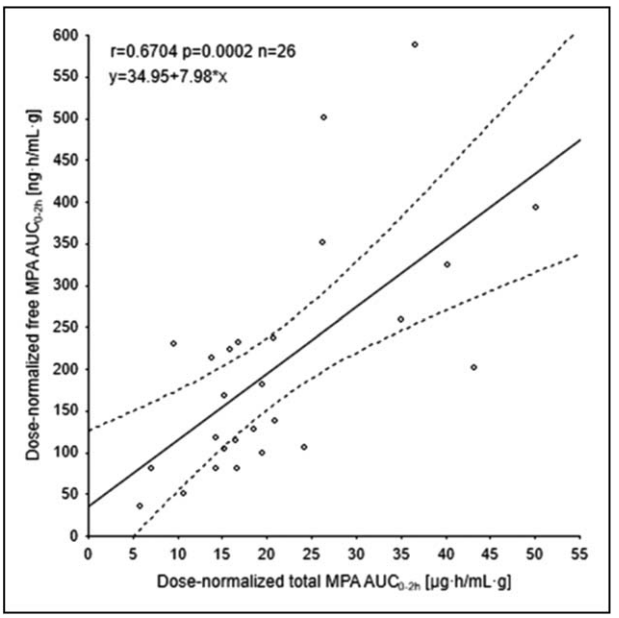

FIGURE 1. Comparison of free vs total (free + bound) AUC_{0-2h} measured in patients receiving MMF. Original figure from [5▪▪]. Reproduced with permission.

Similarly, a meticulous study of pediatric renal transplant patients with sampling over a 12 h period showed variation in the ratio of free to total MPA ranging from 1 to 5% [15]. Free MPA levels were higher in the setting of renal insufficiency and lower serum albumin; consequently, there was wide variation in the ratio of the free AUC to the total AUC [15]. Finally, a study of seven heart transplant patients concluded that there was a poor correlation between free MPA and total MPA concentration ($r^2 = 0.2015$) [16], which has similarly been reported after renal transplant [17].

FACTORS INFLUENCING MYCOPHENOLIC ACID LEVELS

Renal impairment

Renal impairment has long been thought to affect MPA levels because its metabolite, MPAG, is renally excreted and buildup leads to the displacement of MPA from its binding sites [10]. Some studies have found that this leads to an increase in the free fraction of MPA [18–21], however, recommendations to guide alteration to MMF dosing in the setting of renal insufficiency do not exist.

Food intake

MPA blood levels can be altered by food intake. With the ingestion of a fatty meal, the time to maximum concentration is delayed and the maximum concentration of MPA is decreased [22]. In practice, however, these appear to be minor changes that do not change the MPA AUC and it is not necessary to prohibit the ingestion of MMF with meals.

Sex

It is unclear if sex has an effect on the pharmacokinetics of mycophenolate. A study of 67 stable renal transplant patients showed slower MPA clearance among female patients [23]. Scattered studies in lupus nephritis [24] and autoimmune glomerulonephritis [25] have reported increased clearance of MPAG in women but other studies have found no difference between sexes [26].

Race

There have been conflicting results regarding the role race and genetic heritage play on the immunologic effects of MMF. In early trials on allogeneic renal transplantation, an increased dose of MMF from 2 to 3 g/day in Caucasian patients did not improve outcome and produced more side effects, whereas in Black patients a dose of 3 g/day vs 2 g/day improved rates of rejection over azathioprine [27]. As an example of the complexity of the data, a study of 67 stable renal transplant patients made two interesting observations. In this study, African American females received almost twice the MPAG exposure as Caucasian males and the peak associated with enterohepatic circulation was most pronounced in Caucasian females [23]. In a comparison of healthy Chinese and Caucasian subjects there were no significant differences in the pharmacokinetics of MPA aside from a 40% higher rate of clearance of MPAG in Caucasians, which was not thought to be clinically relevant [28]. A study published in the Journal of Clinical Pharmacology in 2000 found that MPA AUC values were comparable for Caucasians and African Americans after renal transplantation [29]. Given the conflicting results, the possibility of genetic differences in metabolism should be kept in mind but clinical significance remains to be seen.

Drug interactions

Numerous drugs are known to affect MPA exposure [30]. The most common medications include calcineurin inhibitors, antacids, metal-containing medications, some antibiotics, sevelamer, salicylates, and fenofibrates [10,26,30–33]. Importantly, studies have found that mycophenolate can decrease the mean AUC_{0-24h} for levonorgestrel. Based on this information it has been recommended that women taking MMF should use additional or nonhormonal method of contraception [33], however, it remains unclear if this interaction is clinically significant.

PHARMACODYNAMICS/THE USE OF AREA UNDER THE CURVE

The body's true exposure to MPA can be best understood with the use of AUC_{0-12h}, which is considered the gold standard measurement [34].

The use of the AUC_{0-12h} has been well documented in the posttransplant literature. Multiple studies have shown an association between attaining a minimum MPA AUC_{0-12h} and a lower risk of renal rejection; a goal range of MPA AUC_{0-12h} 30–60 mg h/L has been proposed [35]. In a study of 150 renal transplant patients, participants were randomized to one of three MPA AUC_{0-12h} target groups: low (16.1 mg h/L), medium (32.2 mg h/L) or high (60.6 mg h/L). The authors concluded that a higher goal MPA AUC_{0-12h} was associated with a reduction in transplant rejection [36]. In the APOYGRE trial (Adaptation de Posologie due MMF en Greffe Renale), 137 renal transplant recipients receiving

basiliximab, cyclosporine A, MMF and corticosteroids were randomized to receive concentration-controlled or fixed-dose MMF. Primary endpoints of the trial included death, graft loss, acute rejection, and MMF discontinuation. Over a 12 months study period there were fewer treatment failures and episodes of acute rejection in the concentration-controlled group with no increase in adverse events [37].

Although the posttransplant literature supports the use of MPA AUC_{0-12h}, the conclusions gathered cannot be directly applied to the use of AUC MMF in autoimmune diseases. Transplant patients are typically on multiagent immunosuppression and the metabolism of MMF can be affected by drug–drug interactions (particularly with calcineurin inhibitors). Transplant patients are also more likely to have rapid changes in renal function and serum albumin. Although these factors could conceivably suggest that modeling of the MPA AUC_{0-12h} in autoimmune diseases is simpler, the changing nature of autoimmune diseases throughout treatment makes response to treatment and appropriate adjustments of treatment more difficult to track.

In reviewing the available literature on MPA AUC_{0-12h} in autoimmune diseases, the studies fall into distinct categories: (A) Observational studies using total MPA AUC_{0-12h}, (B) Interventional studies using total MPA AUC_{0-12h}, and (C) Studies using free MPA AUC_{0-12h}. These categories will be further reviewed in the following sections.

OBSERVATIONAL TRIALS EVALUATING TOTAL MPA AUC_{0-12h}

Several studies have evaluated total MPA AUC_{0-12h} and its relationship with clinical outcomes. In one of the early observational studies looking at 18 patients with active class III/IV ±V lupus nephritis, Lertdumrongluk *et al.* demonstrated that AUC_{0-12h} >45 mg h/L was associated with a good clinical response. Subsequent studies have confirmed this finding although the AUC_{0-12h} value has varied among publications [36,38▪]. A large study of 71 patients with SLE, mainly with renal involvement, concluded that AUC_{0-12h} of >35 mg h/L was associated with less SLE activity based on both BILAG and SLEDAI scores [39]. A 2020 study of 10 patients with class III/IV lupus nephritis reported that a high AUC_{0-12h} earlier in induction therapy was associated with good renal response to fixed dosing of MMF. Finally, the importance of the use of AUC_{0-12h} was assessed in a study of 20 patients with lupus nephritis that concluded that the correlation between MPA AUC_{0-12} and MMF dose was not strong ($r = 0.53$) and that the AUC tended to be higher (although not statistically significant) in the treatment responder group ($P = 0.09$) [40]. Additional observational studies looking at the total MPA AUC_{0-12h} are summarized in Table 1: Observational Studies with Total MPA AUC_{0-12h}.

INTERVENTIONAL TRIALS EVALUATING TOTAL MYCOPHENOLIC ACID AUC_{0-12h}

As fixed dosing of MMF does not ensure adequate MPA exposure, several interventional studies have evaluated the use of AUC-based rather than fixed dosing of MMF and its correlation with clinical outcomes. Daleboudt *et al.* demonstrated that MMF dose titrated to a goal AUC_{0-12h} of 60–90 mg h/L was associated with complete or partial response in 87.5% of patients [34]. Alexander *et al.*, in a study on 34 patients with proliferative lupus nephritis with the dose of MMF titrated to achieve MPA AUC_{0-12h} 30–60 mg h/L, found that an $AUC_{0-12} \geq 30$ mg h/L was associated with better renal response at one year [41]. A 2019 study found that patients treated with concentration-controlled dosing rather than fixed dosing of extended-release MPA in lupus nephritis achieved target AUC_{0-12h} quicker and achieved higher rates of remission [42▪▪]. Interestingly, in one study evaluating maintenance therapy, targeting an AUC_{0-12h} actually allowed for mean dose of MMF to be decreased from 2.8 to 1.9 g/day [43]. Additional studies looking at total MPA AUC_{0-12h} are summarized in Table 2: Interventional Studies with Total MPA AUC_{0-12h}.

USE OF FREE VS TOTAL MYCOPHENOLIC ACID AUC_{0-12h}

Very few studies have evaluated free MPA levels rather than the traditional total MPA levels. Although free MPA levels represent the physiologically active component of MPA, measurement of values is technically difficult and expensive [44].

A 2019 study of lupus nephritis patients by Łuszczyńska *et al.* found a correlation between free MPA concentration at time 0 (C_{0h}) and MPA AUC_{0-2h} as well as total MPA C_{0h} and total MPA AUC_{0-2h}. AUCs were calculated by measuring free and total MPA levels prior to and 0.5 and 2 h after dose of MMF. The authors concluded that measurement of only total MPA concentrations may be sufficient, except for patients with hypoalbuminemia. On further inspection of the data, however, it is noted that even in the range of low-normal albumin with values of 3–4.5 g/dL there is a substantial variation in the free faction of MPA ranging from 0.5 to 3.5% (Fig. 2) [5▪▪]. We postulate this supports the need for a clearer understanding of the correlation between free and total levels.

Table 1. Observational studies with total MPA AUC_{0-12h}

Study	Population	Dose	Sampling time(s)	Outcome	Notes
Lertdumrongluk *et al.* 2010	18 patients with active class III/VI±V lupus nephritis	12 patients: fixed MMF 1000–1500 mg/day 6 patients: EC-MPS 1080–1440 mg/day for 6 months.	30 min, 1, 2, 3, 4, 8, and 12 h after dosing	At 6 month: AUC_{0-12h} >45 mg h/l was associated with clinical response. Positive correlation of trough and 1 h post dose with AUC in MMF group.	ROC analysis showed that MPA-AUC was far superior compared with other laboratory profiles in predicting therapeutic responses Measured 1 month after initiation of MMF
Zahr *et al.* 2010	71 patients with SLE, most with renal involvement	Variable MMF dose ranging 500mg-1500 mg twice daily	40 min, 2 and 3 h after dosing	AUC_{0-12h} >35 mg h/l was associated with less SLE activity (SLEDAI, BILAG).	Measured after 10 weeks of stable dose
Schaier *et al.* 2015 [62]	100 patients with ANCA-associated vasculitis 29 patients with SLE 229 patients without autoimmune disease	MMF 1000–2000mg/day	IMPDH and MPA level at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after the morning dose	Stable disease (based on BVAS score) was associated with MPA AUC_{0-12h}>75 mg h/l ($P<0.05$). Inadequate IMPDH suppression correlates with a higher relapse rate ($P=0.001$).	
Neumann *et al.*, 2008.	38 total patients 26 patients with ANCA-associated vasculitis 12 patients with SLE	MMF 1000 mg twice daily	0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 14 and 24 h after dosing	Significant association between concentration at 12 h (C_{12h}) and AUC_{0-12h}. Remission persisted in all patients with MPA troughs ≥3.5 mg/L. MPA troughs between 3.5 and 4.5 mg/L are favored for efficacy and safety profile.	MMF dose stable for >10 weeks prior to study 12 h overnight fast prior to collection Patients did not receive PM dose of MMF
Djabarouti, Duffau, *et al.* 2010	35 patients with nonrenal SLE	21 patients: MMF 1000 twice daily 14 patients: EC-MPS 720 mg twice daily	0, 0.5, 1, 2, 3, 4, 6, 8, 12 h after dosing	Trough can predict MPA AUC_{0-12h} in MMF group but weak correlation in EC-MPS group. Limited sampling strategy of C_{max} and C_{12h} can predict MPA AUC_{012h} for EC-MPS. For MMF, positive correlation observed between prednisone dose and MPAG C_{max}.	12 h overnight fast prior to collection Standard light meals served 2, 5.5, 8.5 h post administration
Djarbarouti, Breilh, *et al.*, 2010	25 patients with nonrenal SLE	1000–3000mg/day	0, 0.5, 1, 2, 3, 4, 6, 8, and 12 h after dosing	At 6 months: clinical flares were associated with MPA $C_{12h}<3$ mg/L	No significant correlations between AUC_{0-12h} and serum albumin or weight.

Table 1 (*Continued*)

Study	Population	Dose	Sampling time(s)	Outcome	Notes
Streicher, *et al.*, 2014.	23 patients with SLE 21 patients with vasculitis	1500–3000mg/day	0, 0.5, 1, 2, 3, 4, 6, 8 and 12 h after dosing	Strong correlation between MPA AUC_{0-12h} and C_{0h} measured an average of 12.7h after MMF administration At 12 months: Trough levels were significantly lower in active SLE based on SLEDAI ($P=0.048$) and active vasculitis based on BVAS ($P=0.016$). More flares in SLE patients with C_{0h} values below 3mg/L but not statistically significant. In vasculitis, C_{0h} values below 2.5mg/L had significantly more flares ($P=0.003$) Trough level $\geq$ 2.5–3 mg associated with stable disease	
Katsuno *et al.*, 2018.	20 patients with lupus nephritis	250–1000 mg twice daily	0, 1, 3, 6 h after dosing	Correlation between AUC_{0-12h} and MMF dose was not strong ($r=0.53$). Trough values correlated with AUC_{0-12h} ($r=0.73$) AUC tended to be high in the treatment responder ($P=0.09$) but did not correlate with adverse events of infection ($P=0.92$).	
Nakeseko, *et al.*, 2019.	29 pediatric patients with autoimmune diseases	Started 20mg/kg/day and increased to 30–40mg/kg/day	0, 1, 2, 3, 4, 6, 8 h after dosing	The AUC_{0-12h} values and AUC_{0-12h} values corrected for dose per body weight and T max were lower in younger patients. The AUC values corrected for dose per BSA and maximum concentration were comparable among all the groups.	
Zahr, *et al.*, 2008	20 patients with SLE	500mg-1500 mg twice daily	0, 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 8, 12 h after dosing	Large interindividual variability in MPA concentration-time profiles were observed. Constructed a pharmacokinetic model to fit MPA blood-concentration time profiles. Best sampling strategy obtained with the Bayesian estimator of MPA exposition was 40 min, 2 h, 3 h.	Stable dose 10 weeks prior to study. Overnight fast prior to study.
Sagcal-Gironella, *et al.*, 2011.	19 pediatric patients with SLE	1–3g total per day	0, 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 9 h after dosing	AUC_{0-12h} and weight-adjusted MMF dosing were only moderately correlated ($r=0.56$, $P=0.01$) $AUC_{0-12h} \geq 30$ mg h/L was associated with decreased BILAG score ($P=0.002$)	8 h fast prior to study Stable MMF for >3 weeks prior to study

Table 1 (*Continued*)

Study	Population	Dose	Sampling time(s)	Outcome	Notes
Woillard, *et al.*, 2014.	36 pediatric patients with SLE	300–1500 mg twice daily	0, 20 min, 40 min, 1, 1, 2, 3, 4, 6, 8, 12 h after dosing Bayesian estimator	Correlation between observed MPA trough concentrations and AUC_{0-12h}. AUC/dose < 0.06 and AUC <4 mg h/L were associated with active disease. Logistic regression model showed that AUC <44 mg h/L and AUC/dose <0.06 was associated with increased risk of active disease Creation of a model and validation of the limited sampling strategy (20 min, 1, 1.5h) from cohort.	
Prabha, *et al.*, 2016.	26 pediatric patients with SLE	1000–2000 mg twice daily	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, 12 h after dosing Trapezoidal rule	The interindividual variability for dose normalized AUC_{0-12h} and dose normalized trough concentration was 46.5% and 61.1% respectively. Concluded that trough is not ideal as sole parameter for use in therapeutic drug monitoring in pediatric MPA. Recommended 4 point limited sampling strategy equation to predict MPA AUC_{0-12h}.	Overnight fast prior to study
Yap, *et al.*, 2020.	88 patients with class III/IV/V lupus nephritis	Month 1–6: 1000 mg BID Month 7–12: 750 mg BID Month 12–24: 500–750 mg BID	0, 1, 2, 4, 8, 10, 12 h after dosing	Concentrations at 1h, 2h and 12h were correlated with the 12h area under the curve. C_{12h} inversely correlated with hemoglobin, immunoglobulins and leukocyte levels.	

AUC_{0-12h}: area under the curve from 0 to 12 h; C_{max}: maximum concentration; C_{0h}: concentration at 0 h; C_{12h}: concentration 12 h after dose; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

Table 2. Interventional studies using total MPA AUC_{0-12h}

Study	Population	Dose	Sampling time(s)	Outcome	Notes
Daleboudt *et al.* 2013	16 patients with lupus nephritis	MMF dose adjusted to achieve target AUC of 60–90 mg h/l	0, 1,2 and 3 h after dosing	At 12 months: AUC_{0-12h} of 60–90 mg h/l was associated with complete (68.8%) or partial (18.7%) response in 87.5% of patients.	12 h fast prior to study
Alexander, *et al.*, 2014.	34 patients with proliferative lupus nephritis	MMF dose adjusted to achieve AUC 30–60 mg h/L	Limited sampling size but not standardized among patients. Used either AUC_{0-6h} or 5 time points for limited sampling strategy.	$AUC_{0-12h} \geq 30$ mg h/L was associated with better renal response at 1 year. Trough level had weak correlation with AUC.	Patients with serum albumin ≥35 g/L had a greater chance of having an AUC ≥30 mg h/L
Kittanamongkolchai, *et al.*, 2013.	19 patients with class III, IV +/- V lupus nephritis	Started 1500mg/day. Goal dose to achieve MPA C_{1h}>13mg/L.	0, 0.5, 1, 2, 3, 4, 8, 12 h after dosing Measured concentration at 1 h after dose	14/18 patients achieved targeted MPA-AUC_{0-12h} level of 45 mg h/L 3 patients achieved adequate MPA C_{1h} >13mg/L but did not reach MPA-AUC0–12 level of 45 mg h/L, At 24 weeks 21% patients with complete response and 68% with partial response.	
Zabotti, *et al.*, 2015.	5 patients with acute lupus nephritis	Received standard induction with MMF. Maintenance: titrated to goal AUC_{0-12h} of 45–60 mg h/L	0, 30 min, 1.25, 2, 4, 6, 8, 12 h after dosing	The mean dose of MMF was significantly reduced in all patients from 2.8g/day baseline to 1.9g/day based on target AUC_{0-12h}.	

AUC_{0-12h}: area under the curve from 0–12 h; C_{1h}: concentration 1 h after dosing of medication; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

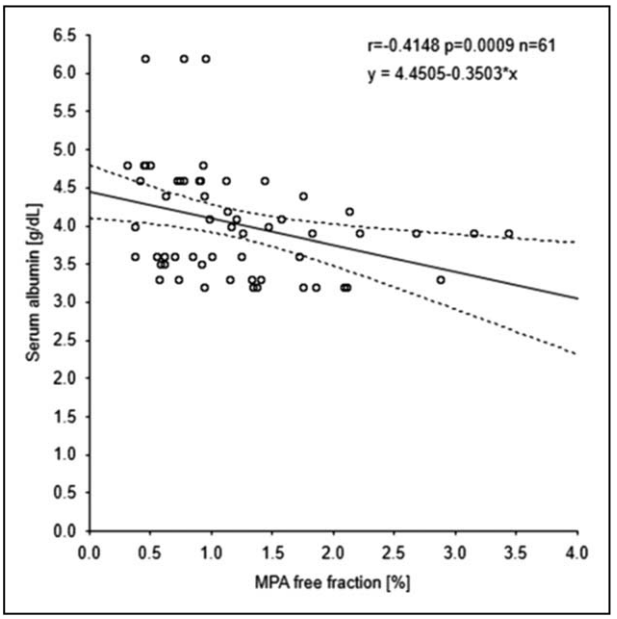

FIGURE 2. Correlation between free MPA fraction and serum albumin concentration. Original figure from [5▪▪]. Reproduced with permission.

In a 2019 study evaluating the use of extended-release MPA in lupus nephritis, patients were randomized to fixed or concentration-controlled dosing of the medication. In the concentration-controlled group, the dose of MPA was adjusted to target AUC_{0-12h} of 40–60 mg h/L for induction and 30–50 mg h/L for maintenance. Overall, concentration-controlled patients achieved the target dose faster and achieved greater rates of remission. Interestingly, the mean free MPA AUC_{0-12h} was significantly lower in those who achieved remission. The study also found a positive correlation between MPA AUC_{0-12h} and C_{0h}, concentration at 12 h (C_{12h}), and maximum concentration (C_{max}) for total and free MPA concentrations [42▪▪]. This has similarly been described in the renal transplant literature [45▪]. The studies utilizing free MPA AUC_{0-12h} rather than total are summarized in Table 3: Studies using free MPA AUC_{0-12h}.

The identification of a reliable model wherein total levels could be measured and then extrapolated to understand the AUC_{0-12h} of free MPA be advantageous to clinical medicine. Colom *et al.*

Table 3. Studies with free MPA AUC_{0-12h}

Study	Population	Dose	Sampling time(s)	Outcome	Notes
Luszczynska *et al.*, 2019.	16 patients with class III/IV lupus nephritis	250–1000 mg twice daily	Calculated AUC_{0-2h} 0, 0.5, 2h	Hypoalbuminemic LN patients (albumin <3.5g/dL) demonstrated significantly elevated MPA free fraction compared to normal albumin ($P=0.0276$). Dose-normalized free MPA concentration at 0h (C_{0h}) and free MPA AUC_{0-2h} significantly correlated with total MPA C_{0h} ($r=0.7909$) and total MPA AUC_{0-2h} ($r=0.6704$).	
Ranganathan *et al.*, 2019.	18 patients with lupus nephritis	Fixed dose group: EC-MPS 30mg/kg body weight for induction. Concentration-controlled group: dose adjusted to target AUC_{0-12h} of 40–60 mg h/L. Target decreased to AUC_{0-12h} of 30–50 mg h/L for maintenance.	Prior to dose and then every 15 min for total of 8 or 12 h of monitoring	Interpatient variability was observed in both groups but more pronounced in fixed dosing group. Concentration-controlled participants achieved target AUC_{0-12h} faster. More concentration-controlled patients achieved remission compared to fixed dose patients. The mean free MPA AUC_{0-12h} was significantly lower in those who had complete remission. Moderate positive correlation observed between MPA AUC_{0-1h} and C_{0h}, C_{12h}, C_{max}.	

AUC_{0-12h}: area under the curve from 0 to 12 h; C_{0h}: concentration at time of dosing of medication; C_{1h}: concentration 1 h after dosing of medication; C_{max}: maximum concentration after dosing of medication; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

developed a model to predict free MPA levels based on measurement of total MPA levels in stable patients after renal transplant [46]. The development of a similar model for autoimmune patients would be a helpful tool for complex clinical cases.

USE OF LIMITED SAMPLING STRATEGIES

Although the measurement of the AUC is arguably the most accurate, the time investment is not practical in clinical medicine. As a result, numerous strategies utilizing a small number of predetermined time point measurements (termed limiting sampling strategies) have been proposed. Currently, there is no accepted standard limited sampling strategy.

The simplest limited sampling strategies involve the use of trough levels, or a single-time point to understand the drug concentration. Some studies report a correlation between the values [40,47–51], whereas others report no correlation [41,52]. For example, in an observational study of 51 patients with lupus nephritis, Pourafshar *et al.* found a statistically significant correlation between trough levels of MPA and MPA AUC_{0-4h} ($r=0.55$) but found that trough levels only explained 30% of the variance in AUC_{0-4h} and all tertiles of trough levels showed significant overlap of MPA AUC_{0-4h} levels [53]. In summary, there is not compelling evidence to support the use of the MPA tough and it should not be used to guide clinical decisions.

Other attempts to identify single timepoint measurements besides a trough value have also been explored but similarly not yielded compelling evidence of clinical validity. Kittanamongkolchai *et al.* utilized the concentration 1 h after MMF dose (C_{1h}) to guide dosage changes and found that 14/18 patients achieved target the MPA AUC_{0-12h} level of 45 mg h/L and at 24 weeks 21% patients had complete response and 68% had partial response [54].

Given the unclear validity of a single timepoint, researchers have proposed limited sampling strategies including a smaller number of time points that can be extrapolated to understand the full MPA AUC_{0-12h}. Lertdumrongluk *et al.* demonstrated a positive correlation of trough and 1 h post dose with AUC_{0-12h} in MMF but not EC-MPS group [50]. Proposed limited sampling strategies have included 3 time point measurements including: 20 min, 1 h, 1.5 h post dose (Woillard *et al.* 2015); 30 min, 2 h, 4 h post dose [55]; 1 h, 2 h, 12 h [56▪]. Prabha *et al.* also suggested a limited sampling strategy using 4 or 5 time points to predict the MPA AUC_{0-12h} [52]. Studies are further delineated in Table 5: Studies that suggest limited sampling strategies.

Use of salivary levels

Salivary MPA concentration monitoring has been suggested as a simple, noninvasive way of analyzing MPA levels. Drug that is not bound to plasma protein (free drug) enters the saliva and equalizes between saliva and plasma. Saliva concentrations

have been hypothesized to follow levels of active free form of MPA in the blood [57▪]. Several studies have found good correlation between total, free and salivary MPA levels in healthy volunteers as well as renal transplant patients [58,59,60▪]. Alsmadi *et al.* used LC-MS to develop a model to predict levels in stable patients [60▪]. Other studies, however, have found poorer correlations and less clinical applicability. A study of renal transplant recipients found that the average salivary concentration of MPA was well correlated with total or free levels with the exception of the morning trough [61]. In study of 20 renal transplant patients taking EC-MPS, the correlation between salivary MPA AUC and total and free AUC was poor ($r^2 = 0.25$ and $r^2 = 0.13$); salivary levels were generally found to be lower [57▪].

AREAS OF INVESTIGATION GOING FORWARD

Despite the acceptability of MPA AUC_{0-12h}, it is infrequently utilized in clinical practice. Further research needs to confirm the finding that alteration in the MPA AUC_{0-12h} alters clinical outcomes. The identification of a single timepoint or a limited sampling strategy that can be extrapolated to understand the MPA AUC_{0-12h} would greatly inform clinical decisions with the use of MMF as well as feasibility in routine clinical practice. If total levels continue to be easiest to measure, could one or several evaluations of total levels be utilized and extrapolated to understand free MPA AUC_{0-12h}?

CONCLUSIONS

After administration of comparable doses of MMF, exposure to its metabolite MPA, varies widely in both transplant and rheumatic disease patients. Evidence is accumulating that achieving a minimum target AUC_{0-12h} of total MPA (free + bound) in both groups of patients is associated with improved clinical outcomes. The utility of following the AUC is limited by the logistical difficulty with obtaining MPA levels at multiple time points. The current literature lends support to the use of abbreviated sampling schedules but does not establish the utility of using measurement at a single-time point, such as trough level, for dose adjustment. Many factors such as renal function, serum albumin levels and coadministration of certain drugs influence exposure but are not currently taken into account with fixed dose administration. An assessment of drug exposure and dose adjustment in an individual patient could potentially result in further improvement in clinical outcomes. Evidence that the AUC predicts success is stronger than the evidence that identifying patients with suboptimal AUC and attempting to increase it using higher drug doses leads to an improved outcome. One reason may be that patients with low AUC cannot tolerate higher doses.

The percentage of free vs. total AUC can vary more than twofold, especially in patients with different serum albumin levels; it is arguable that assessing the free AUC, in addition to more accurately quantifying exposure to the active (free) drug by measuring AUC, would better inform clinical decision making. Currently, logistical considerations and expense have discouraged clinical use of the free AUC. Development of a limited sampling strategy permitting cost effective assessment of the free AUC of MPA has the potential to improve accurate assessment of drug exposure and patient management.

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Conflicts of interest

There are no conflicts of interest.

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Recent advances in the treatment of neuromyelitis optica spectrum disorders

Andrew R. Romeo

Purpose of review
This review examines recently published randomized placebo-controlled trials for the treatment of neuromyelitis optica spectrum disorders (NMOSD).

Recent findings
Until recently, treatments for NMOSD were used-off label and had not been subjected to randomized placebo-controlled trials. Increased understanding of the pathophysiology of NMOSD, particularly aquaporin-4-IgG seropositive NMOSD, lead to the investigation of eculizumab, inebilizumab, and satralizumab for maintenance therapy. Eculizumab inhibits the cleavage of the terminal complement protein C5, inebilizumab depletes immune cells of B-lymphocyte lineage, and satralizumab inhibits interleukin-6 receptors. International, phase 3, randomized, placebo-controlled trials have demonstrated that each of these therapies reduces the risk of NMOSD relapse. In some cases, the studied therapies were administered in conjunction with other immunosuppressants. Each therapy has important safety considerations, notably risk of meningococcal infection with eculizumab and risks of infection and hypogammaglobulinemia with inebilizumab. Reviewing trial design highlights future areas of inquiry for the treatment of NMOSD.

Summary
Eculizumab, inebilizumab, and satralizumab are effective maintenance therapies approved for the treatment of AQP-4 seropositive NMOSD.

Keywords
eculizumab, inebilizumab, neuromyelitis optica, satralizumab

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system (CNS), often with a relapsing course [1]. Optic neuritis (ON) and myelitis (classically longitudinally extensive transverse myelitis (LETM)) are common manifestations, but the spectrum also includes area postrema syndrome (intractable nausea, vomiting, and or hiccups), other brainstem syndromes, diencephalic syndromes, and cerebral syndromes [1,2▪]. The majority of patients with NMOSD (75–90%) are seropositive for IgG against the aquaporin-4 water channel [aquaporin-4-IgG(AQP4-IgG)/NMO-IgG] [3,4]. AQP4 is concentrated on astrocyte end-feet, a component of blood-brain and blood-CSF barriers [5▪]. AQP4-IgG is believed to be primarily produced peripherally rather than intrathecally, consistent with the observation that serum testing for AQP4-IgG is more sensitive than CSF testing [5▪,6]. Binding of AQP4-IgG to AQP4 on astrocytes is proposed to induce a cascade involving complement-mediated cytotoxicity and granulocyte and macrophage infiltration, resulting in damage to astrocytes and oligodendrocytes (thus demyelination) and damage to axons, ultimately neuronal death [5▪,7,8▪▪].

NMOSD exacerbations (attacks/relapses) can be permanently disabling, thus maintenance therapy to reduce the risk of exacerbation is essential [9]. Primarily on the basis of opinion and experience, patients were empirically treated with agents such as chronic corticosteroids, azathioprine, mycophenolate mofetil, and rituximab [2▪]. This review will focus on recently published randomized, placebo-controlled trials of eculizumab, inebilizumab, and satralizumab for treatment of NMOSD (Table 1), including safety considerations. Additional aspects

Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to Andrew R. Romeo, MD, Department of Neurology, 1500 E. Medical Center Drive, Floor 1, Reception C, Ann Arbor, Michigan 48109, USA. Tel: +734 232 0438; e-mail: aromeo@med.umich.edu

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KEY POINTS

- Proposed NMOSD pathophysiology involves AQP4-IgG, a pathogenic auto-antibody produced by plasmablasts and plasma cells, which triggers complement-mediated cytotoxicity and an inflammatory cascade (mediated in part by B-cells, T-cells, and IL-6) resulting in demyelination and neuronal death.
- Eculizumab is a monoclonal antibody against terminal complement protein C5, administered by infusion, which was demonstrated to reduce the risk of relapse compared to placebo, and carries risk of meningococcal infection.
- Inebilizumab is a monoclonal antibody against CD19, which is administered by infusion and depletes B-cells (including their precursors as well as plasmablasts and plasma cells), which was demonstrated to reduce the risk of relapse compared to placebo, and carries risk of infection.
- Satralizumab is a monoclonal antibody against IL-6 receptor, and thus may intervene at multiple points in the NMOSD inflammatory cascade, and was demonstrated to reduce the risk of relapse compared to placebo. Satralizumab carries risk of neutropenia.

of NMOSD pathophysiology are discussed below, in the context of specific therapies.

ECULIZUMAB

Complement pathways serve critical functions in host defence against pathogens, but the complement system is proposed to have a role in multiple auto-immune diseases, including NMOSD, myasthenia gravis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [5▪,8▪▪,10–12]. In the classical complement pathway, antigen-antibody complexes (e.g. AQP4 and AQP4-IgG) activate the C1 complex (C1q, C1r, and C1s), initiating the complement system [10,11]. C5 is the terminal component of the system. Cleavage of C5 generates C5a and C5b; C5a is a chemoattractant and pro-inflammatory molecule, and C5b is part of the membrane attack complex (MAC) [10,11]. The MAC is responsible for cell lysis, specifically astrocyte cytotoxicity in NMOSD, but may have additional proinflammatory functions [10]. Eculizumab is a monoclonal antibody against C5, which inhibits cleavage [13▪▪].

PREVENT was an international, multicenter, randomized, double-blind, placebo-controlled trial of eculizumab for patients with AQP4-IgG seropositive NMOSD [13▪▪]. Participants were at least 18 years old, and met 2006 criteria for NMO or 2007 criteria for NMOSD [3,14]. Included patients had at least 2 relapses in the preceding 12 months or 3 relapses in the preceding 24 months (one in the preceding 12 months), and Expanded Disability Status Scale (EDSS) of 7 or less. (The EDSS was originally developed as a means of rating level of neurologic disability in multiple sclerosis, and has been carried over for clinical studies of NMOSD. Ambulation, specifically maximum distance and/or use of assistive devices, is a major driver of the EDSS score. Higher score indicates greater disability.) Exclusion criteria included rituximab infusion the prior 3 months, treatment with intravenous immune globulin (IVIg) in the prior 3 weeks, or prednisone greater than 20 mg daily (or equivalent). Participants were randomized 2:1 eculizumab to placebo (96 and 47 participants, respectively, both groups with median EDSS 4.0), and allowed to continue immunosuppression if on a stable dose (76% were

Table 1. Randomized, double-blind, placebo-controlled trials of maintenance therapy for NMOSD

Treatment	Mechanism of action	Route of administration	Phase 3 trials	Seronegative patients included?	Concomitant Immuno-suppression?[a]	Primary efficacy endpoint
Eculizumab	Anti-C5 (terminal complement protein)	IV Infusion	PREVENT [13▪▪]	No	Yes	First adjudicated relapse 3% of eculizumab group 43% of placebo group (HR 0.06)
Inebilizumab	Anti-CD19 (B-cell)	IV Infusion	N-MOmentum [21▪▪]	Yes	No	First adjudicated relapse 12% of inebilizumab group 39% of placebo group (HR 0.272)
Satralizumab	Anti-IL6 receptor	Subcutaneous Injection	SAkuraSky [25▪]	Yes	Yes	First protocol-defined relapse 20% of satralizumag group 43% of placebo group (HR 0.38)
			SAkuraStar [26▪▪]	Yes	No	First protocol-defined relapse 30% of satralizumab group 50% of placebo group (HR 0.45)

[a]e.g. mycophenolate mofetil, azathioprine, glucocorticoids.

on concomitant immunosuppression). Eculizumab was dosed 900 mg IV weekly for 4 weeks, then 1200 mg IV every 2 weeks until relapse, discontinuation, or end of trial. Concomitant immunosuppression was categorized as glucocorticoids alone (22% of participants), azathioprine with or without glucocorticoids (39%), mycophenolate mofetil with or without glucocorticoids (18%), or other drug with or without glucocorticoids (5%; cyclosporine, cyclophosphamide, methotrexate, mizoribine, and tacrolimus). Participants were stratified based on EDSS ($\leq$2.0 or 2.5–7.0) and the use of concomitant immunosuppression. The trial was stopped by the sponsor after 23 of 24 prespecified adjudicated relapses. The trial met the primary efficacy endpoint: 3% of participants in the eculizumab group had a relapse, compared to 43% of the placebo group (HR 0.06, 95% CI 0.02–0.2, $P < 0.001$). In prespecified subgroup analyses, eculizumab significantly reduced the risk of adjudicated relapse regardless of concomitant immunosuppression (or none) [15▪]. Adjusted annualized relapse rate (ARR), a secondary efficacy end point, was lower in the eculizumab group compared to the placebo group (0.02 vs 0.35, respectively, $P < 0.001$) [13▪▪]. The remaining hierarchical secondary efficacy end points were not met. In posthoc efficacy analyses, the risk of adjudicated relapse was significantly reduced with eculizumab regardless of disease duration, baseline EDSS, or baseline ARR [15▪]. A higher percentage of participants in the eculizumab group discontinued treatment compared to the placebo group (17% vs 6%) [13▪▪].

The chief safety concern with eculizumab (i.e. complement inhibition) is risk of infection from encapsulated bacteria, particularly Neisseria *meningitidis*. In the PREVENT trial, participants were vaccinated for *N. meningitidis* before treatment (unless a previous vaccination provided adequate coverage, according to Supplementary material), and no cases of meningococcal infection were reported [13▪▪]. Eculizumab was initially approved for the treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria and a CDC investigation identified 16 cases of meningococcal infection in eculizumab treated patients (2008–2016); 14 patients had received MenACWY vaccination and 3 had received MenB vaccination [16]. Isolates from 14 of 16 cases were further characterized and 11 were nongroupable *N. meningitidis*. MenACWY vaccines do not provide cross-protection for nongroupable *N. meningitidis*, and cross-protection with MenB vaccines is uncertain [16]. Guidance regarding vaccination before eculizumab treatment for NMOSD has been an area of concern [17,18]. The Advisory Committee on Immunization Practices in the USA recommends vaccination at least 2 weeks prior to treatment with eculizumab, and the specific schedule depends on the patient's vaccination history [19▪].

The overall rates of adverse events in the PREVENT trial were similar between the eculizumab and placebo groups, but rates of upper respiratory tract infection and headache were higher in the eculizumab group [13▪▪]. One death occurred in the eculizumab group, due to pulmonary empyema in a patient also on azathioprine. The cultured organisms in that case would not be associated with complement deficiency, as the authors point out. In posthoc safety analyses, the rates of infection and serious adverse effects were lower for the eculizumab group on concomitant therapies compared to placebo group on concomitant therapies [15▪].

INEBILIZUMAB

Humoral autoimmunity is fundamental in the pathophysiology of NMOSD [4]. B-lymphocytes differentiate into plasmablasts and plasma cells that produce antibodies. B-lymphocytes (and immune cells of this lineage) may play other roles in NMOSD pathophysiology, such as secretion of pro-inflammatory cytokines and antigen presentation, thereby promoting pathogenic T-cell response and migration of neutrophils and macrophages into the CNS [4]. Rituximab is a chimeric monoclonal antibody against CD20, found on the surface of pre-B-cells, immature B-cells, mature B-cells, and memory B-cells [4]. Rituximab induces B-cell depletion and has been used off label for treatment of NMOSD. Interestingly there is a sub-population of T-cells that also express CD20, and rituximab also depletes these T-cells [20,21▪▪]. Inebilizumab is a humanized monoclonal antibody against CD19 [21▪▪]. CD19 is expressed on pro-B-cells, plasmablasts, and plasma cells, in addition to the CD-20+ B-cells mentioned previously [4,20]. T-cells do not express CD19. Therefore, inebilizumab is more specific for B-cells, and depletes a broader range of this lymphocyte lineage.

N-MOmentum was an international, multicenter, double-blind, placebo-controlled phase 2/3 trial of inebilizumab for NMOSD [21▪▪]. Participants with both seropositive and seronegative NMOSD were enrolled. Participants were included if they were 18 years of age or older, had 1 NMOSD relapse within the preceding year or 2 relapses within the preceding 2 years (requiring rescue therapy), and EDSS 8.0 or less. Seronegative patients were included if they met the aforementioned criteria, as well as 2006 diagnostic criteria for NMO [14]. Participants treated with rituximab during the

6 months prior to screening were excluded, unless lymphocyte counts were normal at enrollment. Treatment with any of the following immunosuppressants in the 3 months preceding randomization also warranted exclusion: eculizumab, tocilizumab, cyclophosphamide, mitoxantrone, cyclosporine, natalizumab, or methotrexate. Participants were randomized 3:1 inebilizumab to placebo. The inebilizumab group received 300 mg IV on days 1 and 15. Participants in either group were not concomitantly treated with mycophenolate mofetil or azathioprine, but did receive oral steroids days 1–14 (followed by a taper to day 21) due to the risk of relapse from discontinuing prior therapy and/or initiating B-cell depletion. The intention-to-treat and as-treated analyses included 174 participants in the inebilizumab group (92% seropositive, median EDSS 4.0) and 56 participants in the placebo group (93% seropositive, median EDSS 3.5). The trial was halted early, before reaching the enrollment target or prespecified number of NMOSD attacks, due to clear efficacy and conditional power greater than 99%. The trial met the primary efficacy endpoint: 12% of the inebilizumab group suffered an attack, vs. 39% of the placebo group (HR 0.272 [CI 0.150–0.496], $P < 0.0001$). Efficacy could not be interpreted in the seronegative cohort. Compared with the placebo group, the inebilizumab group had fewer patients with worsening of EDSS from baseline, less mean cumulative active MRI lesions, and less mean NMOSD-related hospitalizations.

The most common adverse effects in the inebilizumab group were urinary tract infections, arthralgias, and infusion-related reactions [21▪▪]. However, frequency of adverse events was similar between inebilizumab and placebo groups, including infusion-related reactions. Total serum IgG at baseline or following inebilizumab treatment in the N-MOmentum trial was not reported. Observational cohorts suggest that hypogammaglobulinemia is a common complication of B-cell-depleting therapy in NMOSD and other autoimmune disorders [22–24]. Two deaths occurred in the N-MOmentum open-label period. One due to respiratory insufficiency caused by an NMOSD relapse in a participant originally randomized to placebo, 9 days after receiving inebilizumab. The second was a participant originally randomized to the inebilizumab group, who did receive 300 mg on day 1 of the open-label period, and on day 9 developed neurologic worsening, complicated by seizures and respiratory arrest, ultimately dying of cardiopulmonary complications. MRI lesions in this second patient were not felt to be consistent with progressive multifocal leukoencephalopathy, and CSF PCR for JC virus was negative 2 of 3 times (from 3 different laboratories). Cases of PML have been reported in patients taking other B-cell-depleting therapies [25▪].

SATRALIZUMAB

Interleukin-6 is a cytokine produced by multiple cell-types, with many physiologic roles both inside and outside of the immune system [8▪▪]. Neurons, glial cells, and endothelial cells can produce IL-6 in response to injury, and IL-6 receptor (IL-6R) is expressed by glial cells (specifically oligodendrocyte progenitor cells and microglia). IL-6R has membrane-bound and soluble forms, both of which initiate signalling [8▪▪]. Dysregulated IL-6 signalling may have a role in RA, SLE, and giant cell arteritis, among other disorders. Studies in multiple cohorts have demonstrated that serum and CSF IL-6 levels are elevated in NMOSD (particularly during relapse) [8▪▪]. In NMOSD, IL-6 is proposed to promote AQP4-IgG production, disruption of the blood-brain barrier, and mediate differentiation of naïve T-cells into proinflammatory Th17 cells [8▪▪]. Satralizumab is a humanized monoclonal antibody that binds both forms of IL-6R, blocking IL-6 signalling [26▪▪,27▪▪].

Satralizumab has been subjected to two multicenter, international, randomized, double-blind, placebo-controlled phase 3 trials for NMOSD: SAkuraSky, in which satralizumab was added to baseline immunosuppressive therapy, and SAkuraStar, in which satralizumab was used as monotherapy [26▪▪,27▪▪]. SAkuraSky included patients 12–74 years old, with seropositive or seronegative NMOSD according to 2006 criteria [14,26▪▪]. The trial also included AQP4-IgG seropositive participants with single or recurrent LETM, or recurrent or simultaneous ON in both eyes. Seronegative participants were limited to 30% of adults enrolled (reflective of epidemiology of the disease, as mentioned previously). Participants had at least 1 relapse in the 12 months before screening, and at least 2 relapses in the 2 years before screening, with EDSS 6.5 or less. Baseline treatments (concomitant immunosuppression) were at stable dose for 8 weeks prior, and included azathioprine, mycophenolate mofetil, or oral glucocorticoids. Adolescents (12–17 years old) could be on baseline azathioprine or mycophenolate mofetil PLUS glucocorticoids. Participants could not have received rituximab in the 6 months before baseline. Randomization was 1:1 satralizumab to placebo (41 and 42 participants with mean EDSS 3.83 and 3.63, respectively). Participants in the satralizumab group received 120 mg by subcutaneous injection at 0, 2, and 4 weeks, then every 4 weeks thereafter. The double-blind phase concluded after a prespecified total number of 26 protocol-defined relapses. The trial met the primary efficacy

endpoint: 20% of participants in the satralizumab group had a protocol-defined relapse, vs 43% of participants in the placebo group (HR 0.38, 95% CI 0.16–0.88, $P = 0.02$). A higher proportion of participants in the satralizumab group were free from relapse at 48 weeks and 96 weeks (89% vs 66% and 78% vs 59%, respectively). The first of the hierarchical secondary efficacy end points was not significant, thus no inferences can be made from the other secondary efficacy end points. ARR was significantly lower in the satralizumab group, with approximately 66% relative reduction in ARR in favour of satralizumab. Reduction in relapses with satralizumab was significant for both seropositive and seronegative subgroups. Median treatment duration was shorter for the placebo group (32.5 weeks vs 107.4 weeks).

Similarly, SAKuraStar included seropositive and seronegative NMO patients based on 2006 criteria, as well as seropositive patients with single or recurrent LETM or ON [14,27▪▪]. Participants also had EDSS 6.5 or less. Participants had at least one relapse in the prior 12 months. Adolescents were not included. Patients treated in the prior 6 months with an anti-CD20 mab, eculizumab, or anti-B-lymphocyte stimulator were excluded. As mentioned, participants were not on concomitant immunosuppression. Participants were randomized 2:1 satralizumab to placebo (63 and 32 participants with mean EDSS 3.9 and 3.7, respectively). The double-blind period ended 1.5 years after random assignment of the last-enrolled patient. The trial met the primary efficacy endpoint: 30% of the satralizumab group and 50% of the placebo group had protocol-defined relapses (HR 0.45, 95% CI 0.23–0.89, $P = 0.018$). However, there was insufficient evidence to indicate a risk reduction in the seronegative subgroup; 46% of the satralizumab group and 33% of the placebo group experienced a protocol defined relapse (HR 1.19). There was no significant difference in the first of the hierarchical key secondary efficacy end points. Median treatment duration was shorter in the placebo group (54.6 weeks vs 92.3 weeks, respectively).

Rates of adverse events, including infection, were similar between the satralizumab and placebo groups in SAkuraSky, though injection-related reactions were more common in the satralizumab group [26▪▪]. In SAkuraStar, the satralizumab group had a higher rate of severe adverse events, including one case of pneumonia leading to treatment discontinuation [27▪▪]. However, the investigators felt 27 of 37 severe adverse events were unrelated to treatment. The most commonly reported adverse events were urinary tract infection and upper respiratory infection. Again no deaths were reported, and no anaphylactic reactions were reported, including the open-label extension.

DISCUSSION

Eculizumab, inebilizumab, and satralizumab are FDA-approved for AQP4-IgG *seropositive* NMOSD only. As discussed above (also see Table 1), the trials of inebilizumab and satralizumab did include seronegative NMOSD patients, but we cannot draw major conclusions on relative efficacy for seronegative disease. Seronegative NMOSD may be a heterogeneous group, perhaps with mixed treatment responses. Up to 40% of patients that meet criteria for seronegative NMOSD may have serum IgG against myelin oligodendrocyte glycoprotein (MOG-IgG), giving rise to the terms MOG-IgG associated disorder and double-seronegative NMOSD [28▪]. So far no randomized-controlled trials for treatment of MOG-IgG associated disorder have been published. Presumably treatments such as rituximab, mycophenolate mofetil, and azathioprine will continue to be prescribed off label for seronegative NMOSD.

Naturally, all of the discussed trials included patients with active NMOSD (i.e. at least 1 relapse in the 1–2 years preceding enrollment). However, all trials featured an EDSS cutoff, excluding patients with higher levels of neurologic disability. In particular, the satralizumab trials had a cutoff of EDSS 6.5 [26▪▪,27▪▪]. Conceivably the treating neurologist will still encounter NMOSD patients that are nonambulatory (require use of a wheelchair), yet will benefit from maintenance therapy to reduce the risk of relapse and prevent accrual of additional disability. This author has already encountered an insurance plan requiring submission of a patient's EDSS as part of the treatment approval process.

SAkuraSky, the trial of satralizumab added to baseline immunosuppression, did include adolescents with NMOSD, but the other discussed trials did not include pediatric patients. It is estimated that 3–5% of cases of NMOSD are pediatric onset, but estimates vary geographically [29,30]. At least one trial is underway for pediatric NMOSD patients (NCT04155424).

For treatment of multiple sclerosis, monotherapy has thus far been the norm. This is in part (if not entirely) due to safety concerns. Safety data for NMOSD treatment trials that allowed for concomitant immunosuppression (PREVENT, SAkuraSky) appear reassuring, but we may learn more in the postmarketing setting if combination therapy is utilized. At this point it is not clear if NMOSD patients would obtain further reduction of relapse risk from combination therapy compared to

monotherapy, or what the highest efficacy combination may be. Additionally, placebo-controlled trials in NMOSD will no longer be appropriate [31]. A recent phase 2 open-label randomized study of tocilizumab (anti-IL6R administered intravenously) utilized azathioprine as the active comparator [32▪].

Similar to the treatment of multiple sclerosis, shared decision making between provider and patient will be critical in the absence of head-to-head trials, including consideration of routes of administration, dosing frequency, and safety profiles of treatments approved for NMOSD.

CONCLUSION

Eculizumab, inebilizumab, and satralizumab are effective maintenance therapies for the treatment of NMOSD, which will reduce the risk of relapse. Each has a distinct mechanism of action highlighting important aspects of the pathophysiology of NMOSD: the roles of complement, B-lymphocytes, and IL-6. Hopefully the data presented herald a new era of NMOSD treatment, with novel therapies to follow.

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Conflicts of interest

A.R.R. served as a blinded EDSS rater for the N-MOmentum trial of inebilizumab, which is reviewed in this article. No other conflicts of interest.

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Treatment for systemic sclerosis-associated interstitial lung disease

David Roofeh[a], *Alain Lescoat*[a,b,c], *and Dinesh Khanna*[a]

Purpose of review
This review provides an overview of the current treatments for systemic sclerosis-interstitial lung disease (SSc-ILD) and proposes a conceptual framework for disease management with case scenarios.

Recent findings
Broad treatment categories include traditional cytotoxic therapies, biologic disease-modifying rheumatic drugs, antifibrotic agents, autologous hematopoietic stem cell transplant, and lung transplantation. The optimal use of each option varies depending on SSc-ILD severity, progression, and comorbidities of individual patients. A high-quality randomized controlled trial demonstrated nintedanib's ability to retard decline of lung function in patients with limited and diffuse cutaneous disease, with established ILD. Tocilizumab, recently approved by the FDA, provides a unique intervention in those with early SSc associated with ILD with elevated acute-phase reactants: two well designed trials showed lung function preservation in phase 2 and phase 3 trials.

Summary
Stratifying patients based on key SSc-ILD characteristics (e.g. severity, risk of progression, comorbid disease presentation) may provide a useful guide for practitioners treating SSc-ILD.

Keywords
interstitial lung disease, management, systemic sclerosis, treatment

INTRODUCTION

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a common disease feature [1,2] and among the most common causes of death in patients with systemic sclerosis [3–7]. It is the consequence of an autoimmune-mediated inflammatory and fibrotic nexus, leading to pulmonary fibrosis [8]. Traditional SSc-ILD therapies include cytotoxic medications typically initiated in those with clinically impactful disease, aiming to attenuate disease severity or retard disease progression [9–11]. These therapies, to date, have demonstrated modest benefit [12]. The advent of rationally repurposed antifibrotic medication and biologic therapies offer a cache of treatments often without the limiting side effects associated with traditional cytotoxic agents [13–15]. Hematopoietic autologous stem cell transplantation and lung transplantation remain options for a select population of the most severe and treatment-refractory cases [16,17].

TREATMENT OPTIONS

Disease-modifying antirheumatic drugs

Treatment with immunomodulatory agents like cyclophosphamide (CYC) and mycophenolate mofetil (MMF) have proven benefit in key studies in SSc-ILD: Fibrosing Alveolitis in Scleroderma Trial (FAST), Scleroderma-Lung studies I, and II (SLS-I and SLS-II) [18–20]. The paucity of sustained benefit after CYC was discontinued in the SLS-I study provided an impetus to identify a less toxic, long-term strategy to stave off disease progression [21]. The SLS-II trial provided clinicians an equally efficacious treatment for SSc-ILD with MMF, in the absence of significant toxicity or long-term fertility concerns associated with CYC. Historically, these treatments have been reserved for patients with clinical or progressive ILD [22]; patients treated with these agents typically exhibited a significant burden of disease and were

[a]Scleroderma Program, Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA, [b]Department of Internal Medicine and Clinical Immunology, Rennes University Hospital and [c]Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail) - UMR_S 1085, Rennes, France

Correspondence to David Roofeh, Division of Rheumatology, Department of Internal Medicine, 300 North Ingalls St., Suite 7C13, Ann Arbor, MI 48109-5422, USA. Tel: +1 734 936 5561; fax: +1 734 936 3695; e-mail: davroofe@med.umich.edu

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KEY POINTS

- Treatment strategies range from close monitoring of pulmonary function to immunomodulatory/antifibrotic therapies to autologous stem cell and lung transplantations.
- Understanding, which therapy is appropriate involves staging disease severity, risk of progression/inflammatory parameters, burden of extra-pulmonary disease, and need for escalation therapy.
- Sub-classifying patients based on these factors may allow practitioners an opportunity to intervene before advanced fibrosis sets in and cannot be reversed.

treated with a goal to stabilize lung decline/attenuate disease progression.

Biologic disease-modifying antirheumatic drugs

Rituximab (RTX) is a chimeric monoclonal antibody targeting the B-cell-associated marker CD20 approved for the treatment of adult patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis among other indications [23]. RTX therapy has an increasingly substantive body of evidence to support its use for SSc-ILD [24,25]. An open-label, randomized, controlled trial with head-to-head comparison of RTX vs. monthly pulse IV CYC in a population of 60 early, treatment-naive, anti-SCL-70+, dcSSc-ILD patients examined the benefit of RTX on forced vital capacity percentage (FVC%) predicted as its primary endpoint. The average baseline FVC% in the RTX arm was 61.3 (±11.28), placebo arm 59.5 (±12.96). Patients in the CYC group received 500 mg/m^2 intravenous pulses every 4 weeks for 24 weeks; patients in the RTX group received two pulses of 1000 mg at 0 and 15 days. At the end of 6 months, the RTX arm had improved FVC% (improved, 61.3–67.5%) whereas the CYC arm did not (59.3–58.1%), $P = 0.002$ [24]. A meta-analysis of RTX's treatment effects (a total of 597 participants) on cutaneous (including 13 studies) and pulmonary (including 12 studies) outcomes showed long-term improvement in modified Rodnan skin score (mRSS) and stabilization of the FVC and diffusion capacity of carbon monoxide (DLco) [25]. A different meta-analysis of RTX's treatment effects (a total of 575 participants) focusing specifically on RTX's pulmonary (identifying 20 studies) found RTX was not just associated with stabilization but rather a significant improvement in FVC and DLco during the first year of treatment [26]. A recent prospective cohort study did not confirm RTX's pulmonary effect; a well designed randomized controlled trial is needed to properly explore the effects of RTX on lung involvement in SSc [27].

Tocilizumab (TCZ) is an anti-IL6 receptor monoclonal antibody, approved for the treatment of adult patients with rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis, among other indications [37]. Two large double-blind randomized control trials [(faSScinate study, NCT01532869) and (focuSSced study, NCT02453256)] examining TCZ failed to meet their primary endpoints, a reduction in the mRSS. Importantly, both met the key secondary endpoint on FVC% to support TCZ's use in patients with early SSc-ILD [28,29▪▪]. The faSScinate trial ($n = 87$) was a phase 2 trial in early (within 5 years from onset of the first non-Raynaud's phenomenon), diffuse cutaneous, skin-fibrosis progressive SSc patients with a primary endpoint focused on mRSS change [28]. The average baseline FVC (% predicted) in the TCZ arm was 80 (±14), placebo arm 82 (±13). Although the primary endpoint was not met, there was evidence of benefit in the study drug arm in secondary analyses showing fewer patients had a decline in FVC% predicted at 48 weeks compared with the placebo arm: TCZ reduced FVC% decline at 48 weeks: −2.6% (−5.2 to −0.1), compared with −6.3% (−8.9 to −3.8) in the placebo arm. The focuSSced phase 3 trial ($n = 210$) targeted a similar population of early diffuse cutaneous patients with mild baseline FVC% predicted deficits and clinical and biological signs of active inflammatory disease. No concomitant immunosuppressant was allowed at baseline and previous immunomodulating therapies had to be discontinued with an appropriate washout period. The average baseline FVC% predicted in the TCZ arm was 80 (±14), placebo arm 84 (±15). Secondary analyses showed preservation of lung function in the treatment arm compared with the significant worsening seen in the placebo arm: −0.6% (−2.4 to 0.9) in the TCZ arm, compared with −3.9% (−4.8 to −1.6) in the placebo arm. Among the intention-to-treat population and those with SSc-ILD (as determined by a thoracic radiologist's visual read), the TCZ arm demonstrated preserved FVC over 48 weeks, whereas the placebo arm demonstrated a decline: the least squared means (LSM) of FVC change was −0.1% for TCZ, and −6.3% for placebo. The difference between treatment group was 6.2% ($P < 0.0001$). This preservation was seen in those patients ranging from mild-to-severe extent of lung involvement (quantitative ILD, or QILD) and lung fibrosis (quantitative lung fibrosis, or QLF). Importantly, TCZ demonstrated its benefit using quantitative high-resolution chest computerized

tomography (HRCT): at 48 weeks, the overall QILD for the TCZ arm showed a statistically significant improvement [mean change (95% confidence interval; CI) −1.8 (−3.5 to −0.2), $P = 0.02$]. In terms of fibrosis, there was a statistically significant increase in QLF scores at 48 weeks in the PBO arm [0.7 (0.3–1.1), $P < 0.01$] that was not seen in the TCZ arm [−0.5 (−1.1 to 0.2), $P = 0.12$] [30▪].

RTX and TCZ present important additions to cytotoxic therapy options for SSc-ILD. The TCZ was recently approved by the United States Food and Drug Administration (FDA) for management for SSc-ILD and the data represent an important option to initiate therapy in early ILD and prevent decline of lung function before it happens, rather than waiting until patients show clinical symptoms and a functional decline to initiate cytotoxic therapy.

Antifibrotics

Nintedanib (NIN) is a tyrosine kinase inhibitor approved for use in idiopathic pulmonary fibrosis (IPF) by the US FDA in 2014, and the European Medicines Agency in 2015 [31]. This medication stops intracellular signalling by competitively binding to ATP-binding pockets of receptors (PDGF receptor alpha and beta, FGF receptor 1–3, and VEGF receptor 1–3). It prevents the release of growth factors that would lead to fibrotic consequences, with demonstration of benefit *in vitro* and *in vivo* [32,33] NIN became the first FDA medication approved for SSc-ILD in 2019. The Safety and Efficacy of NIN in Systemic Sclerosis (SENSCIS) trial was a 52-week randomized double-blind, placebo-controlled trial of patients with SSC-ILD, with a minimum of 10% of lung involvement as determined by HRCT [34]. The NIN arm was 150 mg twice daily ($N = 288$) compared with a placebo arm ($N = 288$), in a population of patients with an average baseline FVC% predicted in the NIN arm of 72.4 (±16.8), and placebo arm 72.7 (±16.6). At 52-week follow-up, NIN demonstrated a statistically significant reduction in the annual rate of decline of FVC in the treatment arm [−52.4 ml (−1.4%), compared with −93.3 ml (−2.6%) in the placebo arm]. The adjusted mean annual rate of decline in FVC% predicted was −1.4% (±0.4) in the NIN arm and −2.6% (±0.4) in the placebo arm (difference 1.2; 95% CI 0.1–2.2). There was no effect of NIN on skin score and respiratory and other patient-reported outcomes [34].

The safety and tolerability of the antifibrotic medication pirfenidone (PFD) were assessed in a multinational, open-label, randomized, parallel-group, 16-week phase 2 study in patients with SSc-ILD (the LOTUSS trial) [35]. All patients received PFD and were randomized 1 : 1 to either a 2-week or 4-week titration period. No safety or tolerability signal was detected in this pilot study, notably in patients with concomitant use of MMF (63.5% of the population). Scleroderma Lung Study-III (SLS-III) (clinical trials.gov: NCT03221257) is thus examining the combination of MMF and PFD in SSc-ILD. It will examine efficacy with the primary endpoint of change in FVC% predicted over 18 months; secondary endpoints include change in DLco% predicted, mRSS, the extent of fibrosis and total ILD on HRCT, and patient-reported outcomes [36].

Hematopoietic autologous stem cell transplantation

In the last decade, three key trials have examined the use of autologous hematopoietic stem cell transplantation (ASCT) for treatment of SSc-ILD: Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial (ASSIST), Autologous Stem Cell Transplantation International Scleroderma (ASTIS), and Scleroderma Cyclophosphamide or Transplantation (SCOT) studies [37–39]. These interventions are the only treatments listed here with demonstrated survival benefit, although the modest benefits noted in the other trials may be framed in the context of a limited window of observation (1 year), as compared with the transplant trials (several years). In the ASTIS trial, despite early treatment-related mortality (10.1%) and an increase in serious adverse events, the transplant arm demonstrated a long-term survival benefit at year 1, year 2, and year 4. In the SCOT trial, survival at 54 months posttreatment showed 91% of transplant patients were alive, compared with 77% of the comparator arm of monthly CYC.

The SCOT trial was a multicenter, randomized phase 3 trial including 75 patients with early dcSSc; 100% of patients in the HSCT group had ILD. HSCT patients ($n = 36$) were conditioned with CYC (120 mg/kg), antithymocyte globulin, received total body irradiation (800 cGy) and received a stem cell transplant (CD34þ selected); the comparator arm received CYC (750 mg/m^2) ×12 months ($n = 39$). At baseline, the two groups had similar FVC% predicted averages: 74.5% (±14.8) in the ASCT arm compared with 73.8 (±17) in the CYC arm. More patients receiving ASCT improved in FVC than those in the CYC group at 54 months: 36% of the ASCT patients improved (relative increase of FVC by ≥10%) compared with 23% of the CYC patients. Conversely, fewer patients in the ASCT group worsened (relative decrease by ≥10%) compared with the CYC group (17 vs. 41%, respectively) [39]. The percentage of patients who had an adverse event of grade 3 or more was higher in the ASCT group than

in the CYC group suggesting that careful patient selection and monitoring is needed for ASCT.

Lung transplantation

Analysis of survival or chronic lung allograft dysfunction (CLAD) in carefully selected patients with SSc-ILD highlights that SSc-patients undergoing lung transplantation have short-term and long-term mortality comparable to other ILD-groups (predominantly including patients with IPF) as well as similar freedom from CLAD duration [17,40,41]. These data suggest that lung transplantation may be considered for specific SSc-ILD patients with nonsevere extrapulmonary disease but severe clinical SSc-ILD refractory to first-line therapy, although controlled studies are still lacking.

FRAMEWORK FOR TREATMENT

In our practice, treatment algorithms are based on data from clinical trials and expert opinion [12]. We recommend stratifying treatment based on disease severity (subclinical vs. clinical ILD) and tailoring therapy in the context of a patient's risk of developing progressive SSc-ILD and the severity/extent of extra pulmonary disease (e.g. lung predominant vs. multiorgan involvement). Figure 1 outlines a recommended treatment strategy based on this approach. The overall strategy aims to identify patients as early as possible in the course of SSc-ILD, prevent symptomatic disease whenever possible, and retard progression if already present.

No standardized definitions of clinical ILD exist at this time. It may be conceptualized as a disease

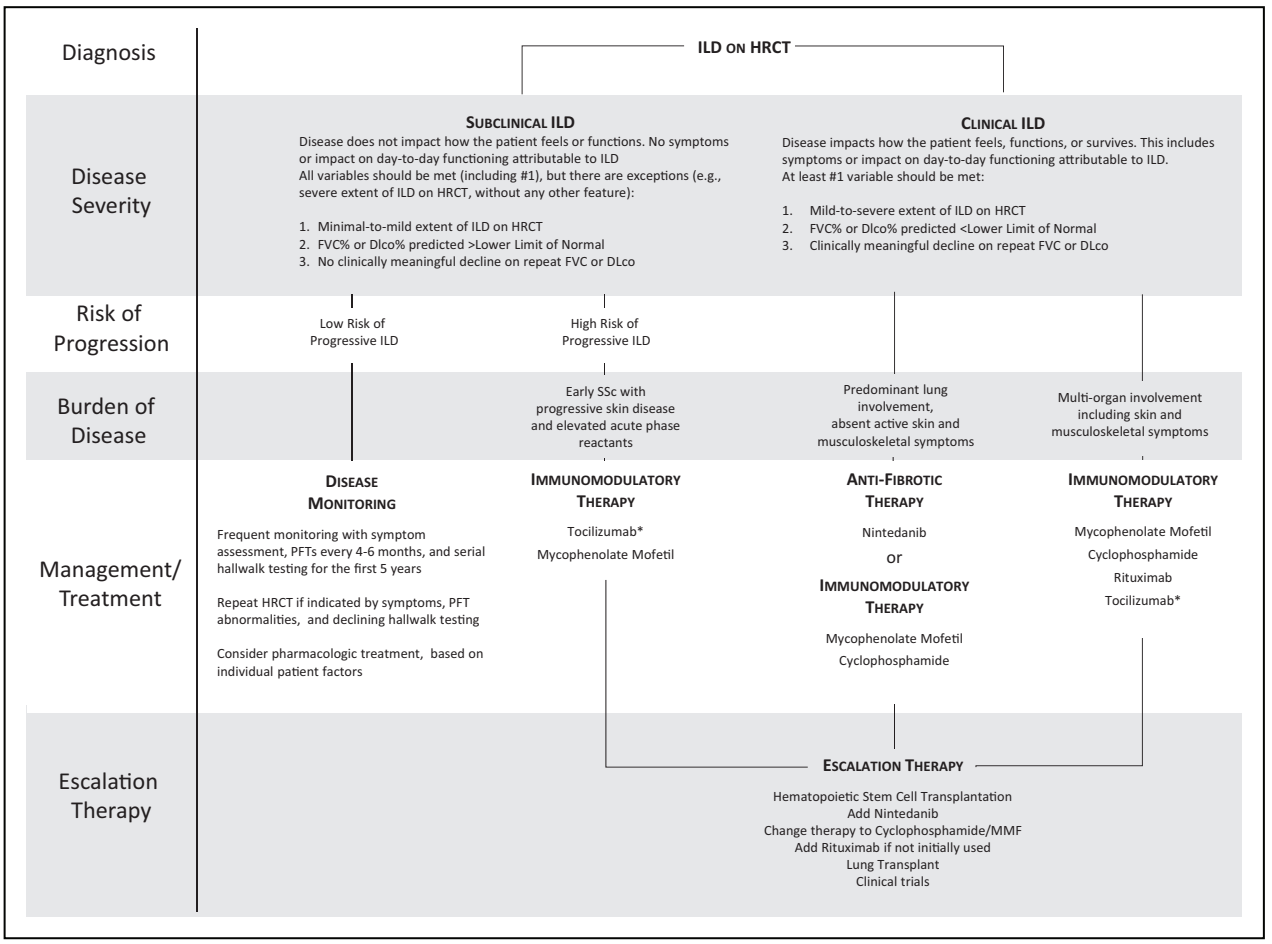

FIGURE 1. Treatment algorithm for systemic sclerosis-interstitial lung disease based on evidence-based recommendations and expert opinion/unpublished clinical experiences. Modified from the EULAR Online Course on Systemic Sclerosis, In depth discussion Module 9 (Management of SSc-ILD), updated 2020. *In those with early SSc with progressive skin and elevated acute phase reactants. Clinically meaningful change: if greater than one PFT available, a clinically meaningful decline is defined as FVC levels of more than 10% from baseline or decline in FVC greater than 5% to less than 10% and more than 15% relative decline in DLco. Testing acronyms: DLco%, diffusion capacity of carbon monoxide percentage predicted; FVC%, forced vital capacity percentage predicted; HRCT, high-resolution chest computerized tomography; PFT, pulmonary function testing. Disease acronyms: dcSSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease.

state that affects how a patient feels, functions, or survives, in the setting of mild-to-severe extent of ILD on HRCT. These patients have symptomatic SSc-ILD (e.g. cough or dyspnea attributed to the ILD) or impact on day-to-day functioning, although significant arthritis and other disease features may preclude exertion, making this a challenging disease feature to reliably identify. These patients may show impairment on spirometry and DLco (below the lower limit of normal, and/or a clinically meaningful decline in FVC% or DLco%), and may show desaturation during cardiopulmonary exercise testing [42]. Subclinical ILD may be characterized by minimal-to-mild extent of ILD on HRCT in the setting of absent SSc-ILD symptoms or impact on day-to-day functioning, FVC% and DLco% above the lower limit of normal, and without clinically meaningful declines within the previous 12 months [43]. There are several risk factors for developing SSc-ILD including demographics (African American ethnicity, older age at disease onset, male sex) and disease-specific features (short disease duration, presence of anti-SCL 70 antibody or RNA polymerase III and/or absence of anticentromere antibody) [44–47]. Elevated C-reactive protein (CRP) represents an important serological marker associated with progressive ILD and has been demonstrated in dcSSc to be predictive of severe disease worsening (including new-onset internal organ involvement and death) [48,49]. The Goh staging algorithm [50] provides a prognostic risk stratification by combining pulmonary function testing (PFT) and extent of ILD on HRCT. Progressive ILD is worsening in terms of disease severity, identified by an expanding extent of fibrosis on HRCT and deficits in FVC and DLco. An advancing HRCT extent [>20% involvement on HRCT (fibrosis/ground-glass opacifications on transverse cuts)] and impaired PFT (%FVC <70%), or those with significant declines in the preceding 12-months FVC (% >10% or FVC >5% to <10% with >15% decline in DLco) have demonstrated correlates with morbidity and mortality [50–52].

All patients with SSc during their initial visit should receive an HRCT, even in the absence of respiratory symptoms [53]. Preclinical interstitial abnormalities present in this high-risk population [54] allows for risk stratification in Fig. 1. For those meeting the above definition of subclinical ILD with low risk of progression (e.g. mild extent of disease on HRCT, no elevation in CRP, anticentromere antibody positivity), we recommend frequent monitoring of respiratory symptoms, with routine PFTs every 4–6 months and serial 6 min walk distance (6MWD) assessments for the first 3–5 years following their first non-Raynaud''s phenomenon [1]. Deficits on PFTs should be interpreted in the context of symptoms and concomitant electrocardiogram and echocardiography, as well as alternative causes for restrictive lung disease (such as inflammatory myopathy) and declining DLco (such as pulmonary SSc-associated vasculopathy). A repeat HRCT should be performed if the PFT deficits and advancing respiratory symptoms are suspected to be because of advancing parenchymal lung disease [43].

Patients with early and subclinical ILD with other risk factors (e.g. dcSSc, elevated CRP, or anti-SCL-70 positivity) should be considered for immunomodulatory treatment. TCZ is supported by data from two RCTs and is now FDA-approved. Currently, we utilize MMF in this scenario but TCZ is now available for this indication. Patients with early clinical SSc-ILD with risk factors above should also be offered have TCZ. Those with clinical ILD in whom active skin or musculoskeletal symptoms are absent (a small subset in clinical centers) can be considered for NIN monotherapy. Gastrointestinal upset is a common side effect and may lead to discontinuation of treatment [32]. In our practice, we typically offer induction therapy with CYC or MMF, with preference for MMF given its favourable side effect profile relative to CYC, and the ability to transition to mycophenolic acid for those unable to tolerate gastrointestinal side effects. About half of the patients in the SENSCIS trial were on background MMF; these patients tend to benefit from combination therapy with a decreased decline in FVC (−40.2 ml/year) compared with those on NIN monotherapy (−63.9 ml/year). Nonetheless, at present, there are insufficient data to discern if upfront combination therapy (MMF + NIN) is more efficacious than monotherapy.

For patients with clinical SSc-ILD and active skin or musculoskeletal disease, we prescribe CYC, MMF, RTX, or TCZ with preference given to MMF because of its demonstrated benefit for SSc-ILD, skin, and favorable side effect profile [20,55]. TCZ, with recent approval may be an appropriate indication for this. If MMF is unavailable or cannot be tolerated, CYC provides an option with well established efficacy, based on data from two well designed clinical trials. The use of intravenous CYC compared with oral CYC has not demonstrated that one route is superior; intravenous CYC is associated with a favorable side effect profile and decreased long-term side effects (e.g. ovarian dysfunction, risk of malignancy) with a lower total cumulative dose [56]. Whenever implemented, we recommend intravenous CYC use consistent with the SCOT trial (intravenous CYC 750 mg/m^2 monthly) typically for 6 months, followed by transition to MMF therapy, assuming normal renal and hepatic function. Considerations for

fertility and hormone preservation in premenopausal women, concomitant liver or renal insufficiency, and inflammatory arthritis may favor use of RTX or TCZ over MMF and CYC as initial therapy. Concerns for medical nonadherence with oral medication may make intravenous CYC or RTX an attractive option.

Refractory and progressive SSc-ILD represents a considerable challenge in management. Evidence-based decisions regarding management of treatment-refractory patients are limited and recommendations are based on expert opinion. For those patients who have failed MMF, we often consider therapy with CYC [57] or RTX [58]. A recently published case series identified 24 SSc-ILD patients with progressive disease despite MMF treatment (relative decline of $\geq$10% in the FVC% or $\geq$15% in the DLco%, or a relative decline FVC% of 5–10% or DLco% decline of $<$15% alongside worsening of respiratory symptoms and increased fibrosis on HRCT). After 1 year of treatment with RTX (1000 mg/dose, divided by 14 days, administered every 6 months), there was a significant improvement in FVC% (+8.8%, 95% CI −13.7 to −3.9; $P=0.001$) and DLco% (+4.6%, 95% CI −8.2 to −0.8; $P=0.018$) [58]. The results of this retrospective observational study needs to be evaluated in a randomized, placebo-controlled trial before a stronger recommendation may be made for its use. For those with severe, refractory multisystemic disease with sufficient renal and cardiac reserve to tolerate transplantation, ASCT should be considered. Although once thought to be a contraindication for lung transplant because of extrapulmonary comorbidities, several studies have demonstrated posttransplant survival rates in SSc similar to other indications for transplant [40,41]. Enrollment of SSc-ILD participants in clinical treatment trials may provide an option for investigational use of medications not yet approved by the FDA, for appropriate patients.

CASE SCENARIOS

Case scenario 1: subclinical systemic sclerosis-associated interstitial lung disease with high risk for progressive disease

Fifty-year-old man presents with a new diagnosis of dcSSc. His symptoms of puffy hands started 2 years ago. He does not report dyspnea at rest or with exertion. The physical examination shows an mRSS of 18/51. Bloodwork shows a positive anti-SCL-70 antibody; CRP is elevated at 1.4 mg/dl (upper limit of normal $<$0.6 mg/dl). Spirometry shows a normal total lung capacity, a FVC% of 88% and a DLco of 80%; HRCT shows mild ILD (visual read estimates 5% whole lung involvement).

This patient may be classified as subclinical SSc-ILD given the absence of respiratory symptoms, mild extent of involvement on HRCT, and normal FVC% and DLco% (Fig. 1). He is considered high risk for progression given his dcSSC status, anti-SCL-70 antibody positivity, and elevated CRP. A potential misstep is the failure to recognize the risk of advancing lung disease in this SSc-ILD subset. Disease monitoring alone would be inappropriate given his high risk for progression. Taking into account the cutaneous disease and the risk for irreversible lung function loss, at this time the data support the initiation of TCZ to prevent decline of FVC% (with a strength of recommendation coming from at least one randomized controlled trial and level of evidence based on two RCTs with positive secondary or exploratory endpoint and large effect size) [29▪▪,59]. Other immunomodulatory therapies may also be an option, including consideration for MMF or ASCT; at this time, those treatments would not be indicated based on lack of available clinical trial data.

Case scenario 2: clinical systemic sclerosis-associated interstitial lung disease

Twenty-eight-year-old women presents with lcSSc and an onset of sclerodactyly 3 years ago. Over the last 6 months, she has developed shortness of breath with moderate exertion. Her physical examination shows crackles at bilateral bases independent of positioning and an mRSS of 5/51. There is no jugular venous pressure increase, prominent P2 on auscultation, or lower extremity swelling/edema; there are telangiectasias about the face and hands. She is anticentromere antibody-positive; NT-proBNP is normal, as is uric acid. She has restrictive lung disease with a total lung capacity of 70%, FVC% of 66%, and DLco% of 55%. Her HRCT shows interstitial markings that persist on prone imaging and is read as nonspecific interstitial pneumonia (NSIP) pneumonitis.

This patient has clinical ILD based on dyspnea on exertion that may be attributed to symptomatic ILD, restrictive lung disease, and lung fibrosis. Monitoring with no pharmacotherapy is inappropriate, given the burden of her disease and the opportunity to attenuate progression of lung decline. Patients with clinical ILD should be initiated on an immunomodulatory agent, antifibrotic, or both. MMF at 3 g/day in divided dosing (1500 mg every 12 h) is a reasonable choice based on the SLS-II data, noting the need for routine lab monitoring and reliable contraception, given the risk for teratogenicity with this medication. NIN is another reasonable choice

for this patient based on the SENSCIS trial findings in patients with SSc-ILD, at 150 mg every 12 h, also confirming reliable contraception as this medication can cause risk to the fetus if she were to become pregnant. The determination of which agent is initiated may depend on institutional experience and preference, side effect profiles and patient tolerability, and insurance coverage/cost: our preference is to use MMF as the initial agent to target the underlying immune dysfunction. Combination therapy (immunosuppression with MMF and antifibrotic therapy with NIN) is supported by data in terms of safety but there are insufficient data to know if initial combination therapy or step-up therapy should be implemented for routine practice in treating SSc-ILD [60]. In this treatment-naive patient, lung transplantation would not be the first step in her management.

Case scenario 3: rapidly progressive systemic sclerosis-associated interstitial lung disease

A 50-year-old woman is diagnosed with NSIP pattern SSc-ILD: she has rapidly progressive dcSSc, no scleroderma-specific autoantibodies, and an estimated onset of disease within the last 2 years. Examination shows an mRSS escalation from 12 to 31 in that time period. Renal and cardiac function is unimpaired; she was noted to have elevated platelet levels developing over the last 2 years. Serial spirometry with DLco shows a decline in FVC% by 15% and DLco of 20% over a year despite MMF 3 g/day with excellent adherence for the last year. HRCT provides an estimate of 25% whole lung involvement.

This patient clearly has progressive SSc-ILD, alongside progressive cutaneous disease. ASCT is currently the only disease-modifying strategy that has demonstrated evidence for improving long-term survival [16]. This is reserved for those with early rapidly progressive dcSSc who have yet to progress to severe internal organ involvement but have a poor prognosis for survival despite adequate therapy. Benefits of treatment in this population also include improved skin scores, FVC, extent of fibrosis on HRCT, and physical and mental health-related quality of life [38,39,61]. Other considerations for her include switching therapy to CYC or RTX, or adding in RTX to MMF [12]. Tocilizumab may be appropriate for this patient given recently published data showing TCZ stabilizes FVC and attenuates progression of the extent of lung involvement over 48 weeks [30▪]. Her clinical scenario is similar to a section of the focuSSced population with early dcSSc, progressive skin disease, elevated acute phase reactants (including elevated CRP and platelet levels), and clinically significant SSc-ILD: about one-third of participants in this trial had a severe extent of lung involvement on HRCT (≥20%) and deficits on FVC [30▪]. Importantly, the medication was shown to be effective in preserving lung function across a broad extent of lung involvement on HRCT (≥5% to >20%). Tocilizumab's use in treatment-refractory cases or in addition to MMF has not been studied. An option like NIN may benefit lung disease but will have no effect on skin progression. There are no data to support adding corticosteroid treatment for fibrotic NSIP, the predominant disease type of SSc-ILD. Escalation therapy may include a clinical trial but not prior to considering other, established therapies.

Case scenario 4: alternative considerations for advancing dyspnea in systemic sclerosis-associated interstitial lung disease

A 60-year-old woman was diagnosed with dcSSc 15 years ago; she has no scleroderma-specific antibodies and NSIP pattern SSc-ILD. She had routine spirometry with DLco for the first 10 years, showing FVC% ranging from 72 to 77%, and DLco% ranging from 68 to 78%, with testing every 6 months. Previous treatment included oral CYC for the first year of disease. She was lost to follow-up for the last 5 years and presents to your office on no immunomodulatory therapy. In the last 6 months, she reports advancing dyspnea with mild exertion and a persistent dry cough. Her examination shows telangiectasias on her face and hands; her mRSS is 5/51. EKG shows the presence of right axis deviation and echocardiogram shows a right ventricular systolic pressure of 45 mmHg. Serum urate and NT-proBNP are elevated above the upper limit of normal. Repeat testing shows FVC% declining to 60%, DLco declining to 35%.

This case highlights the need to identify the several potential causes of FVC% and DLco% decline, which may coincide with the presence of SSc-ILD. Progressive shortness of breath may not be due directly to advancing SSc-ILD and failure to identify alternative causes of dyspnea may lead to incomplete or inappropriate management. Measurement inaccuracy should always be considered and ruled out with repeat testing, especially if the spirometry and gas exchange decline do not coincide with reports of development or progression of dyspnea. A repeat set of pulmonary testing should be conducted making sure accuracy and reliability meet the American Thoracic Society standards [62] and corroborated with ancillary testing like the 6MWD. Late-onset progressive ILD is possible but not the most likely cause of her progressive dyspnea with spirometry and gas exchange decline. SSc-ILD

will typically show progression in the first 3–5 years from the onset of the first non-Raynaud's phenomenon; in this patient's case, she is 15 years from the onset of her disease. Aspiration pneumonitis results from uncontrolled esophageal reflux disease; occult aspiration is suspected to be a contributing factor in SSc-ILD [63,64]. An HRCT will be important to provide insight into her disease, as specific CT findings are useful in differentiating the cause of radiographic changes associated with FVC and DLco changes [65]. Pulmonary hypertension may cause progressive dyspnea and decline in spirometry and DLco [66]. The DETECT algorithm is an evidence-based screening method to detect pulmonary arterial hypertension in patients with SSc [67]. This suspicion should be carefully investigated to determine the underlying cause: group 1 (pulmonary arterial hypertension), group 2 (pulmonary hypertension related to left-heart disease), group 3 (pulmonary hypertension related to chronic hypoxia), or a combination of the three. A right heart catheterization, along with degree of ILD on HRCT, must be performed to distinguish amongst these possibilities. Finally, scleroderma-associated myopathy may be seen in 13–25% of patients with SSc [68] and progressive disease can produce a restrictive lung disease physiology. This is usually common in early disease but should be part of the differential diagnosis. The work-up includes evaluation of biochemical muscle breakdown products, electromyogram and nerve conduction study, as well as maximal inspiratory and expiratory pressures to assess diaphragm weakness.

CONCLUSION

The clinical course of SSc-ILD is variable [11,69]. Early identification to risk stratify, monitor progression, and intervene whenever necessary is critical in improving our management of this potentially deadly complication of SSc. Features important in risk stratification include patient demographics, SSc-specific features like skin distribution and disease duration, serological markers, PFT, and extent of lung disease on HRCT. The clinical scenarios presented here provide examples of how we approach these cases but should not be interpreted as strict guidelines for management. Personalized medicine may become a reality for these patients as our ability to predict, which patients are likely to progress improves alongside the development of less toxic, more specific targeted therapies. Advances in understanding the pathophysiology of this disease has led to targeted biologic therapies, which allow for a favorable benefit/risk ratio, which may allow intervention prior to a state where advanced fibrosis has set in and cannot be reversed. At this time, stem cell therapy remains the only intervention with proven survival benefit but is appropriate only for a narrow province of patients with clinical SSc-ILD.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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Practical management strategies for benign hypermobility syndromes

Deeba Minhas

Purpose of review
Patients with symptomatic hypermobility syndrome such as hypermobile Ehlers-Danlos syndromes (hEDS) and hypermobility spectrum disorders (HSD) commonly present to rheumatologists with joint pain and functional disability. Providers often have difficulty with diagnosis due to a lack of knowledge on the range of associated manifestations and the available therapeutic modalities. This review will discuss recent updates on diagnostic measures and treatment options for rheumatologists to help patients navigate hEDS/HSD.

Recent findings
This article describes newer diagnostic measures and assessment of hEDS/HSD manifestations. Evidence supporting physical therapy and occupational therapy is provided, as well as recent updates on assistive devices, compressive garments, orthoses, and surgical interventions. Given patient heterogeneity specific guidance about the amount and type of therapies required to produce a beneficial effect is lacking. Treatment should be individualized, and many of the studies focus on regional joint complaints rather than a whole-body approach.

Summary
Physical therapy and occupational therapy remain the cornerstone of treatment.

Keywords
Ehlers-Danlos syndrome, heritable disorders of connective tissue, hypermobility spectrum disorders, joint hypermobility

HYPERMOBILE EHLERS-DANLOS SYNDROMES (hEDS) AND HYPERMOBILITY SPECTRUM DISORDERS (HSD)

Joint hypermobility (JH) is the ability to move beyond a joint's normal range of motion and is fairly common in the general population, with a prevalence ranging between 10 and 40% [1]. It is also a key characteristic of the Ehlers-Danlos syndromes (EDS) [2], a group of heritable connective tissue disorders characterized by abnormal collagen synthesis [2]. The 2017 EDS classification criteria identify with 13 subtypes, with proposed autosomal dominant inheritance and most with confirmatory genetic testing. The most common subtype is Hypermobile EDS (hEDS). The new criteria for hEDS are more rigorous in the recent nosology; providing a more homogenous population to aid in future research trials and identifying underlying genetics. Patients with symptomatic JH that do not meet the criteria for hEDS are given the diagnosis of hypermobility spectrum disorders (HSDs) [3]. There is considerable variability within the spectrum and the degree of hypermobility does not predict the degree of disability.

MECHANISMS, SYMPTOMS, AND CO-MORBIDITIES

Joint stability is determined by passive (ligaments, tendons), active (muscles), and neural subsystems. hEDS/HSD is defined by a disruption in the passive subsystem, with ligamentous laxity, predisposing the joint to subluxations and dislocations. The large

Department of Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence to Deeba Minhas, Clinical Lecturer, Department of Internal Medicine, Division of Rheumatology, University of Michigan, 300 North Ingalls Building Ann Arbor, Michigan 48109-5422, USA. Tel: +734 936 5566; fax: +734 763 1253; e-mail: minhasde@med.umich.edu

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KEY POINTS

- Patients with hEDS/HSD are frequently referred to rheumatology with joint pain and other co-morbidities but are underdiagnosed.
- New diagnostic methods are being studied, and quantitative measures of tissue mechanics could provide objective tools for the diagnosis of hEDS/HSD, further validation is needed.
- Physical therapy and occupational therapy remain the cornerstone of treatment.

muscles responsible for functional movement compensate by tensing, trying to provide stabilization while also being responsible for movement. The stabilizer muscle complexes, such as the rotator cuff, spinal multifidus, and deep hip complexes, are by comparison much smaller. They are particularly likely to atrophy quickly if they are not engaged. The resulting imbalance of the active subsystem predisposes to altered biomechanics of joints at other body sites, muscle spasms, tears, pain, and fatigue. It can also alter the neural subsystem leading to proprioceptive and balance deficits [2].

Patient presentations are very heterogeneous, ranging from minimal joint symptoms to joint instability, subluxations, dislocations, recurring sprains, strains, and multiple co-morbidities.

Gastrointestinal

hEDS/HSDs can frequently be associated with increased gastric dysmotility [4]; functional abdominal disorders are predominant [5]. A recent case-control study reported significantly higher proportion of gastrointestinal drug prescription claims among persons with EDS compared to matched controls: at least one gastrointestinal drug group (38.6% vs 16.4%), irritable bowel syndrome (IBS) drugs (16.0% vs. 6.8%), acid suppressants (23.4% vs. 8.8%), antiemetic/prokinetic drugs (16.7% vs. 4.9%) [6]. Patients with JH and IBS have shown significant improvement on a low fermentable oligo-,di-monosaccharides, and polyols (FODMAP) diet, even more so than those with IBS alone [7▪▪].

Gynecologic

Women with hEDS/HSD experience menstrual cramps, heavy menstrual bleeding [8], pelvic girdle pain especially during pregnancy [9] increased risk of hemorrhage and perineal tearing during delivery [10] and pelvic prolapses [10]. Pelvic girdle pain responds to physical therapy, [9] assistive devices such as pelvic belts and crutches may be helpful [11]. As these gynecologic symptoms can severely impact wellbeing, a multidisciplinary approach with ObGyn should be taken.

Dysautonomia

In an observational study of 102 hEDS/HSD patients, postural orthostatic hypotension syndrome, orthostatic intolerance (OI), and hypotension were frequently seen [12]. Increasing fluid and salt intake, avoiding caffeine and alcohol, keeping feet elevated, and wearing support hose are ways can be helpful. The Levine and Dallas/CHOPS Protocol are exercise-based physical therapy regimens that include close kinetic chain exercises that start in a horizontal position and then slowly work up to a vertical position. It includes heart rate variability training and increasing stabilizer strength.

Bone health

Patients with hEDS have increased fracture risk, and smaller cortical bone area thickness, but normal bone/muscle area ratio when compared to healthy controls [13]. As patients with hEDS/HSD have altered muscle-tendon properties, the reduced muscle strength, recurrent injuries, and decreased physical activity result in unfavorable bone properties [13].

Pain

Patients with HSD have higher levels of centralized pain. Leone *et al.* demonstrated a deficit of the descending inhibitory pain control [14]. Fearing dislocations or falls due to impaired balance, many patients develop kinesiophobia leading to worsening deconditioning, and physical and emotional outcomes [15]. Despite the prevalence of hEDS/HSD, there are significant diagnostic delays, and patients note an overall lack of awareness of this disorder among healthcare professionals [16].

DIAGNOSING AND ASSESSING HYPERMOBILITY

The Beighton Scoring system has been traditionally used to assess hEDS/HSD as it can easily be performed in the clinic, and has high inter-rater reliability [17]. However, there are limitations because it does not include many of the commonly affected joints such as the shoulders and hips. The Beighton score decreases with age and varies widely on gender, training, and racial background [18▪].

By the time patients present to a rheumatology clinic with joint pain, they may have decreased joint range of motion due to the various body adaptation and compensation methods as well as deconditioning, leading to muscle loss. Unfortunately, despite the reduction in the degree of their hypermobility, patients may have worsening of their co-morbidities. The five-item Hakim and Grahame questionnaire [1] can be a useful screening tool as it queries current and past symptoms with a 'yes' to two or more of these questions suggesting hypermobility with a sensitivity of 85% and specificity of 90% [1].

The above measures rely on the assessment of joint range of motion that may be influenced by other factors rather than assessing the elasticity of connective tissue that is the underlying defect. A recent systematic review evaluated a range of quantitative measures of tissue mechanics, including diagnostic ultrasound, to see if it could discriminate between hEDS/HSD and healthy tissues. Overall, three of the four studies found that at least one measure of tissue mechanics distinguished between people with hEDS/HSD and healthy controls, including tissue stiffness, extensibility or elasticity of muscle, tendon, connective tissue, or skin [19].

Recently, the Bristol Impact of Hypermobility questionnaire was tested and found to have known-group validity in distinguishing patients with and without JH. Patients, clinicians and researchers created a template of 55 scored items assessing a wide range of impairments, activity limitations, and participation restrictions, including items such as joint pain, fatigue, joint instability, and the effects on activity [20].

MANAGEMENT

Although there is a lack of high-quality evidence to guide specific recommendations, successful management often requires a multidisciplinary approach. Treatment plans should be personalized based on each patients' unique presentation. Physical therapy and occupational therapy are considered the cornerstone of management. This may be combined with assistive devices, pharmacotherapy, and occasionally procedures.

EDUCATIONAL, EXERCISE, AND SELF-MANAGEMENT PROGRAMS

Goals of physical rehabilitation include core stabilization, instruction of proper joint awareness and movement, proprioception enhancing exercises and creating a lifelong general fitness program [21]. Neuromuscular re-training is useful for correcting imbalances and proprioception deficits caused by muscular tension and the compensatory mechanisms by activating stabilizer muscle groups and relaxing dominant overactive muscle [18▪]. Techniques that are useful include manual therapy such as visceral manipulation with muscle release [22].

A systemic review by Palmer *et al.* [23] found in separate trials that inspiratory muscle training [24], spinal stabilization exercises [25], and a combined exercise program (closed kinetic chain exercises and proprioception exercises) [26] all displayed effectiveness from pre to posttreatment. However, no clear recommendations could be made about the superiority of particular types of conservative interventions over others, and further robust randomized controlled trial evidence is needed [23].

In a recent study by Chaleat-Valayer *et al.*, a patient education program and EDS (PrEduSED) had high satisfaction and significantly improve knowledge about the disease, pain management, reduced fatigue, and episodes of instability through learning adaptive skills [27].

Paxton *et al.* reported that group-based physiotherapy intervention consisting of four sessions focusing on patient education, exercises, and lifestyle advice was well received. Patients found meeting others with similar concerns to be valuable, and all patients reported actively implementing advice, exercises, and techniques into their lifestyle [28].

REGIONAL MANAGEMENT

Spine

Excessive cervical ligamentous laxity forces the muscles of the neck and upper back to contract almost continuously to provide head and neck stabilization. This can lead to muscle strain, spasm, migraine, daily persistent headache, temporomandibular joint dysfunction, and cervicogenic (postural related) headaches [18▪]. A recent large multidisciplinary retrospective study of patients with hEDS/HSD, Malhotra *et al.* found that 66% reported head or neck symptoms, and 53% reporting both [29]. Cervical spondylosis was reported by 61% of patients. Of these, 59% who underwent cervical facet interventional procedures noted improvement [29].

Hip

The hips are one of the most common areas affected by hypermobility. Commonly characterized by subluxations, dislocations, snapping hip syndrome. hEDS/HSD patients pose a management challenge with limited medical options and surgical options complicated by soft tissue laxity.

Patients with EDS are noted to have altered neuromuscular activation during gait with higher levels of rectus femoris and tensor fascia latae activation. This likely compensates for the tight hip flexors and weak abductors impairing the ability to stabilize forward stride during walking [30].

Prolonged gluteus medius activation, which is the primary mover of the hip, was noted. Delayed vastus medialis and lateralis activation thought to be due to impaired proprioception during the loading phase of gait [30].

Guier *et al.* evaluated the clinical outcomes and complications of patients with EDS undergoing total hip arthroplasty (THA) for OA. Patients with EDS had significant improvements in their Harris Hip Scores, similar to matched controls [31]. There was no significant difference in postop wound complications or infections. There was a higher dislocation rate in patients with EDS (15.4%) than in controls (5.1%), this observation appears to be meaningful even though it fails to reach statistical significance [31].

The degree of hip instability presents a very difficult problem, and patients' expectations regarding outcomes must be carefully managed [32].

SHOULDER

Patients with hEDS/HSD frequently experience multidimensional instability (MDI). MDI leads to an impaired shoulder function and altered shoulder kinematics including excessive humeral head translations (HHT) leading to subluxation, dislocation, and pain.

An ultrasound study measuring the acromiohumeral and humeral glenoid distance found that during isometric shoulder extension, flexion, and elbow extension, significant superior translation was observed. During isometric external rotation and dumbbell loading, significant inferior translation was observed [33]. This is helpful in tailoring rehabilitation as the rotator cuff muscles function as stabilizers by limiting excessive HHT in the anterior-posterior direction. The deltoid is responsible for superior-inferior stability and supporting the hesitation many clinicians have on using heavy strengthening during rehabilitation.

Liaghat *et al.* conducted a recent feasibility study of 12 adults with HSD/hEDS with shoulder complaints to challenge the general assumption that heavy strengthening should be avoided. They found patients could safely complete a 16-week progressive heavy shoulder strengthening program with clinical benefits in self-reported shoulder function and objective measurements [34].

In an RCT they will be testing the effectiveness of a 16-week progressive heavy shoulder strengthening program and general advice (HEAVY) compared with low-load training and general advice (LIGHT) measuring self-reported shoulder symptoms function and quality of life with 100 hEDS/HSD patients [35▪].

Compressive garments have been found to be effective in VETCOSED (VETements COmpressifs pour le syndrome d'Ehlers Danlos), promoting the expression of shoulder stabilizers [36▪]. During 4 weeks of wearing a compressive CICATREX jacket, increased power in shoulder rotators, mainly observed in external rotators and significant at high speed (180/s), significantly improved shoulder stability and trend to decreased pain in patients with hEDS [36▪]. Increasing external rotators power and strength stabilizes the scapula and gives a fixed point for the use of the shoulder, decreasing pain and increasing shoulder function.

ANKLE AND FOOT

Patients with hEDS/HSD will have altered ankle and foot kinematics during gait, as well as altered arch shapes with pes cavus and flexible pes planus (high arches that collapse upon standing). This can promote pain in the knees, hips, back, and fatigue. Orthotics have been helpful, with a recent observational study showed that the use of custom-made foot orthoses for 3 months improved foot pain, disability-related to foot pain, and foot functionality in patients with EDS [37▪].

Vermeulen *et al.* reported that increased medial forefoot eversion during stance, increased dorsiflexion in the medial and lateral forefoot and the rearfoot, increased plantar flexion in the midfoot, and at the level of the hallux a decreased dorsiflexion, and increased inversion and abduction in subjects with hEDS/HSD vs. controls [38]. They recommended that orthoses should be designed for the entire foot, inclusive of the forefoot and midfoot, and should not be limited to the rearfoot [38]. The efficacy of custom orthotics, which can be very expensive, has not been tested against over the counter insoles.

HAND

Patients with hEDS/HSD tend to have significant hand and wrist involvement due to the high number of ligaments connecting the bones of finger segments. As tendons and ligaments overstretch, tendons can slip causing MCP, IP laxity, and subluxations[18▪]. Repetitive tasks such as hand writing, typing, mobile devices can exacerbate pain. The small joints of the hand can spontaneously sublux making the activities of daily living painful.

The carpometacarpal joint of the thumb (CMC) may be particularly susceptible to instability and

early osteoarthritis due to laxity of the anterior oblique ligament, which is the key stabilizer preventing subluxation [39].

Occupational therapy is the most commonly prescribed and most effective option in a recent cohort study by Song *et al.*, with 70% of patients with hEDS/HSD reporting improvement with digital ring splints and bracing [40▪]. Another recent study confirmed nonsurgical management of CMC instability resulted in a clinically relevant decrease in pain and improvement in performing activities of daily living, work performance, and satisfaction with hand function [41].

Custom-fit finger orthoses can significantly reduce the time to perform functional hand tests [42▪▪] by providing joint stability and facilitating proprioception.

PHARMACOTHERAPY AND OTHER TREATMENTS

No single drug therapy exists to treat the pain and other co-morbidities in hEDS/HSD, therapy is guided by the patients' manifestations[43].

Nonsteroidal anti-inflammatory drugs are first-line for pain [43], self-reported in 66–92% of patients [40▪,44]. Ibuprofen was most effective and best tolerated; 68% reported oral and topical diclofenac were the least effective and provided to effect [40▪].

Neuropathic modulators, such as tricyclic antidepressants, anticonvulsants, serotonin, and norepinephrine reuptake inhibitors are traditionally helpful for centralized pain. Their use in hEDS/HSD is limited with 47% of patients noting adverse effects including worsening dysautonomia [8].

Though opioid use has been found to be nearly double in EDS patients (62%) compared with control (34.1%) [45] they can exacerbate preexisting fatigue, gastrointestinal, proprioceptive issues and lead to hyperalgesia, they are not recommended for long term use [43].

Demes *et al.* reported noted 1/3 of patients using marijuana, with 52.5% in states where marijuana is legalized, and 27.3% in 'illegal' states. It was self-reported as most effective in the cohort [44].

Of muscle relaxants, botulinum toxin injections were most effective benefitting 67% patients[40▪]. Other muscle relaxants including baclofen can be helpful for painful muscle spasms, but should be used with caution due to the risk of increasing joint instability [43].

There are various reports of patients with hEDS/HSD having potentially decreased response to local anesthetics such as lidocaine injections in dental procedures. However, anesthetics and dry needling may also be effective when injected into trigger points or localized areas of pain after subluxation [43]. Especially effective if combined with PT and stretching.

Peripheral nerve blocks can be effective and have similar block failure rates as patients without EDS [46]. Song *et al.* found that nerve blocks demonstrated pain relief in 69% of patients [40▪]. A 10% dextrose prolotherapy has also been shown to be helpful for various joint conditions, most notably TMJ dysfunction [40▪]. A recent study found the addition of arthrodesis to prolotherapy was more effective than prolotherapy alone, and decreased the frequency of locking episodes [47].

Rhythmic sensory stimulation is defined as the stimulation of the senses in a periodic manner within a range of low frequencies. A pilot study found 43% of hEDS reported significant improvements in pain interference, and depression, with responders having a high prevalence of depression, anxiety, insomnia, IBS, and fibromyalgia [48].

CONCLUSION

Patients with hEDS/HSD are frequently referred to rheumatology with joint pain and other co-morbidities but are underdiagnosed. New diagnostic methods are being studied, and quantitative measures of tissue mechanics could provide objective tools for the diagnosis of hEDS/HSD, though further validation is needed. Physical therapy and occupational therapy remain the cornerstone of treatment, though more studies on a larger scale are indicated.

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Conflicts of interest

There are no conflicts of interest.
D.M. has no disclosures.

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- ▪ of special interest
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REVIEW

COVID-19 and rheumatoid arthritis

Kristin M. D'Silva[a,b,c] *and Zachary S. Wallace*[a,b,c]

Purpose of review
The coronavirus disease 2019 (COVID-19) pandemic has caused significant morbidity and mortality worldwide. Patients with rheumatoid arthritis (RA) face unique challenges during the pandemic, including concerns regarding infection risk, drug shortages, limited access to care, social isolation, and mental health. This review will examine the multifaceted impacts of the COVID-19 pandemic on patients living with RA.

Recent findings
In patients with RA, risk factors for severe COVID-19 outcomes include older age and comorbidities, similar to those in the general population. Glucocorticoids, but not other classes of disease-modifying antirheumatic drugs (DMARDs), appear to be associated with a higher risk of severe COVID-19 outcomes. RA patients have been affected by changes in access to care, telemedicine, drug shortages, anxiety, and social isolation, which may contribute to disease flares.

Summary
Glucocorticoids, but not other DMARDs, are associated with a higher risk of severe COVID-19 outcomes in RA patients. Further studies are needed to explore the impact of specific DMARDs on COVID-19 outcomes, understand the broader implications of the COVID-19 pandemic on RA disease activity, and optimize the use of telemedicine in RA management.

Keywords
coronavirus, coronavirus disease 2019, rheumatoid arthritis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an unprecedented global health crisis [1]. Since the onset of the pandemic, patients with rheumatoid arthritis (RA) have expressed concerns regarding potential higher risks of poor COVID-19 outcomes due to immunosuppressive treatments, an underlying inflammatory state, associated comorbidities such as interstitial lung disease (ILD) and glucocorticoid-induced diabetes mellitus, and racial/ethnic and socioeconomic disparities [2▪]. Reports from early in the pandemic suggested that rheumatic disease patients may be at higher risk of respiratory failure and death from COVID-19 (Table 1) [3▪,4▪,5▪▪]. However, accumulating evidence suggests patients with rheumatic disease may not be at higher risk of severe COVID-19 outcomes after accounting for age, comorbidities, and glucocorticoid use [6▪,7,8▪,9▪]. In addition, the risk for infection and certain outcomes may vary according to rheumatic disease type, disease activity, and specific disease-modifying antirheumatic drugs (DMARDs).

In addition to concerns regarding COVID-19 outcomes, patients with RA have faced unique challenges during the pandemic (Fig. 1). For example, early in the pandemic, hydroxychloroquine was promoted as a potential COVID-19 prophylactic and treatment, leading to drug shortages for patients with rheumatic diseases, including RA [10]. Many patients also faced difficulties with accessing care because of transitions to telemedicine and loss of health insurance resulting from unemployment [2▪]. In addition, the pandemic has led to increased rates of fear, anxiety, depression, and

[a]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, [b]Clinical Epidemiology Program, Mongan Institute, Department of Medicine, Massachusetts General Hospital and [c]Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Zachary S. Wallace, MD, MSc, Clinical Epidemiology Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, 100 Cambridge Street, 16th Floor, Boston, MA 02114, USA. Tel: +1 617 724 2507;
e-mail: zswallace@mgh.harvard.edu

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KEY POINTS

- Whether patients with rheumatoid arthritis (RA) or those who use certain disease-modifying antirheumatic drugs (DMARDs) are at higher risk for severe COVID-19 remains poorly understood, but patients with RA who are on glucocorticoids appear to have a higher risk of severe COVID-19.
- The COVID-19 pandemic has created unique challenges for RA patients, including changes in access to care, drug shortages, social isolation, and anxiety, all of which may be associated with RA flares.
- Further studies are needed to determine the optimal use of telemedicine to achieve early diagnosis and treat-to-target management in RA care.

social isolation in the general population, all of which can be magnified in patients living with chronic diseases like RA and may contribute to RA flares [2▪,11].

In this review, we will examine the multifaceted impacts of the COVID-19 pandemic on patients with RA. We will first examine outcomes of COVID-19 in patients with rheumatic diseases including RA. We will then examine the secondary impacts of the pandemic, including drug shortages, access to care, and mental health.

COVID-19 OUTCOMES IN RA PATIENTS

Prior to the COVID-19 pandemic, evidence showed that RA patients had a higher risk of infection than the general population, due to a number of factors, including immunosuppression, a chronic inflammatory state, and comorbidities [12]. For instance, Doran *et al.* compared the frequency of infections in a population-based incidence cohort of RA patients to general population comparators and found that RA patients had a higher risk of infections than comparators without RA (adjusted hazard ratio [HR] 1.70, 95% confidence interval [CI] 1.42–2.03) [13]. The most common infections included those affecting the respiratory tract, skin, and musculoskeletal system [13]. In a study using the Consortium of Rheumatology Researchers of North America (CORRONA) registry, higher RA disease activity was associated with higher rates of infection [14]. Additionally, prednisone doses >7.5 mg daily were associated with six-fold higher rates of infections requiring hospitalization, and tumor necrosis factor (TNF) inhibitors and methotrexate were associated with a higher risk of outpatient infections [14]. However, these studies mainly examined the risk of bacterial infections. There are limited data suggesting that glucocorticoids, Janus kinase inhibitors (JAK) inhibitors, and TNF inhibitors may be associated with a higher risk of viral respiratory infections [12,15].

These prior observations led to concerns that RA patients would have a higher risk of COVID-19 and poor COVID-19 outcomes compared to the general population. However, there remains significant uncertainty given observational studies and clinical trials suggesting that some immunosuppressive agents commonly used to treat RA may actually improve COVID-19 outcomes [16,17▪▪,18▪▪]. The largest study to date evaluating the risk of severe COVID-19 in patients with RA, called OpenSAFELY, was completed early in the first 3 months of the pandemic [5▪▪]. In this population-based observational study, investigators examined risk factors for COVID-19 related death in a population of 17.2 million adults in the United Kingdom [5▪▪]. In addition to risk factors such as older age, male sex, obesity, nonwhite race, and diabetes, a diagnosis of RA, lupus, or psoriasis was associated with greater risk of COVID-19 related death (adjusted HR 1.19, 95% CI 1.11–1.27) [5▪▪]. Although there were a number of strengths to this study, including its large size and use of a hard outcome like mortality, there were also several methodologic limitations, including multiple testing, unmeasured confounding, adjustment for causal intermediates, the inclusion of nonlaboratory confirmed COVID-19 cases, and missing data regarding smoking, obesity, and ethnicity. Information on the use of immunosuppressive agents and rheumatic disease activity were not available. Perhaps most importantly, this study combined RA, lupus, and psoriasis into a single category, although these diseases are quite distinct from one another, limiting conclusions that can be drawn regarding the risk for RA patients [19].

In contrast to the OpenSAFELY study, early case series reported generally mild COVID-19 clinical courses in patients with rheumatic diseases, and observational studies from single-center and multicenter cohorts reported a similar incidence of COVID-19 among rheumatic disease patients and the general population [20–23,24▪,25]. However, early comparative cohort studies from Wuhan, China, and Boston, MA, reported a higher risk of respiratory failure requiring mechanical ventilation in COVID-19 patients with rheumatic diseases versus comparators [3▪,4▪]. In the Wuhan study, 21 rheumatic disease patients with COVID-19 (eight of whom had RA) were identified among 2326 COVID-19 patients, and respiratory failure was more common in rheumatic disease patients than comparators (38% versus 10%, $P < 0.01$) [3▪]. However, due to the small sample size, this study could not adjust for confounders.

Table 1. Key studies examining COVID-19 outcomes in rheumatic disease patients

Reference	Location	Study population	COVID-19 ascertainment	Primary finding	Limitations
Williamson *et al.* (OpenSAFELY) [5▪▪]	United Kingdom	General population (>17 million adults)	Positive molecular testing	RA/SLE/psoriasis associated with a higher risk of COVID-19-related death (HR 1.19, 95% CI 1.11–1.27).	Multiple testing; adjusting for causal intermediates[a]; unmeasured confounding[b]; inclusion of nonlaboratory confirmed COVID-19 cases; missing data; lumping of RA, SLE, and psoriasis; lack of information about DMARDs and disease activity
Ye *et al.* [3▪]	Wuhan, China	COVID-19 patients with rheumatic disease versus without rheumatic disease	Positive molecular testing ($n=20$) or positive IgM and IgG ($n=1$)	Respiratory failure is more common in rheumatic disease patients than comparators (38% versus 10%, $P<0.01$)	Small sample size ($n=21$ rheumatic disease patients); unmeasured confounding; collider bias[c]
D'Silva and Serling-Boyd *et al.* [4▪]; Serling-Boyd and D'Silva *et al.* [6▪]	Boston, MA	COVID-19 patients with rheumatic disease versus without rheumatic disease	Positive molecular testing	Higher odds of mechanical ventilation in rheumatic disease patients versus comparators in the first 2 months of pandemic (OR 3.11, 95% CI 1.07–9.05). Improved risk of mechanical ventilation 6 months into the pandemic.	Collider bias may bias results toward null; adjusting for causal intermediates
D'Silva and Jorge *et al.* [9▪]	United States	COVID-19 patients with rheumatic disease versus without rheumatic disease	Positive molecular testing or diagnostic code	Higher risks of hospitalization and acute renal failure mediated by comorbidities. Higher risk of venous thromboembolism (RR 1.60, 95% CI 1.14–2.25), regardless of comorbidities.	Unmeasured confounding; inaccuracies in ICD-10 coding; lack of geographic information; collider bias
Pablos *et al.* [30▪]	Spain	COVID-19 patients with rheumatic disease versus without rheumatic disease	Positive molecular testing	Higher odds of severe COVID-19 with glucocorticoids (OR 2.20, 95% CI 1.36–3.54)	Limited to hospitalized patients; small sample sizes in subgroups; collider bias
Gianfrancesco *et al.* [31▪▪]	International Physician-Reported Registry	Hospitalized versus nonhospitalized rheumatic disease patients with COVID-19	Physician-reported diagnosis	Prednisone doses ≥10 mg daily associated with higher odds of hospitalization (OR 2.05, 95% CI 1.06–3.96). TNF inhibitors associated with lower odds of hospitalization (OR 0.40, 95% CI 0.19–0.81).	Selection bias (more severe cases more likely to be captured); unmeasured confounding; a large number of unresolved cases (35%) at time of publication

CI, confidence interval; COVID-19, coronavirus disease 2019; DMARD, disease-modifying antirheumatic drug; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; OR, odds ratio; RA, rheumatoid arthritis; RR, relative risk; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.
[a]Causal intermediates are covariates that are causally influenced by the exposure and also causally affect the outcome of interest. For example, if the exposure is a rheumatic disease and the outcome is COVID-19 related death, a comorbidity such as diabetes may be a causal intermediate as rheumatic disease treatments such as glucocorticoids can cause diabetes, which in turn can cause more severe COVID-19.
[b]Unmeasured confounding refers to covariates that may not be measured and/or adjusted for in analyses. For example, glucocorticoid use may be an unmeasured confounder in the OpenSAFELY study.
[c]Collider bias occurs when analyses are restricted by a collider variable, which is a variable that is a common effect of the exposure and outcome. In studies where the exposure is COVID-19 infection and the outcomes are COVID-19-related outcomes such as hospitalization, mechanical ventilation, or death, conditioning on the common effect of COVID-19 may bias results toward the null.

In the Boston study, patients with COVID-19 by positive molecular test and rheumatic disease were systematically identified using diagnostic codes followed by chart review [4▪]. Fifty-two rheumatic disease patients (of whom 19 [37%] had RA) were identified and matched by age, sex, and date of COVID-19 diagnosis to 104 comparators without rheumatic disease 2 months into the pandemic [4▪]. Patients with the rheumatic disease had higher odds of requiring mechanical ventilation than comparators (multivariable odds ratio [OR] 3.11, 95% CI 1.07–9.05) after adjusting for age, body mass index, smoking, and a number of comorbidities [4▪]. In an extension of this study that included 143 patients

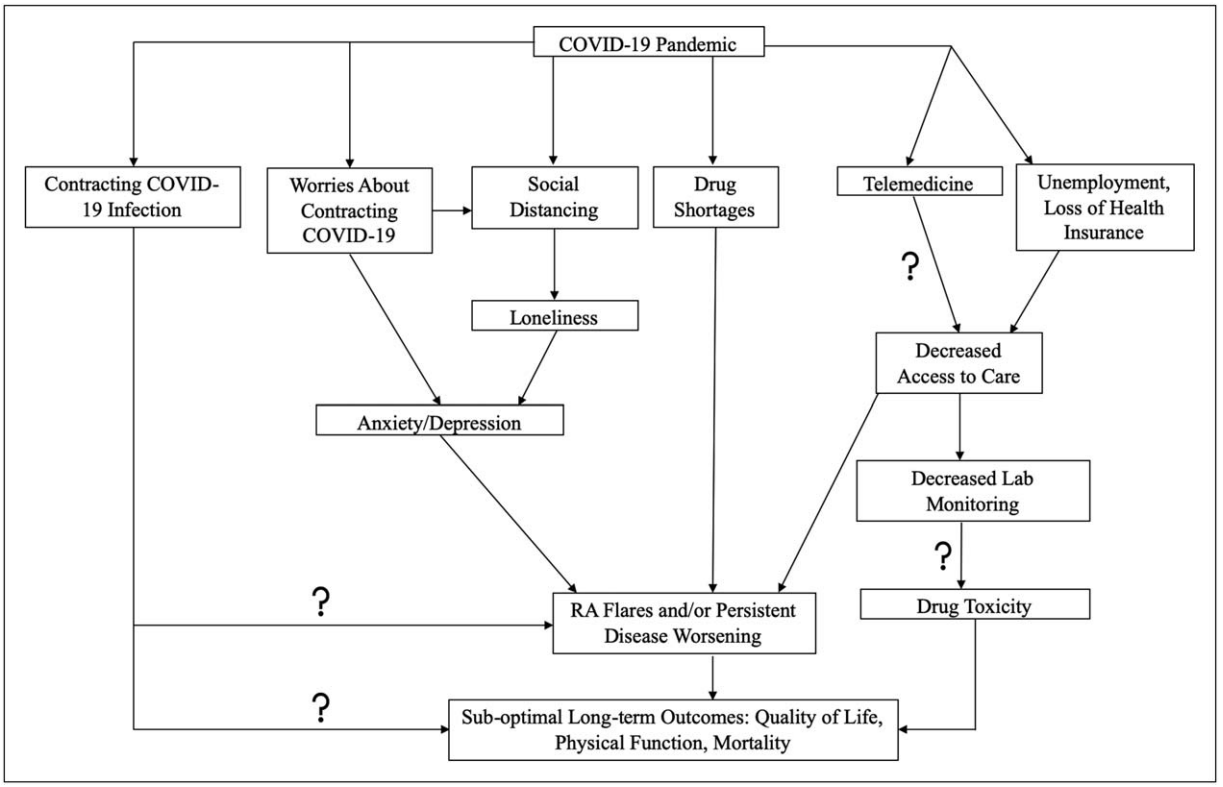

FIGURE 1. Impacts of the COVID-19 pandemic on patients living with rheumatoid arthritis. COVID-19, coronavirus disease 2019; RA, rheumatoid arthritis. The question mark indicates further research needed.

with a rheumatic disease (44 [31%] with RA) 6 months into the pandemic, the risk of mechanical ventilation in rheumatic disease patients versus comparators was attenuated (adjusted HR 1.51, 95% CI 0.93–2.44), and there was a trend toward improvement in mechanical ventilation risk over time [6▪]. The improvement in COVID-19 outcomes in rheumatic disease patients as the pandemic progresses have been replicated in other studies and may reflect the detection of milder cases and improvements in therapies and supportive care for COVID-19 [26▪].

In a large multicenter electronic health record network in the United States, COVID-19 outcomes were examined in patients living with systemic autoimmune rheumatic diseases (SARDs) versus exposure-score matched comparators [9▪]. COVID-19 was determined by diagnostic codes or positive molecular testing. In total, 2379 SARD patients were identified, of whom 1181 (50%) had RA [9▪]. In the primary model, in which SARD patients were matched to comparators on age, sex, race/ethnicity, and body mass index, SARD patients had significantly higher risks of hospitalization (relative risk [RR] 1.14, 95% CI 1.03–1.26), renal failure requiring renal replacement therapy (RR 1.81, 95% CI 1.07–3.07), and venous thromboembolism (VTE, RR 1.74, 95% CI 1.23–2.45) versus comparators [9▪]. In an extended model that also matched for comorbidities, all risks were largely attenuated, except for the risk of VTE [9▪]. This and the studies from Boston suggest that comorbidities are an important mediator and/or confounder of the risk of poor COVID-19 outcomes in patients with rheumatic diseases, similar to risk factors in the general population [9▪]. Patients with RA are at baseline at a higher risk of VTE than the general population and require close monitoring for VTE during COVID-19 [27]. In addition, given the association between RA and lung disease (such as ILD, bronchiectasis, and bronchiolitis), a significant risk factor in the general population for poor COVID-19 outcomes, it is important to closely monitor RA patients with lung disease for COVID-19 complications [28,29▪].

Several studies have examined the impact of DMARDs on COVID-19 outcomes. A comparative cohort study from Spain of patients with COVID-19 infection included 228 rheumatic disease patients and 228 comparators without the rheumatic disease [30▪]. In this study, the investigators found no higher odds of severe COVID-19 associated with hydroxychloroquine, conventional synthetic DMARDs, or biologic/targeted synthetic DMARDs [30▪]. However, there were higher odds of severe

COVID-19 associated with glucocorticoid use (OR 2.20, 95% CI 1.36–3.54) [30▪]. A French cohort study demonstrated similar findings [8▪].

The Global Rheumatology Alliance (GRA) physician-reported registry has also examined the relationship between DMARDs and severe COVID-19. In an early study, the GRA reported risk factors for hospitalization in 600 rheumatic disease patients with COVID-19 (230 [38%] with RA) [31▪▪]. Prednisone doses ≥10 mg daily were associated with higher odds of hospitalization (adjusted OR 2.05, 95% CI 1.06–3.96), while conventional synthetic and biologic/targeted synthetic DMARDs were not [31▪▪]. Interestingly, TNF inhibitors were associated with a reduced odds of hospitalization (adjusted OR 0.40, 95% CI 0.19–0.81), suggesting a possible protective effect that is also supported by evidence of exuberant TNF responses in postmortem lymph node specimens from patients with fatal COVID-19 [31▪▪,32▪]. Additional studies are needed to further investigate these associations. The GRA study is limited by selection bias (as physicians may report more severe cases), unmeasured confounding, and lack of an active comparator for medication analyses.

In summary, the available evidence at this time suggests that many risk factors associated with poor COVID-19 outcomes in rheumatic disease patients are similar to those observed in the general population, including older age, comorbidities, and obesity. There may be a slightly higher risk of severe COVID-19 outcomes in rheumatic disease patients, as observed in some studies such as OpenSAFELY, and these associations may be driven by certain disease-specific factors such as glucocorticoid use [5▪▪,31▪▪]. The relationship between glucocorticoid use and severe COVID-19 outcomes may be related to confounding by indication, as patients with the more severe rheumatic disease may be more likely to take glucocorticoids, and increased disease activity has been associated with a higher risk of other infections prior to COVID-19 [14]. The timing of glucocorticoid exposure may also affect the risk of severe COVID-19. Early glucocorticoid exposure may be associated with harm, while late glucocorticoid exposure may reduce COVID-19 mortality by treating hyperinflammation, as observed in the RECOVERY trial of dexamethasone versus placebo in COVID-19 [17▪▪].

The American College of Rheumatology (ACR) has released guidance regarding the management of rheumatic diseases during the ongoing COVID-19 pandemic, with frequent updates to capture the rapidly evolving literature [33]. For patients with a known SARS-CoV-2 exposure or confirmed COVID-19, the ACR recommends holding most DMARDs and resuming within 7–14 days of symptom resolution [33]. Hydroxychloroquine may be continued during COVID-19 infection, and patients and providers can engage in shared decision-making to determine whether to continue or hold interleukin (IL)-6 receptor inhibitors given some reports of their efficacy for the treatment of COVID-19 [33,34▪]. Regardless of exposure or infection status, glucocorticoids should be kept at the lowest possible dose to maintain control of the rheumatic disease [33]. These guidelines are consistent with the results of the observational studies reviewed herein.

SECONDARY IMPACTS OF THE COVID-19 PANDEMIC ON RA PATIENTS

In addition to potentially higher risks of infection and poor outcomes, patients with RA have faced many other challenges during the COVID-19 pandemic, including changes in access to care due to the switch to telemedicine and unemployment, drug shortages, social isolation, and anxiety and depression. During the first 2 weeks of the pandemic in the United States, a cross-sectional survey of 530 patients with rheumatic disease, 61% of whom had RA, was conducted [2▪]. Almost 200 patients (42%) reported changes in care, such as cancelled/postponed appointments and switch to telemedicine visits [2▪]. Seventy-four patients (14%) reported self-imposed changes to medications or doses, and 58 (11%) had physician-directed medication changes [2▪]. In qualitative analyses, many patients noted anxiety, loneliness, and worsening arthritis symptoms [2▪].

Indeed, the pandemic has had significant implications on mental health and rheumatic disease symptoms. In open-ended interviews with 112 patients in New York City, patients reported increased fatigue, anxiety, stress, and worsening musculoskeletal symptoms and cognitive function [35▪]. In addition to worries about developing COVID-19, patients expressed worries about medication changes, family, work, and finances [35▪]. Many patients with rheumatic diseases believe they are at higher risk of poor COVID-19 outcomes and therefore follow strict social distancing measures [36▪]. Although necessary to prevent the spread of COVID-19, strict social distancing can foster loneliness, which can exacerbate anxiety, depression, and rheumatic disease flares.

The GRA also conducted a Patient Experience Survey to capture the impact of the COVID-19 pandemic on rheumatic disease patients [37]. These data have demonstrated the consequences of hydroxychloroquine drug shortages [38▪]. Among 9393 patient respondents from around the world, 3872

(41%) were taking an antimalarial treatment [38▪]. Of these, 230 (6%) were unable to continue antimalarial treatment due to drug shortages [38▪]. Patients experiencing drug shortages reported higher levels of rheumatic disease activity and poorer mental and physical health [38▪].

Meanwhile, the switch to telemedicine has caused significant shifts in rheumatic disease care, and the impact of telemedicine on the diagnosis and management of RA remains unclear. Using validated instruments to measure disease activity and functional status is crucial to achieving treat-to-target objectives in RA management [39]. An ACR working group recommended adaptations to disease activity and functional status measures for use in telemedicine, including replacing provider-assessed joint counts with patient-reported joint counts [39]. Further studies are needed to optimize the implementation of patient-reported outcomes, treat-to-target strategies, and laboratory monitoring for high-risk medications in the telemedicine setting [40].

In addition to patient-reported surveys, survey studies of rheumatology providers have also revealed changes in care due to the pandemic. A survey of 1286 providers was conducted in countries belonging to the European League Against Rheumatism (EULAR) [41▪]. Over 80% of respondents reported cancelling new and follow-up in-person visits, many of which were replaced with virtual evaluation [41▪]. Seventy-four percent of respondents reported that they were less likely to start a biologic/targeted synthetic DMARD during the pandemic [41▪]. Lastly, 58% of respondents noted a longer interval between symptom onset and rheumatologic evaluation, which may significantly affect the ability to achieve early diagnosis and treat-to-target management [41▪].

CONCLUSION

The COVID-19 pandemic has had profound implications for patients living with RA. In general, observational studies have not consistently found that patients with RA are at higher risk of poor outcomes from COVID-19 compared to the general population. However, rheumatic disease patients with comorbidities and those on glucocorticoids do seem to be at higher risk of severe COVID-19. Additional population-based studies are needed to examine whether having RA or using specific DMARDs are associated with greater COVID-19 risk and/or more severe COVID-19 outcomes. In addition to concerns regarding infection risk, patients with RA have faced challenges including changes in access to care, drug shortages, anxiety, and social isolation, all of which may be associated with worse RA control. Further studies are needed to optimize the use of telemedicine in RA care.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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2. ▪ Michaud K, Wipfler K, Shaw Y, *et al.* Experiences of patients with rheumatic diseases in the US during early days of the COVID-19 pandemic. ACR Open Rheumatol 2020; 2:335–343.

This is the first survey study of rheumatic disease patients during the COVID-19 pandemic. This article demonstrated changes in access to care, medication changes, and feelings of anxiety and loneliness among rheumatic disease patients during the first 2 weeks of the pandemic.

3. ▪ Ye C, Cai S, Shen G, *et al.* Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. Ann Rheum Dis 2020; 79:1007–1013.

This is an early study from the first few months of the COVID-19 pandemic in Wuhan, China. This study showed COVID-19 patients with rheumatic disease had higher odds of respiratory failure versus patients without rheumatic disease.

4. ▪ D'Silva KM, Serling-Boyd N, Wallwork R, *et al.* Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a United States 'hot spot'. Ann Rheum Dis 2020; 79:1156–1162.

This is an early study from the first two months of the COVID-19 pandemic in Boston, Massachusetts, USA. This study showed COVID-19 patients with rheumatic disease had higher odds of mechanical ventilation versus comparators without rheumatic disease matched on age, sex, and date of COVID-19 diagnosis.

5. ▪▪ Williamson E, Walker AJ, Bhaskaran KJ, *et al.* OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. Nature 2020; 584:430–436.

This is the largest general population-based study to date examining risk factors for COVID-19 mortality. This study showed that patients with rheumatoid arthritis, systemic lupus erythematosus, or psoriasis had slightly higher risk of COVID-19 mortality than those without these diseases.

6. ▪ Serling-Boyd N, D'Silva KM, Hsu TY, *et al.* Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis 2020; Advance Online Publications.

This study examined COVID-19 outcomes in rheumatic disease patients versus comparators 6 months into the COVID-19 pandemic and found no significantly higher risk of hospitalization, mechanical ventilation, or death after adjusting for confounders, and there was a trend towards improvement in risk of mechanical ventilation over time.

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8. ▪ Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. Ann Rheum Dis 2020; Advance Online Publications.

This study from a French cohort of patients with rheumatic diseases and COVID-19 showed that patients with rheumatic diseases on glucocorticoids, but not other DMARDs, were at higher risk of severe COVID-19.

9. D'Silva KM, Jorge A, Cohen A, *et al.* COVID-19 outcomes in patients with ■ systemic autoimmune rheumatic diseases (SARDs) compared to the general population: a US Multi-Center Comparative Cohort Study. Arthritis Rheum 2020; Advance Online Publications.

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16. McInnes IB. COVID-19 and rheumatology: first steps towards a different future? Ann Rheum Dis 2020; 79:551–552.

17. Horby PW, Landray MJ. Dexamethasone in hospitalized patients with ■■ COVID-19: preliminary report. N Engl J Med 2020; Advance Online Publications.

This landmark randomized clinical trial (RECOVERY) demonstrated that dexamethasone reduced mortality among patients with severe COVID-19 requiring oxygen supplementation or mechanical ventilation.

18. Kalil AC, Patterson TF, Mehta AK, *et al.* Baricitinib plus Remdesivir for ■■ hospitalized adults with COVID-19. N Engl J Med 2020; Advance Online Publications.

This landmark double-blind placebo-controlled randomized clinical trial showed that baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time among hospitalized COVID-19 patients.

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21. Monti S, Balduzzi S, Delvino P, *et al.* Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020; 79:667–668.

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24. Michelena X, Borrell H, Lopez-Corbeto M, *et al.* Incidence of COVID-19 in a ■ cohort of adult and pediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2020; 50:564–570.

This early study investigated the incidence of COVID-19 among rheumatic disease patients in Barcelona, Spain, using telephone surveys and electronic health record review. The study found a similar incidence rate of COVID-19 in rheumatic disease patients and the general population.

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26. Jorge A, D'Silva KM, Cohen A, *et al.* Temporal trends in severe COVID-19 ■ outcomes in patients with rheumatic disease: a cohort study. Lancet Rheumatol 2020; Advance Online Publications.

This study examined temporal trends in COVID-19 outcomes in rheumatic disease patients using a large multicenter electronic health record network. The study found improvements in severe COVID-19 outcomes in rheumatic disease patients over time during the pandemic.

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29. Drake TM, Docherty AB, Harrison EM, *et al.* Outcome of hospitalization for ■ COVID-19 in patients with interstitial lung disease. An international multicenter study. Am J Respir Crit Care Med 2020; 202:1656–1665.

This study found that patients with interstitial lung disease, including both idiopathic pulmonary fibrosis and other fibrosing lung diseases, are at increased risk of death from COVID-19 compared to age, sex, and comorbidity matched comparators without ILD.

30. Pablos JL, Galindo M, Carmona L, *et al.* Clinical outcomes of hospitalised ■ patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis 2020; Advance Online Publications.

This comparative cohort study from Spain showed that older age, male sex, comorbidities, and glucocorticoid use (but not other DMARDs) were associated with severe COVID-19 in rheumatic disease patients versus comparators without rheumatic disease.

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This early study from the Global Rheumatology Alliance Physician-Reported COVID-19 registry showed that rheumatic disease patients on glucocorticoids, but not other DMARDs, had higher odds of hospitalization. TNF inhibitor use was associated with lower odds of hospitalization.

32. Kaneko N, Kuo H-H, Boucau J, *et al.* Loss of Bcl-6-expressing T follicular ■ helper cells and germinal centers in COVID-19. Cell 2020; 183:1–15.

This study of lymph nodes from patients with fatal COVID-19 showed excessive TNF levels and aberrant germinal center formation, suggesting inhibition of TNF may promote a more robust and effective immunologic response to COVID-19. Further studies are needed to explore this hypothesis.

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34. Salama C, Han J, Yau L, *et al.* Tocilizumab in patients hospitalized with ■ COVID-19 pneumonia. N Engl J Med 2020; 0:1–12.

This randomized clinical trial showed that tocilizumab was associated with reduced likelihood of progression to the composite outcome of mechanical ventilation or death versus placebo in patients hospitalized with COVID-19. Given that this finding differs from prior negative clinical trials, further studies are needed to determine which COVID-19 patients may benefit from tocilizumab

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This study used open-ended interviews with rheumatic disease patients to determine the impact of the COVID-19 pandemic. Patients reported fatigue, anxiety, stress, and worsening musculoskeletal symptoms and cognitive function due to the pandemic.

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This study from the Netherlands showed that patients with rheumatic diseases adhered to more strict social distancing than what was recommended by the public health department.

37. Sirotich E, Dillingham S, Grainger R, *et al.* Capturing patient-reported outcomes during the COVID-19 pandemic: development of the COVID-19 Global Rheumatology Alliance Patient Experience Survey. Arthritis Care Res 2020; 72:871–873.

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This study from the Global Rheumatology Alliance Patient Experience Survey showed that many patients on hydroxychloroquine experienced drug shortages during the pandemic, and patients experiencing drug shortages reported worse rheumatic disease symptoms.

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40. Taylor PC. Adopting PROs in virtual and outpatient management of RA. Nat Rev Rheumatol 2020; 16:477–478.

41. Dejaco C, Alunno A, Bijlsma JW, *et al.* Influence of COVID-19 pandemic on ■ decisions for the management of people with inflammatory rheumatic and musculoskeletal diseases: a survey among EULAR countries. Ann Rheum Dis 2020; Advance Online Publications.

This survey study of rheumatology providers reported that providers were less likely to start biologic or targeted synthetic DMARDs during the pandemic compared to prior to the pandemic.

Telerheumatology: before, during, and after a global pandemic

Rachel A. Matsumoto[a] *and Jennifer L. Barton*[a,b]

Purpose of review
In early 2020, the COVID-19 global pandemic shifted most healthcare to remote delivery methods to protect patients, clinicians, and hospital staff. Such remote care delivery methods include the use of telehealth technologies including clinical video telehealth or telephone visits. Prior to this, research on the acceptability, feasibility, and efficacy of telehealth applied to rheumatology, or telerheumatology, has been limited.

Recent findings
Telerheumatology visits were found to be noninferior to in-person visits and are often more time and cost effective for patients. Clinicians and patients both noted the lack of a physical exam in telehealth visits and patients missed the opportunity to have lab work done or other diagnostic tests they are afforded with in-person visits. Overall, patients and clinicians had positive attitudes toward the use of telerheumatology and agreed on its usefulness, even beyond the pandemic.

Summary
Although telerheumatology has the potential to expand the reach of rheumatology practice, some of the most vulnerable patients still lack the most basic resources required for a telehealth visit. As the literature on telerheumatology continues to expand, attention should be paid to health equity, the digital divide, as well as patient preferences in order to foster true shared decision-making over telehealth.

Keywords
COVID-19, rheumatoid arthritis, telehealth, telerheumatology

INTRODUCTION

Telemedicine is defined by the World Health Organization (WHO) as 'the delivery of healthcare services, where distance is a critical factor, and by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injury…' [1]. Telemedicine can be categorized as either asynchronous (e.g., 'store and forward' technologies, e-Consults, E-Mail) or synchronous (e.g., clinical video telehealth, telephone, video telemedicine) [2]. Such technologies have been proposed as solutions to equity, access, and quality of care barriers for many specialties such as dermatology, cardiology, psychology [1]. However, telemedicine applied to rheumatology, also referred to as telerheumatology, has been on the periphery of rheumatology practice for several years. There is a paucity of research on the acceptability and feasibility from the perspective of both patients and clinicians in addition to the efficacy of telerheumatology modalities on health outcomes.

Within the field of rheumatology, telemedicine has the potential to address several barriers to care including current and worsening workforce shortages [3] and caring for rural patients without access to a rheumatology clinic [4]. Research has shown that patients with rheumatoid arthritis (RA) treated by a rheumatologist have improved quality of care and health outcomes including higher functional status, fewer painful joints, and lower pain ratings than patients who see a nonrheumatologist [5]. Furthermore, the farther a patient lives from a rheumatology clinic, the less likely they are to receive an RA diagnosis or appropriate treatment [6]. With a

[a]Center to Improve Veteran Involvement in Care, VA Portland Health Care System and [b]Oregon Health & Science University, Portland, Oregon, USA

Correspondence to Jennifer L. Barton, 3710 SW US Veterans Hospital Road, R&D 64, Portland, Oregon 97239, USA. Tel: +503 220 8262; e-mail: Jennifer.Barton1@va.gov

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KEY POINTS

- Leading up to and during the COVID-19 pandemic, research on the acceptability, feasibility, and efficacy of telehealth applied to rheumatology (telerheumatology) has been limited.
- In this review, telerheumatology visits were found to be noninferior to in-person visits in terms of health outcomes, and often more time and cost effective for patients.
- A challenge to telerheumatology identified by both clinicians and patients was the lack of a physical exam.
- Although telerheumatology has the potential to expand the reach of rheumatology practice, some patients still lack the most basic resources required for a telehealth visit.
- As literature on telerheumatology continues to expand, attention should be paid to health equity, the digital divide, as well as patient preferences in order to foster true shared decision-making over telehealth.

decreasing workforce, increasing clinic size or number is an improbable solution. Telerheumatology, however, has the potential to offer many benefits. Clinics can prioritize patients, reduce the impacts of no-shows, and extend their reach [4]. Patients have access to earlier appointments, reduce their travel time and costs, and avoid missing work [7,8].

The COVID-19 pandemic declared in March 2020 introduced an added layer of difficulty in delivering safe and effective care [9]. Around this time, health systems began to shift their care to remote delivery systems following guidelines from the Centers for Disease Control and Prevention (CDC) and WHO in order to help prevent the spread of the virus [10]. With the urgent push to telemedicine across clinical specialties due to the COVID-19 pandemic, a second chapter for telerheumatology began.

The goal of this scoping review was to review literature published in the last 2 years of telehealth modalities for the care of patients with RA. A secondary goal was to review the uses of telerheumatology internationally during a global pandemic.

METHODS

To identify articles related to telerheumatology and RA, a PubMed database search was performed in December 2020. Results were limited to include articles published within the last 2 years and those written in English. The following search terms in the title or abstract identified potential articles of interest: 'telehealth,' 'telemedicine,' 'telerheumatology,' 'rheumatology,' and 'rheumatoid arthritis'. Articles that discussed pediatric rheumatology, were editorials or letters to the editor, non-English language, published prior to 2018, or included interventions that were not considered synchronous telemedicine (i.e., e-Consults, E-Mail, educational interventions) were excluded. The authors (R.A.M. and J.B.) independently reviewed titles and abstracts for inclusion, eliminated articles that did not fit the scope, and then completed a full text review. Disagreements were discussed until consensus was reached.

Data extraction

Data extraction was performed independently by both authors (R.A.M. and J.B.) using an extraction tool and then jointly corroborated. Extracted data were summarized qualitatively in order to provide an overview of the literature. Elements extracted were grouped into study characteristics, mode of telemedicine, participant characteristics, intervention (if applicable), results, and barriers to telehealth.

RESULTS

Twenty of the 66 articles identified in the search were included in the final review. A brief description and summary of findings for each article can be found in Tables 1 and 2. A total of 10 were from the prepandemic era and 10 reported on experiences during the pandemic. A total of 46 countries are represented.

Effectiveness of telerheumatology on health outcomes

Four studies evaluated disease activity ($n = 2$ observational; $n = 2$ randomized controlled trials, RCT) among established RA patients [8,11,12,13▪]. Telehealth was noninferior to in-person visits in terms of disease activity and function. No study identified reported worse health outcomes among patients who received telehealth. It should be noted that all studies that examined RA health outcomes were conducted in the pre-Covid era. Of the two RCTs, one conducted in Saskatchewan, Canada, randomized established RA patients in rural areas to either telehealth (in-person clinic visits with a physical therapist at spoke sites, rheumatologist seen over video at hub site) or in-person visit at the rheumatology clinic in Saskatoon (hub site) [13▪]. Patients were followed for nine months. The primary outcome was disease activity and quality of life. Eighty-five patients were enrolled, 80% female with an

Table 1. Summary of reviewed telerheumatology studies

Author/Year	Study Characteristics	Telemedicine Methods	Findings	Conclusion
Effectiveness of Telerheumatology				
de Thurah *et al.* 2018	Design: RCT Duration: 12 months Patients: $n=294$ Time period: Pre-Covid Region: Denmark	Phase of care: follow up Method: telephone Specialist: rheumatologist, rheumatology nurse	Telehealth rheumatologist and rheumatology nurse delivered care noninferior in outcome of disease activity (DAS-28), no difference in function, quality of life, or self-efficacy; >80% very satisfied with care across all groups	Telerheumatology care delivery noninferior to face to face for established RA patients in terms of disease activity and satisfaction with care
England *et al.* 2020	Design: Expert panel Time period: Covid Region: US		PAS-II and RAPID3 for disease activity and HAQ-II, MDHAQ and PROMIS PF-10 for function are entirely self-reported & easily adaptable for telehealth; measure collection via EMR advantageous however patient level barriers of language, literacy, computer access	If feasible, patient-reported measures entered into EMR has highest potential; strategies to modify existing measures are presented.
Ferucci *et al.* 2020	Design: observational Duration: 12 months Patients: $n=122$ (63 telehealth) Time period: pre-Covid Region: Alaska	Phase of care: follow up Method: video teleconference Specialist: rheumatologist Presenter: nonphysician	No difference in change in disease activity or function over 12 months between telehealth and nontelehealth groups (these were higher at baseline in the telehealth group); patient perceptions of telehealth and clinician telehealth frequency of use associated with patient use of telehealth; lower capture of PROs among telehealth group	No variation in change in disease activity or function over 12 months between patients receiving telehealth compared with in person follow up; lower capture of disease activity among telehealth group
Nguyen-Oghalai *et al.* 2018	Design: observational Patients: $n=39$ Time period: pre-Covid Region: US	Phase of care: Diagnosis Method: Clinical video telehealth Specialist: Rheumatologist Presenter: Nurse Practitioner	Clinical video telehealth visits correctly identified 79% of rheumatologic conditions. All patients who presented with inflammatory arthritis were correctly identified via clinical video telehealth. Patient satisfaction of telehealth and in person visits were rated similarly high.	Clinical video telehealth is similarly effective to in person visits in the diagnosis of rheumatologic conditions. Patient satisfaction of telehealth visits is similarly high to in person visits.
Rezaian *et al.* 2020	Design: observational Patients: $n=4,270$ Time period: pre-Covid Region: Iran	Phase of care: Diagnosis or follow up Method: Clinical video telehealth Specialist: Rheumatologist (US) Presenter: General practitioner (Iran)	13.4% of patients were diagnosed with RA. Most common medications that were prescribed were NSAIDs (16.3%), methotrexate (15.7%). Technology failures, distance to the clinic, and poverty were barriers for patients seeking care.	Despite economic and societal constraints, the USA to Iran clinical video telehealth program has been successful and has the potential to act as a proof of concept for similar telehealth structures globally.
Shenoy *et al.* 2020	Design: observational, survey Patients: $n=100$ Time period: Covid Region: India	Phase of care: Diagnosis or follow up Method: Video teleconferencing (WhatsApp) Specialist: Rheumatologist	Moving to video teleconferencing reduced clinic foot traffic. Telehealth visits were rated high by patients (median= 9) and were recommended by patients (median= 9.5). 20% of patients felt uncomfortable without a physical exam. Continuing telehealth visits was influenced by the patient's belief that social distancing will reduce the pandemic, by the belief that the doctor may have missed something, and by their satisfaction with the virtual visit.	In response to the COVID-19 pandemic, moving to virtual visits through WhatsApp was an effective way to reduce clinic traffic and encourage social distancing.
Taylor-Gjevre *et al.* 2018	Design: RCT Duration: 9 months Patients: $n=85$ Time period: Precovid Region: Canada	Phase of care: Follow up Method: Clinical video telehealth Specialist: Rheumatologist Presenter: Physical Therapist trained in RA	There were no statistically significant differences in disease activity or quality of life between patients seen via telehealth and those seen in person. Nor was there a significant difference in changes in disease activity or quality of life over the study period. Both in person and telehealth patients were satisfied with their care although telehealth patients rated their care as 'excellent' more often than in person patients	Although quality of care is comparable between clinical video telehealth and in person visits, other factors such as distance to spoke site or patient's desire to travel to the city should be considered in choosing treatment modalities.

Table 1 (*Continued*)

Author/Year	Study Characteristics	Telemedicine Methods	Findings	Conclusion
Wood & Caplan 2019	Design: Prospective pilot Duration: 12 months Patients: $n=85$ Time period: Pre-Covid Region: US	Phase of care: Follow up Method: Video teleconferencing Specialist: Rheumatologist	There were no differences in disease activity or patient satisfaction at baseline; however, patients in the telemedicine group traveled farther and incurred greater cost than those in the usual care group at baseline.	There is no difference in disease activity managed through telehealth versus usual care. Higher disease activity and further travel distance were associated with lower satisfaction with the care received during the visit.
Patient Perceptions of Telerheumatology				
Antony *et al.* 2020	Design: observational, online survey Patients: $n=550$ Time period: Covid Region: Australia	Phase of care: follow-up Specialist: rheumatologist	98.4% considered use of telehealth appropriate; factors important in accepting telehealth included well controlled condition (60%), if consultation was with rheumatologist knew their case well (55%), and if unwell and unable to attend face to face (34%)	Telerheumatology appropriate modality during pandemic
Devadula *et al.* 2020	Design: mixed methods Duration: 6 months Patients: $n=48$ survey; $n=8$ focus groups Time period: pre-Covid Region: Australia	Phase of care: follow up Method: video teleconference Specialist: rheumatologist Presenter: trained nurse	Quantitative: Telehealth saved time, money, absence from work; 98% able to talk openly with rheumatologist, similar to face to face; nearly one-third expressed need for physical exam and 25% agreed that face to face establishes better rapport Qualitative: themes of acceptability (convenience), adjustment (initial concern evolved to satisfaction) and understanding (model of care clear, role of nurse presenter less clear)	Overwhelming satisfaction with telerheumatology consultation for follow up; convenience of reduced travel, stress, cost and time off work
Ferucci, Holck *et al.* 2020	Design: observational Duration: 12 months Patients: $n=122$ (56 telehealth) Time period: pre-Covid Region: Alaska	Phase of care: follow up Method: video teleconference Specialist: rheumatologist Presenter: nonphysician	46% seen at least once over telehealth; factors associated with use of telehealth included higher disease activity, higher number of rheumatologist visits in prior year, more positive perceptions of telehealth, visit with a physician who used telehealth more often	When available, patients with higher disease activity and more positive perceptions of telehealth more likely to use video telemedicine however patients still expressed desire for in person visits.
George *et al.* 2020	Design: observational, survey Duration: March 29-May 26, 2020 Patients: $n=1517$ Time period: Covid Region: US and Puerto Rico		29.5% reported use of telehealth that was more common in urban areas; DMARDs were stopped among 14.9% and was more common among those who reported lack of telehealth (OR 2.26, 95% CI 1.25–4.08). Healthcare providers were more commonly a source of information among those reporting a telehealth visit (63.4% vs 34.9%)	During early days of the pandemic, DMARD interruptions were associated with an absence of telehealth availability as well as socioeconomic status and without physician advice.
Knudsen *et al.* 2018	Design: qualitative Patients: $n=15$ Time period: pre-Covid Region: Denmark	Phase of care: follow up Method: telephone Specialist: rheumatologist, rheumatology nurse Presenter:	Qualitative: Telehealth viewed as flexible, convenient, and reduced burden. Two overarching patient types defined as either 'keen' or 'reluctant'. Keen patient values autonomy and actively self-manages disease whereas reluctant patient is more reactive, relies on clinician to be expert.	The 'keen' patient with characteristics of more autonomy and greater self-efficacy more likely to embrace telehealth whereas the 'reluctant' patient who is more reactive and reliant on clinician expertise may prefer in-person care.
Opinc *et al.* 2020	Design: observational, online survey Patients: $n=244$ Time period: Covid Region: Poland	Phase of care: Follow up Method: Video teleconferencing, telephone Specialist: Rheumatologist	Patients valued qualities of in person visits such as a physical exam, direct conversation, and the ability to perform a physical exam. The most preferred telehealth modality was telephone (82%). 88.5% of patients felt the option for telehealth visits should remain past the COVID-19 pandemic.	Patients consider in person visits valuable but are open to the idea of telerheumatology visits and agree that they should be available even after the pandemic.

Table 1 (*Continued*)

Author/Year	Study Characteristics	Telemedicine Methods	Findings	Conclusion
Ziade *et al.* 2020	Design: Observational, online survey Patients: $n=2,163$ Time period: Covid Region: Arab countries	Phase of care: Follow up Method: Telemedicine Specialist: Rheumatologist	Nearly all (98.8%) of Arab patients surveyed would accept a telehealth remote visits with their rheumatologist during the COVID-19 pandemic. 50% of patients would attend through the internet and 48.8% would attend an appointment via telephone.	During the COVID-19 pandemic, remote telerheumatoloy visits were considered acceptable by Arab patients.
Clinician perceptions of telerheumatology				
Akintayo *et al.* 2020	Design: Observational, online survey Duration: 2 weeks Clinicians: $n=554$ Time period: Covid Region: Africa (20 countries)	Method: video (9.6%), telephone (60.5%), E-Mail (16.3%), WhatsApp (43.5%) Specialist: rheumatologist	Rheumatologists advised patients to self-isolate, physical distance, and completely shield (<50%). No change in DMARDs (90.3%) during Covid-19	Despite no clinical guidelines for treatment during a pandemic, there was a shift to remote consultations with telephone and apps being most popular.
Bonfa *et al.* 2020	Design: qualitative Clinicians: $n=5$ Time period: Covid Region: US, China, Brazil, England, France		Qualitative: Wide range of experiences and reactions to use of telehealth during the pandemic with some having no prior use of telehealth; concern over personal safety and safety of patients; mourning loss of prior practice face to face	Varied experience among rheumatologists across 4 continents identify benefits and potential downsides with concern for digital divide
Matsumoto *et al.* 2020	Design: observational, online survey Duration: 2 weeks Clinicians: $n=45$ Time period: pre-Covid Region: US	Phase of care: Follow up and diagnosis Method: Clinical video telehealth Specialist: Rheumatologist	Regardless of experience, clinicians feel the lack of a physical exam is the greatest barrier to effective telerheumatology. Additionally, phase of care and rheumatologic disease are important considerations in determining the appropriateness of telerheumatology.	Overall, telerheumatology has the potential to increase access to care despite barriers such as lack of physical exam.
Singh *et al.* 2020	Design: observational, online survey Duration: 4 weeks Clinicans: $n=103$ Time period: Covid Region: US	Method: clinical video telehealth, Video teleconferencing, or telephone Specialist: Rheumatologist	Most clinicians considered telephone to be the best modality for remote care. 68% felt they could provide care safely through telehealth. 50% reported spending a lot more time providing care via telehealth. Overall, clinicians were more comfortable providing care to established patients.	Clinicians prefer telerheumatology for established patients, but most feel they can provide safe care via telehealth.
Ziade Hmamouchi *et al.* 2020	Design: Observational, online survey Clinicans: $n=858$ Time period: Covid Region: Arab countries	Phase of care: Follow up Method: Telemedicine Specialist: Rheumatologist	COVID-19 has decreased healthcare activities in the Arab countries by 65%. Clinicians used telemedicine in 70% of cases which was reimbursed 12% of cases. 54% of clinicians fully agreed to use telehealth, 24% would agree if fully reimbursed and 22% do not agree to use it at all.	Despite frequent use of telerheumatology visits during the COVID-19 pandemic, clinicians report some hesitancy in remote care partly due to reimbursement rates and regional healthcare system structure.

DMARD, disease-modifying anti-rheumatic drug; EMR, electronic medical record; NSAID, Nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RCT, randomized controlled trial.

average age of 56, and mean disease duration 13.9 years. At study end there were no significant differences in the main outcomes and both groups were satisfied with their care, though those in the telehealth arm rated their care as 'excellent' more often. Interestingly, distance traveled to the spoke sites was still far, and the study had a high drop-out rate as participants desired to go to the city (for errands and to see family). The second RCT conducted in Denmark randomized 294 established RA (>2 years disease duration) patients 1:1:1 to 1) patient-reported outcome-based telehealth follow up by a nurse or 2) a rheumatologist, or 3) conventional outpatient in-person follow up [11]. The primary outcome was change in a composite measure of disease activity (DAS-28) after 52 weeks. There were no significant differences in baseline characteristics across the three groups (65–72% female, average age 60–61, mean disease duration 12 years, low mean DAS-28: 2.0–2.1). Both telehealth groups were noninferior to conventional care in change in DAS-28 (reduction of −0.16 and −0.26 in the rheumatologist vs nurse-led telehealth respectively compared with −0.06 in control). There were 19 dropouts during the study and noncompleters had higher DAS compared with those who completed the study (2.6 [2.02–2.99] vs 1.95 [1.52–2.50], $P=0.009$).

Table 2. Characteristics of included studies

	Studies (*n*)	Clinicians (*n*)	Patients (*n*)
Overall totals	20	1,565	9,656
Date of publication			
2018	4	–	433
2019	1	–	85
2020	15	1,565	9,138
Region			
North America	11	149	1,970
South America	1	1	–
Africa	1	554	–
Europe	4	2	555
Asia	5	859	6,533
Australia	2	–	598
Study design			
RCT	2	–	379
Observational	16	1,560	9,262
Qualitative	2	5	15
Phase of care			
Diagnosis	1	–	39
Follow-up	9	858	3,728
Multiple or not specified	10	707	5,889
Telerheumatology method			
Clinical video telehealth	3	–	4,394
Telephone	2	–	309
Video teleconferencing	10	1,457	2,884
Multiple or not specified	3	108	2,069

England *et al.* convened an expert panel and generated recommendations for which outcome measures can be used during telehealth visits with some being 100% patient reported (RAPID-3, PAS-II) and others that could be modified [14]. Leveraging the electronic health record and patient portals to collect these data will be key moving forward.

Although the majority of clinicians favor use of telerheumatology for follow-up care in RA [15], several studies reported on use of telerheumatology for diagnosis [16–18], with high accuracy in one small US study (79% overall correlation with remote diagnosis followed by gold-standard in-person evaluation) [16]. A 4-year experience with remote consultation for nearly 5,000 patients (13% RA) in Iran provided care to nearly 50% Afghan refugees using it both for diagnosis and follow up [17].

Patient experience with telerheumatology

A total of nine studies measured patient acceptance or satisfaction with telerheumatology (6 pre-COVID). Overwhelmingly, patients found telehealth acceptable and were satisfied with care. The benefits included reduction in distance traveled [7,8], work loss, saving time and money. Patients felt they could establish rapport easily with clinicians [7]. Patient perceptions of telehealth were more positive when their clinicians had more experience [19], and patients often became more comfortable over time. During the pandemic, telehealth was embraced internationally [18,20,21] but not without concern that lack of a physical exam or ability to have lab tests could be detrimental [22].

Qualitative studies dug deeper. A separate qualitative study of RA patients in Denmark from a pre-Covid RCT [23] identified two distinct archetypes of patients: 'keen' and 'reluctant.' The 'keen' patient values autonomy and takes an active role in RA self-management and thus, more open to telehealth. The 'reluctant' patient however relies on their clinician to be the expert and valued in-person visits. This rich study highlights the inability to approach telehealth as a 'one-size fits all' mode of care delivery and that it requires an exploration of patient preferences and a shared decision between clinician and patient about what the best mode of follow up should be. A second qualitative study of RA patients in Australia identified three main themes: acceptability, adjustment, and understanding. Telehealth was viewed as very convenient and acceptable however there was an initial adjustment period (largely getting used to viewing oneself over video) and an appreciation and understanding for why telehealth was important [7].

Clinician experience

A pre-COVID survey of rheumatology clinicians within the VA, a leader in telehealth over the past decade with over a million visits in 2018, found that the majority agreed it would help improve access to care and that it would be most useful for managing rheumatic diseases (as opposed to diagnosing) [24]. Rheumatology clinicians identified inability to perform a physical exam as the number one barrier to telerheumatology that was echoed throughout studies in this review, and among patients as well [7,18,22]. A separate national survey of VA rheumatologists on the management of rheumatic diseases during the pandemic reported that clinician resilience was associated with greater comfort with telephone or video visits [15]. More than 2,000 rheumatologists across 15 Arab countries in the Levant, Gulf and Northern Africa, were surveyed electronically in the early days of the pandemic to assess patient attitudes toward telemedicine [25]. The overwhelming majority of patients accepted

telemedicine with nearly half indicating a preference for phone and 50% via internet. Similarly in a survey of rheumatology clinicians in 20 African nations, patients received care via telephone in the majority of cases, followed by mobile apps, then E-Mail and video which introduced technology barriers [26]. Five rheumatologists from around the world (Brazil, China, England, France, USA) offered their viewpoints on the pandemic and how it affected their practices – both seeing patients and conducting research [27]. One clinician from Boston, underscored how essential the physical exam was to the practice of rheumatology, and highlighted the real risk of inequity with telehealth: 'Video visits expose the digital divide of our society, and some of our patients are unable to fully take advantage of our infrastructure, especially those who are of fewer means, have poorer internet access or are older and less comfortable with technology' - Dr Soumya Raychaudhuri.

Equity, access, and barriers

As pointed out above, the shift to include more telerheumatology even during and then beyond a global pandemic introduces potential issues related to equity, access and barriers. Thirteen percent of Americans lack high-speed internet [28]. Possession of a smart phone or computer ranges between 30 and 40% of those with incomes of $30,000 or less [28]. Although not specifically measured among patients with RA across the globe, a number of studies indicated a potential digital divide and how it was overcome. Shenoy *et al.* surveyed 100 patients in India of whom half relied on family or friends to use their phone or app to attend a teleconsultation. This critical bridge to care is notable in that 44% said if they had not had a telemedicine option they would have stopped their medicine, and 30% said they would have self-medicated [18]. A descriptive study of the implementation of telehealth for rheumatology patients in Iran highlights the ingenuity and do-it-yourself determination to provide care. Rezaian *et al.* describe their experience of providing rheumatology telehealth to 4,270 patients (of whom 50% were Afghan refugees) using one rheumatologist located in the U.S. and general practice clinicians as presenters. Of those seen over a 4-year period, 13.4% were diagnosed with RA. Number of clinic days increased over time given high demand and through word of mouth. Technology barriers were overcome in part with a tower constructed on site specifically to provide the necessary internet bandwidth to care for these patients over Skype [17].

DISCUSSION

The landscape of telerheumatology experienced a seismic shift in 2020 with the arrival of a global pandemic. Prior to COVID-19, patient and clinician experience with telehealth for RA was largely positive, with an emphasis on it being most appropriate for managing RA. Telerheumatology was important to provide care for rural patients and help offset a looming workforce shortage. Advantages included saving patients from excessive travel and costs associated with that and having no significant impact on health outcomes. One study identified two patient archetypes, one 'keen' on telehealth and the other 'reluctant'. Identifying patients and using telehealth for the right patient in the right situation seems crucial to success and acceptability [23].

Clinicians generally find telerheumatology a positive addition to rheumatology practice but are cautious about the most appropriate use. Like patients, clinicians point to the lack of physical exam as a barrier to effective and safe remote rheumatology care. Additionally, phase of care and patient preferences are important considerations. One study highlighted the need to elicit patient preference and that while in some contexts saving distanced traveled may not be a high priority and that rural patients may prioritize benefits of travel beyond their medical care [29].

The COVID-19 pandemic wrought havoc on outpatient rheumatology. It forced the rapid uptake of telehealth for many patients and clinicians across the globe. Some adapted more effortlessly than others. Patient concerns spanned those related to risk of their medications and underlying conditions in the face of possible infection; the lack of physical exam or ability to perform tests was a concern. Some clinicians expressed a fear that the rapid and urgent push to remote care due to the pandemic will result in 'temporizing' cases and fundamentally change the practice of rheumatology [27].

Telerheumatology has the potential to expand access to care but its reach may not be far enough. Depending on the care model, the distance traveled to a spoke site may still be time- and cost-prohibitive for patients. Technology barriers such as lack of high-speed internet or more fundamentally, lack of communication technologies (e.g., phone, tablet, computer), continue to impede telehealth solutions, particularly for patients in rural or frontier communities.

CONCLUSION

Telerheumatology is noninferior to in-person care for patients with RA offering a positive solution to

barriers to access to care. However promising, telerheumatology fails to address the digital divide leaving some patients in care deserts and may not be suitable for all patients. Overall, patients and clinicians consider telerheumatology to be an acceptable and positive alternative to in-person care; particularly in the case of a global pandemic. Buy-in from local, state, and federal leaders will be necessary to expand and develop the telehealth infrastructure and the reach of telerheumatology. Although research in this area has expanded from the original systematic review on this topic by McDougall *et al.* in 2017, a future research agenda must include an examination of health equity, the digital divide, patient preferences and ability to foster true shared decision-making over telehealth, as well as a possible hybrid model of combined in-person and virtual care. Research to explore how and whether telerheumatology can further quality of care in RA is another area in need of study.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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Osteoporosis and fractures in rheumatoid arthritis

Katherine D. Wysham[a], *Joshua F. Baker*[b], *and Dolores M. Shoback*[c]

Purpose of review
Rheumatoid arthritis (RA) is associated with increased risk for osteoporotic fracture. We highlight RA-specific risk factors for bone mineral density (BMD) loss and fractures and considerations regarding the diagnosis and treatment of osteoporosis in patients with RA.

Recent findings
Anticitrullinated protein antibody (ACPA) positivity, although associated with low BMD in early RA, is not associated with accelerated BMD loss over time when compared to ACPA negative individuals. Studies have found reduced BMD in individuals on low doses of glucocorticoids (GCs). Poor functional status and frailty are additional important risk factors for low BMD and fractures. Heightened fracture risk in RA may be mitigated by tight disease control, and biologic therapies are associated with more stable BMD compared to nonbiologic therapies. Evidence-based guidelines specific for treating osteoporosis in patients with RA do not exist. Thus, treatment decisions are based on general osteoporosis guidelines, taking into account additional RA-specific risk factors.

Summary
Recent studies have advanced knowledge of RA-specific risk factors for BMD loss and fractures. Future studies applying these findings to modify established fracture risk algorithms as well as evaluating osteoporosis treatments in RA cohorts are needed to reduce the risk of disabling fractures in these patients.

Keywords
bone mineral density, osteoporosis, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that damages the joints and causes bone demineralization [1], thereby doubling the risk of osteoporotic fractures compared to the general population [2]. Osteoporotic fractures in people with RA are associated with greater mortality [3,4], yet bone mineral density (BMD) screening rates are low patients with RA [5]. Osteoporosis is common in RA, affecting nearly one-third of the RA population [6,7]. Although RA is included in fracture risk calculators (such as the FRAX [8]), the binary representation of RA in such algorithms does not adequately capture the complexity of the disease (severity, duration, auto-antibody status, and treatment regimen and response) [2,9–11]. The heightened risk of skeletal fragility in RA is thought to be due to a combination of factors: the disease itself, medications used to treat it, and alterations in body composition that increase the risk of frailty, falls and fragility fractures (Fig. 1) [6,12–16]. Traditional osteoporosis risk factors must also be considered in the RA population and are detailed in Table 1. There is evidence that with improved RA therapies and less dependence on glucocorticoids (GCs), osteoporosis rates may be on the decline [17▪], however, these studies may be confounded by the lack of adequate osteoporosis testing [5]. Unfortunately, findings from a meta-analysis including all published studies through 2017 suggest that fracture risk in RA remains high, compared to the general population [18], and a study from Spain found increasing hip fracture rates from 1999 to 2015 [19].

[a]Rheumatology Section, VA Puget Sound Healthcare System, Division of Rheumatology, University of Washington, Seattle, Washington, [b]Rheumatology and Epidemiology, Corporal Michael J. Crescenz VA Medical Center, University of Pennsylvania, Philadelphia, Pennsylvania and [c]Endocrine Research Unit, SFVAMC, UCSF, UCSF Training Program in Diabetes, Endocrinology and Metabolism, San Francisco, California, USA

Correspondence to Katherine D. Wysham, MD, VA Puget Sound HCS Seattle Division: VA Puget Sound Healthcare System, 1660 South Columbian Way, S-151-A, Seattle, WA 98108, USA.
Tel: +1 206 764 2251; e-mail: kwysham@uw.edu

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KEY POINTS

- Many risk factors for reduced bone mineral density (BMD) and fractures in rheumatoid arthritis (RA) overlap with those in the general population, but RA-specific factors should be considered to best understand fracture risk.
- BMD screening in patients with RA should be considered at age 50 years or earlier if chronically high disease activity, long disease duration, anticitrullinated protein antibody positivity or significant glucocorticoid exposure are present.
- The evaluation of fall risk, functional status, and frailty is important in patients with RA because these increase risk for fracture.

Table 1. Risk factors for bone mineral density loss in the general population and specific to rheumatoid arthritis

General population	Rheumatoid arthritis
Age	Disease duration
Female sex	Disease activity/ inflammation
Low body mass index	Auto-antibody positivity (notably ACPA)
Current smoking	Erosive disease
Alcohol intake >3 units per day	
Family history of osteoporosis	
Prior fracture	
Glucocorticoid use	
Low vitamin D	
Immobility/disability	
Frailty	
Hypogonadism/menopause	
Secondary osteoporosis[a]	

ACPA, anticyclic citrullinated antibody.
[a]Type 1 diabetes, osteogenesis imperfecta, untreated hyperthyroidism, malnutrition, malabsorption, chronic liver disease, hyperparathyroidism, and many others.

RA-RELATED RISK FACTORS FOR OSTEOPOROSIS AND FRACTURES

Auto-antibodies

Anticitrullinated protein antibodies (ACPAs) have been implicated in the pathogenesis of local joint erosions and systemic bone loss in RA. It is hypothesized that ACPAs bind to and directly stimulate osteoclasts [20] and are markers of more severe disease with higher levels of inflammation-causing systemic bone loss [6]. The finding of low BMD in early RA supports the direct contribution of ACPAs to bone loss, because ACPAs are often present years before RA diagnosis [21▪▪,22–24]. Studies have found conflicting results regarding the association between ACPA levels and BMD [21▪▪,25,26]. A recent study found that ACPA positivity was associated with lower BMD at enrollment in two early RA cohorts but was not associated with an increased risk for BMD loss over time, when compared to ACPA negative patients [21▪▪]. The authors hypothesized that BMD loss was stabilized due to the tight RA disease control and reduced inflammation that was achieved in both groups. A 2019 study found ACPA level, rather than positivity, to be associated with BMD loss at the total hip, but not at the lumbar spine and forearm [27▪]. There are also mixed data regarding the association of rheumatoid factor and anticarbamylated protein antibodies and BMD in RA [24,28]. Given the significant overlap of autoantibodies in RA, it is unclear whether the relationships

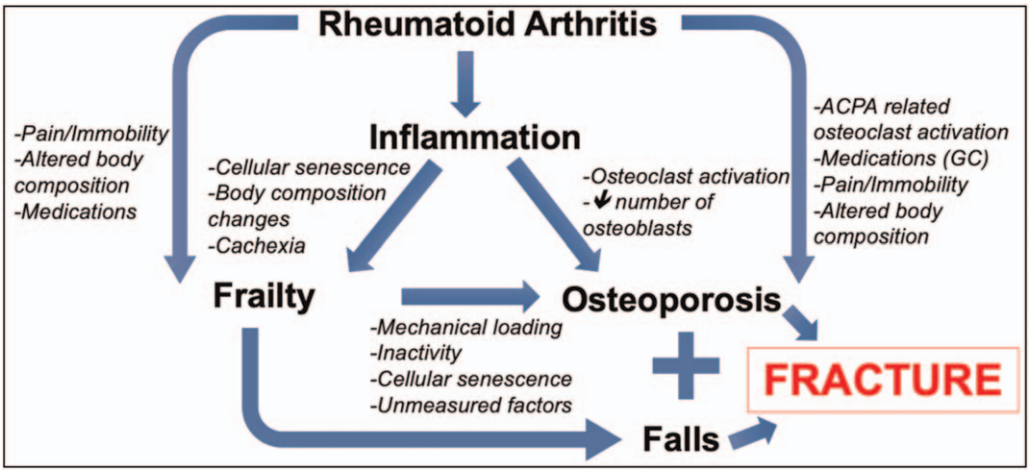

FIGURE 1. Conceptual model showing the relationship between rheumatoid arthritis, inflammation, frailty, osteoporosis, and fracture.

between these autoantibodies and BMD are independent of ACPA status [21▪▪].

Disease activity and associated inflammation

Inflammation influences the development of osteoporosis in the general population and is central to the pathogenesis of RA [1]. Inflammatory cytokines trigger bone resorption by stimulating osteoclasts directly and by inhibiting osteoblast function [29,30]. Higher disease activity as well as erosive disease have been shown to be associated with lower BMD in RA [6,15,31,32]. A recent study utilized propensity score matching between individuals with RA in remission and those without RA and found no significant difference in BMD at the spine and hip, suggesting that tight control of inflammation may mitigate RA as a risk factor for BMD loss [33▪▪]. In addition to effects on bone, inflammation causes loss of muscle mass and muscle function, which through unloading can further diminish bone mass and increase the rate of frailty and falls [34,35]. Treatment of RA with medications that inhibit specific inflammatory cytokines, such as interleukin (IL-6) and tumor necrosis factor alpha (TNFα), has been shown to improve both BMD and physical function [36,37].

Glucocorticoids

GCs increase bone resorption, decrease bone formation, and alter the bone quality, which together significantly increase the risk for osteoporotic fractures [38]. Additionally, GC excess leads to deficits in muscle mass and muscle function, which can exacerbate bone loss and increase fracture risk through decreased mobility, imbalance, and falls [39,40]. On the other hand, GCs are potent anti-inflammatory agents, and this may mitigate inflammation-related bone resorption. GCs also decrease joint pain and stiffness in RA, thereby leading to increased physical activity, which can provide mechanical stimulation for bone. These contradictory effects of GCs on BMD in RA have led to many studies aimed at understanding whether there is an ideal GC dose as it pertains to bone outcomes. Unfortunately, the findings have been conflicting [41,42]. The evolving treatment landscape in RA, the advent of new biologic therapies, and the changing definition of ''low dose GC'' from prednisone equivalents of <10 to now <5–7.5 mg/day in more recent studies, further complicate comparisons. A meta-analysis of randomized controlled trials (RCTs) in patients with RA did not show a statistically significant difference in BMD between GC treatment arms and placebo. Only one study, however, included patients on biologic therapy [41]. A more recent meta-analysis of observational studies found GC use in RA, even at low doses, to be associated with BMD loss compared to studies in those not on GCs [42]. In a study of $>30\,000$ people with RA in the United Kingdom, Wilson *et al.* also found that, even at GC doses <5 mg/day, osteoporosis risk was significantly elevated in RA [43▪▪]. Given the likelihood that even these low doses of GCs are deleterious to skeletal health, the newly proposed 2020 American College of Rheumatology (ACR) RA guideline conditionally recommends a ''treat-to-target'' strategy that avoids GCs, which should prevent unnecessary bone loss in these high-risk individuals [44].

Functional status and disability

The effects of RA disease activity and treatment on BMD and fracture risk are cumulative. It has been consistently shown that patients with longer disease duration and poor functional status have lower BMD and more fractures [7,17▪,31,45]. This is likely because such patients represent a multitude of difficult-to-measure factors such as cumulative inflammatory burden, medication exposures, physical inactivity, body composition changes, as well as joint damage and disability. Recent studies have further explored functional status and found frailty to be associated with low BMD and fractures [46▪,47▪]. Detailed analyses of body composition and performance showed muscle mass [48] and function [47▪] to be associated with BMD in RA, an observation that is consistent with the findings in the general population [49,50]. Obesity, which is common in RA, may also represent an important risk factor for lower extremity fractures, perhaps through its impact on both physical functioning and bone quality [51].

Falls are an important risk factor for osteoporotic fractures in RA and are often overlooked. A recent study found higher disability scores, more foot deformities, and greater use of antihypertensive medications to be significantly associated with falls in an RA cohort [52▪]. If a patient reports falls or unsteady gait or has any of the above risk factors, a formal fall risk assessment is warranted. Lastly, it is important to consider high-risk medications when managing fall risk and fractures in RA. Ozen *et al.* found that in addition to GC, opiates and selective serotonin reuptake inhibitors were associated with increased risks of fracture [53▪▪], whereas TNF inhibitor use was associated with a decreased risk of fracture. Thus, assessments of disability, frailty, falls and high-risk medications followed by interventions targeted to reverse these risks are important components of fracture prevention in RA.

OSTEOPOROSIS DIAGNOSIS

Who to screen

Despite the observation that patients with RA are at high risk for osteoporosis, screening is underperformed [5]. Screening should involve DXA testing if available. Both the National Osteoporosis Foundation (NOF) 2014 osteoporosis [54] and the 2017 ACR glucocorticoid-induced osteoporosis (GIOP) guidelines [55] provide recommendations for BMD screening that can be applied to the RA population. The NOF guideline supports BMD screening in all patients with RA aged 50 years and older [54]. The ACR GIOP guideline recommends BMD screening for anyone 40 years and older who are taking $\geq$2.5 mg prednisone equivalents per day for 3 months or longer [55] and provides guidance for BMD testing for those younger than 40 years with significant risk factors [55].

Fracture risk assessment

It is recommended that clinicians assess fracture risk using the FRAX calculator, which can be done with or without BMD measurements [8]. FRAX takes advantage of a number established clinical risk factors for the fracture to provide 10-year risks of major osteoporotic fracture (MOF) or hip fracture. As mentioned above, FRAX does not take into account any RA-specific characteristics (Table 1) and therefore may not accurately estimate fracture risk in this population [9,10]. We think that RA-specific risk factors should be considered when interpreting fracture risk estimates and that rheumatologists should take an active role in osteoporosis care in these high-risk patients.

Bone mineral density assessments

Dual-energy X-ray absorptiometry (DXA) of the lumbar spine (trabecular site) and of the total hip, and femoral neck (both cortical sites) is the gold standard for BMD assessment. Trabecular bone loss can be exacerbated by both inflammation and GC exposure [56] whereas physical inactivity and sarcopenia frequently lead to cortical bone loss [48]. Screening need not be performed more frequently than every 2 years for most patients with ongoing risk factors. Patients with normal BMD, well-controlled disease, and not using GCs may require even less frequent monitoring (every 3–5 years) [57]. The trabecular bone score (TBS) is also a helpful complement to BMD assessments, and may improve prediction of fracture over BMD alone [58]. Notably, both GC use and RA are factors associated with significant reclassification based on established osteoporosis treatment thresholds [58].

Other screening methods

Although other imaging methods have been used to assess bone mass deficits and independently predict fractures such as ultrasound or peripheral quantitative computed tomography [59], these approaches are not recommended as routine screening tests. There is insufficient evidence to support the use of bone turnover markers in the management of osteoporosis in RA.

OSTEOPOROSIS TREATMENT

Whom to treat

There are no guidelines for the prevention and treatment of osteoporosis that are specific to patients with RA. We recommend consulting the following: ACR GIOP [55], the Endocrine Society [60,61], and American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) Guidelines for the treatment of postmenopausal osteoporosis [57]. For all postmenopausal females or males older than 50 with RA, these guidelines would recommend initiating pharmacologic treatment at *T*-scores of -2.5 or less or at *T*-scores between -1 and -2.5 with a FRAX 10-year risk $\geq$20% for MOF or $\geq$3% for hip fracture [57,60,61]. The ACR GIOP guideline recommends considering pharmacologic treatment for osteoporosis at lower FRAX thresholds for those on chronic GCs (MOF $\geq$ 10% or hip fracture $>$ 1%) [55] and also includes recommendations for people $<$40 years old who are at particularly high-risk including women of childbearing potential and children [55]. Lastly, the ACR GIOP guideline recommends modifying the FRAX calculation for individuals taking $\geq$7.5 mg prednisone equivalent/day by multiplying the MOF risk score by 1.15 and the hip fracture risk score by 1.2 [55]. RA-specific risk factors (Table 1), additional comorbid diagnoses, functional status, fall risk as well as patient preferences should further inform treatment decisions.

Treatment of underlying RA

In 2019, Orsolini *et al.* reported that trials evaluating the effects of medications for RA on BMD demonstrate stabilization or improvement of BMD [62]. The authors highlighted that it is unclear whether the effects on BMD are due to specific medication effects or generally from the control of the inflammation and symptoms caused by RA [62]. There are

emerging observational data supporting the use of biologic medications for maintaining spine and hip BMD in RA. In 2020, Chen *et al.* utilized propensity score matching to demonstrate that biologic RA medications were associated with no significant change in BMD over 3 years, whereas the use of nonbiologic RA medications was associated with BMD loss [63▪]. The study used propensity score matching based on important variables related to BMD in RA (e.g. age, sex, menopausal status, body mass index, ACPA positivity), but these investigators were unable to match for baseline and mean disease activity and functional status, which are known to influence BMD and impact DMARD choice. Another observational study in 2020 also utilized propensity score matching on important clinical variables and found no statistically significant difference in rates of fractures between users of TNF-inhibitors and abatacept or tocilizumab, although the number of fractures might limit the ability to detect differences between groups [64▪]. Currently, there are limited data on the effects of conventional synthetic disease-modifying antirheumatic drugs or janus kinase inhibitors on BMD in RA. Currently, there are no RA treatments that are recommended specifically to preserve BMD and reduce fractures beyond the goal of minimizing disease activity

Calcium and vitamin D

Adequate calcium and vitamin D are necessary to maintain BMD, and these interventions are particularly important in persons with RA. Ensuring adequate calcium intake through diet and supplementation with a target of 1000–1200 mg/day is important to promote bone health. The 2017 ACR GIOP guideline recommends serum 25-hydroxyvitamin D assessment and achieving a goal of $\geq$20 ng/ml with a daily maintenance dose of 600–800 IU cholecalciferol whereas the AACE/ACE guideline sets a target of $\geq$30 ng/ml (range: 30–50 ng/ml) with daily cholecalciferol dose of 1000–2000 IU [55,57].

Osteoporosis-specific therapies

Although the Endocrine Society [60,61] and AACE/ACE Guidelines [57] are specifically for the treatment of postmenopausal osteoporosis, one can apply them to the treatment of people with RA based on using calculated 10-year fracture risk based on FRAX. The ACR GIOP guideline provides detailed information for those on GCs and generally recommends consideration of oral bisphosphonates as first-line treatment, given less experience with the use of other osteoporosis treatments for GIOP [55].

Few trials have evaluated osteoporosis treatments specifically in patients with RA, yet many of the studies on the treatment of GIOP enrolled substantial proportions of participants with RA. Bisphosphonates [65] are approved for both prevention and treatment of GIOP whereas teriparatide [66] and denosumab [67▪] are approved only for the treatment of GIOP. A 2019 GIOP RCT, where one-third of the study population had RA, found denosumab superior to risedronate at increasing BMD at both the spine and hip, although fracture rates were similar between groups [67▪]. Newer anti-osteoporotic therapies, abaloparatide, and romosozumab, have yet to be studied in GIOP but can be considered as off-label treatments for people with RA, if they are at very high risk for fracture [57,60,61].

Denosumab is an inhibitor of receptor activator of nuclear factor kB ligand (RANKL), which is required for osteoclast activation and survival. Denosumab has been studied specifically in RA to determine if it and methotrexate can decrease disease activity and erosions, as well as increase BMD. RCTs have shown that denosumab increases BMD and decreases RA-related erosions, but does not decrease inflammation or joint space narrowing [68▪]. Therefore, denosumab should not be used to treat RA disease activity, but as a potent antiresorptive, it can be considered for the treatment of osteoporosis in this high-risk group. In contrast, a study of RA patients well controlled on TNF-inhibitors did not find the addition of teriparatide to have a significant effect on erosions [69].

Treatment courses and monitoring of therapies are not within the scope of this review. We recommend the guidelines discussed above to help inform these important decisions [54,55,57,60,61].

CONCLUSIONS

RA is an important risk factor for BMD loss and fractures, which can have devastating outcomes such as pain, disability and death. Many risk factors for reduced BMD and increased fracture rates in RA overlap with those in the general population. We have highlighted important RA-specific risk factors for BMD loss and fracture (Table 1). It is important to consider early BMD screening and intervention in people with RA with high disease activity, longer disease duration, ACPA positivity as well as significant GC exposure. It is also important to routinely address physical functioning and falls. Although RA-specific osteoporosis guidelines do not exist, risk-stratification based on FRAX and application of

established treatment guidelines provide a critical framework for the management of osteoporosis in this high-risk population.

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Conflicts of interest

There are no conflicts of interest.

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Glucocorticoid and opioid use in rheumatoid arthritis management

Meriah N. Moore[a] *and Beth I. Wallace*[a,b]

Purpose of review
Glucocorticoids and opioids are longstanding, common treatments for rheumatoid arthritis (RA) symptoms. High-quality clinical trials have established that glucocorticoids improve outcomes in RA, but debate continues as to whether their benefits outweigh their risks. We reviewed recent studies on patterns of glucocorticoid and opioid prescribing in RA, and associated harms.

Recent findings
At present, a large proportion of RA patients remain on glucocorticoids and/or opioids long-term. Likelihood and risk of both glucocorticoid and opioid exposure vary across the population, and are influenced by provider factors. Opioids are also associated with delays in disease-modifying treatment initiation. Recent evidence increasingly demonstrates toxicity associated with even low-dose glucocorticoids ($\leq$7.5 mg/day). Up to two-thirds of RA patients may be able to discontinue chronic low-dose glucocorticoids without flare or adrenal insufficiency. These new data have led to changes in clinical practice guidelines for glucocorticoid use in RA.

Summary
Although low-dose and short-term glucocorticoid use is extremely common and effective in RA management, increasing evidence of toxicity has led experts to begin recommending that such exposure be minimized. Despite a lack of data to suggest opioids improve RA disease activity, they are used commonly, continued long-term, and associated with delayed effective therapy.

Keywords
glucocorticoids, opioids, rheumatoid arthritis

INTRODUCTION

Glucocorticoids and opioids have been used for decades to manage symptoms of rheumatoid arthritis (RA). Although their physiologic mechanisms are quite different, both drug classes are commonly prescribed for short-term pain relief, or as a 'bridge' to manage symptoms while waiting for disease-modifying antirheumatic drugs (DMARDs) to take effect. The unfavorable risk profiles of both glucocorticoids and opioids are well characterized, yet prolonged use of drugs in both classes remains common in RA [1,2▪▪]. It is thus important to frequently evaluate the prescribing patterns and risk profile of these well-established medications.

The present review will focus on current practices of glucocorticoid and opioid utilization in RA, recent evaluations of their risk profiles, and ongoing efforts to optimize their prescribing in order to improve patient outcomes.

GLUCOCORTICOID PRACTICE PATTERNS

Although treatment guidelines recommend limiting glucocorticoid use to the shortest possible duration, recent studies suggest that long-term, low-dose glucocorticoid use ($\leq$10 mg/day prednisone or less, for $\geq$3 months) is extremely common (Table 1). Hanly *et al.* evaluated glucocorticoid utilization by 8420 elderly RA patients in Nova Scotia from 1997 to 2017 [3▪]. Despite substantial changes in RA treatment guidelines during this time, >30% of these patients received >9 months of glucocorticoids in both 1997 and 2017, with as many as 50% receiving these prolonged durations in the mid-2000s. Recent studies in several other administrative and registry cohorts yielded similar results, with between one-third and two-thirds of RA patients using long-term, low-dose glucocorticoids (Table 1). Of particular concern, many of these patients may be taking

[a]University of Michigan Medical School and [b]VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

Correspondence to Beth I. Wallace, MD, MSc, Division of Rheumatology, University of Michigan, 300 North Ingalls Building, Room 7C27, Ann Arbor, MI 48109, USA. Tel: +1 734 936 1439; e-mail: brennerb@umich.edu

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KEY POINTS

- Both glucocorticoid and opioid use are common among patients with rheumatoid arthritis (RA). The likelihood and risks of exposure to both drug classes vary across the RA population, and are influenced by provider factors.
- As even very low dose glucocorticoids are associated with demonstrable adverse effects, and many patients with RA may be able to discontinue them successfully, the risks of using glucocorticoids to maintain disease control in RA may outweigh the benefits.
- Chronic opioid use has recently increased among patients with RA despite its inability to effectively modify RA-related pain or reduce disease activity.
- Opioid exposure is associated with delays in disease-modifying treatment initiation among patients with RA.

glucocorticoids even once their RA is in remission or low disease activity [1,4].

Several studies suggest that long-term glucocorticoid use may not be uniform across the RA population. George *et al.* used a 155 539-patient cohort of Medicare beneficiaries to evaluate the effect of rheumatologist 'preference' for glucocorticoids, defined as the frequency of prescribing relative to other providers. After controlling for claims-based measures of demographics, overall health, and RA disease status, patients with rheumatologists in the highest preference quintile had a 2-fold higher prevalence of prednisone use $\geq$5 mg/day relative to those in the lowest quintile [5▪]. Other recent studies support previous findings that long-term glucocorticoid use is more common in patients with older age, male sex, and higher comorbidity burden [6–8]. Although confounding by indication and/or reverse causality may contribute to this finding, patient and provider concerns about the risks of biologic and/or DMARD use may also encourage prolonged glucocorticoid use in these high-risk individuals.

GLUCOCORTICOID RISK PROFILE

In the past two decades, multiple clinical trials have demonstrated reduced radiographic damage, improved physical function, and decreased RA activity when low-dose glucocorticoids (prednisone 10 mg/day or less) are added to synthetic DMARDs [9]. As this evidence mounted, many providers and experts felt the benefits of using short-term and/or low dose glucocorticoids for RA management might be worth the potential risks [10–12]. In this setting, the 2013 European League Against Rheumatism (EULAR) and 2015 American College of Rheumatology (ACR) RA treatment guidelines both recommended considering glucocorticoids as a 'bridge' when starting or escalating DMARDs, though stipulating that they should be used at the lowest possible dose for the shortest possible time [13,14]. In the years since, multiple high-quality observational studies have demonstrated small, but significant, associations between short-term and low-dose glucocorticoid use and adverse events in RA, leading to a shift in how these treatments are perceived.

Multiple recent studies demonstrate associations between long-term use of low-dose glucocorticoids and adverse events. In a cohort of 9387 British patients followed for a median of 8 years, RA patients who received glucocorticoids (median 5.8 mg/day for 9.5 months) had significantly higher

Table 1. Practice patterns of long-term glucocorticoid use in RA

Study	Population	Time period	Percent of RA patients using GCs	Mean GC dose	Mean GC duration
Hanly *et al.* J Rheumatol 2020 [3▪]	Nova Scotia Medical Services Insurance Program	1997–2017	31%	4–5 mg/day[a]	- 11–20% 3–6 months[a] - 11–18% 6–9 months[a] - 32% >9 months[a]
George *et al.* Arthritis Care Res 2020 [5▪]	Medicare	2006–2015	47%	1–10 mg/day	6 months
Wallace *et al.* Semin Arthritis Rheum 2020 [38]	Optum	2010–2014	31%	10 mg/day	6 months
Pappas *et al.* Rheumatol Ther 2019 [47]	CORRONA registry	2010	34%	7.7 mg/day	70% continued for >6 months
Roubille *et al.* Rheumatol 2020 [48]	ESPOIR cohort	2002–2015	65%	1.9 mg/day	44 months

CORRONA, Consortium of Rheumatology Researchers of North America; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récente (translation: 'Study and Followup of Undifferentiated Early Arthritis'); GCs, glucocorticoids; RA, rheumatoid arthritis.
[a]Estimated from figures, exact statistics not listed.

incidence rates of diabetes, osteoporosis, fractures, hypertension, thrombotic stroke or myocardial infarction, gastrointestinal (GI) perforation or bleeding, hospitalization for infection, and death compared to those who did not [15▪▪]. Absolute risk differences ranged from 0.2 to 7.8 per 1000 patient-years (for fractures and death, respectively). These effects were dose-dependent, and persisted after adjusting for baseline comorbidities and claims-based measures of RA disease activity. Other recent studies report similar independent associations between prolonged low-dose glucocorticoid use (2.5–7.5 mg/day) and increased risk of cardiovascular disease [8], severe infections [16▪▪], hypertension [17], osteoporosis and fractures [18–20], diabetes [21], and mortality [22]. Although absolute risk increases in these studies were relatively small, this excess harm is important given the large number of patients exposed to low-dose glucocorticoids. Additionally, the likelihood of such adverse events appears unevenly distributed across the RA population, with the elderly and those with baseline comorbidities at higher risk [22]. Reported risk increases may thus underestimate the true harm attributable to chronic glucocorticoid use among these vulnerable yet frequently exposed populations.

Although not specific to RA, two recent studies of national and international administrative databases suggest even very short glucocorticoid 'bursts' (median 3–6 days) are independently associated with increased rates of sepsis, venous thromboembolism, fracture, GI bleeding, and heart failure for up to 90 days after exposure [23▪,24]. Both studies used a self-controlled case series design that compares individuals' event rates before and after glucocorticoid exposure. Although this method substantially reduces time-invariant confounding, it does not address the impact of underlying conditions (such as RA), or differences in prescribing indication, on both the exposure and the outcome. Rate increases were seen even among young healthy patients, and increased with increasing age and comorbidity. Although absolute risk increases were again small (range 0.8–10.3 per 1000 patient-years for sepsis and GI bleeding respectively), these trends suggest even patients in the general population perceived to be 'low risk' for glucocorticoid-associated harm may also suffer substantial morbidity attributable to glucocorticoid exposure.

EFFORTS TO OPTIMIZE GLUCOCORTICOID PRESCRIBING

In response to the evidence above, the 2020 ACR guidelines for RA management contain significantly altered recommendations for glucocorticoid use (Table 2) [25▪▪]. Prior versions conditionally recommended glucocorticoid 'bridging' when escalating DMARD therapy, and supported an individualized approach to the use of long-term glucocorticoids to maintain disease activity [13]. In contrast, revised ACR guidelines conditionally recommend against bridging, and strongly recommend discontinuing long-term glucocorticoids, when RA is well controlled. The 2019 EULAR guidelines reiterate that providers should avoid using long-term glucocorticoids to maintain treatment target, but continue to support bridging therapy [26▪].

There is ongoing interest in conducting clinical trials to evaluate the impact of long-term glucocorticoid use [27]. Such trials, while important, face limitations in their ability to detect glucocorticoid-

Table 2. Guideline recommendations for use of glucocorticoids in rheumatoid arthritis management

	ACR 2015 [16▪▪]	EULAR 2013 [14]	ACR 2020 [28]	EULAR 2019 [29]
GC 'bridging'	Addition of low-dose glucocorticoids conditionally recommended when initiating or escalating treatment in patients with moderate or high RA disease activity	Low-dose GC should be combined with initial DMARD treatment for 'up to 6 months, but should be tapered as rapidly as clinically feasible'	Initiation of DMARDs without bridging GCs conditionally recommended overuse of bridging GCs, regardless of RA disease activity	Clinicians are encouraged to consider short-term glucocorticoids when initiating or changing DMARDS, but recommended to taper them 'as rapidly as clinically feasible'
Long-term GCs to remain at target	Recommended individualized approach, using 'lowest possible dose for the shortest possible duration to provide the best risk-benefit ratio for the patient'	Long-term use not directly addressed, but GC should be withdrawn in those with persistent remission	Long-term GCs strongly discouraged, providers encouraged to add or switch DMARDs to avoid long-term GC use	Not directly addressed in a recommendation. Manuscript notes that failure to sustain target disease activity when GCs are tapered should prompt treatment escalation

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; GCs, glucocorticoids.

related toxicity. First, many of the most serious harms related to glucocorticoid use (myocardial infarction, stroke, severe infection, death) are relatively rare, can take years to manifest, and/or are expensive to screen for, limiting the ability of most clinical trials to assess event rates accurately. Trials may attempt to mitigate this by collapsing adverse events into a single safety outcome, using a co-primary endpoint for safety and efficacy, or relying on participant and/or provider-reported adverse events. Although understandable, these decisions can complicate the interpretation of safety results, reducing their utility to providers. Second, clinical trials often exclude patients with relevant health conditions (diabetes, hypertension, osteoporosis, 'uncontrolled comorbidities') [27], despite the fact that such patients are both more likely to receive glucocorticoids, and more likely to be harmed by them, in routine practice [6]. Lastly, since clinical trials often recruit patients from rheumatologist's offices or are sponsored by pharmaceutical companies, they may not adequately represent populations with barriers to specialty care [28].

With rising evidence of harm, there has been increasing interest in discontinuing long-term glucocorticoids, especially in patients with well-controlled RA or risk factors associated with increased toxicity [3▪,29,30]. However, despite explicit support for prompt glucocorticoid tapering in both national and international RA treatment guidelines, there is little data to guide clinicians and patients attempting to discontinue glucocorticoids [31▪]. Data have been especially limited for established RA patients using long-term glucocorticoids, despite their higher risk of exposure-related toxicity [31▪]. Burmester *et al.* recently published the Steroid EliMination In RA (SEMIRA) trial, one of the first double-blind multicenter randomized controlled trials of glucocorticoid discontinuation [32▪▪]. The 259 participants, all long-term glucocorticoid users with well-controlled RA, were randomized to either continue 5 mg/day prednisone, or taper off over 16 weeks. No DMARD escalation was permitted during the study period. The withdrawal rate postrandomization was 13% for both treatment groups. Sixty-five percent of participants randomized to taper were able to do so with no disease flare, and no participants developed clinical adrenal insufficiency.

The SEMIRA trial provides evidence for the efficacy of a common clinical practice: tapering long-term glucocorticoids by 1 mg/month. It also suggests clinical adrenal insufficiency is rare when tapering low-dose glucocorticoids, even among long-term users. However, this trial was not powered to evaluate how non-RA factors like age, disability, glucocorticoid withdrawal symptoms, and chronic non-inflammatory pain conditions may have affected the success of glucocorticoid discontinuation. Selection bias was also an issue; 55 of 246 participants (55%) were not randomized due to inability to taper their glucocorticoid dose to 5 mg/day during lead-in. Additional studies are needed to explore these unanswered questions.

OPIOID PRACTICE PATTERNS

In the past decade, the opioid epidemic has become a significant public health focus due to high rates of opioid use and associated mortality in the general population. Patients with RA are at increased risk of chronic opioid use relative to others, with utilization increasing over time (Table 3). A study of 33 739 participants in the Consortium of Rheumatology Researchers of North America (CORRONA) registry found the prevalence of chronic opioid use more than doubled between 2002 and 2015, from 7.4% to 16.9% [2▪▪]. Data from other populations also suggest high opioid use by patients with RA, with a concerning rise over the past 10 years (Table 3) [33–35].

Risk factors for chronic opioid use in the RA population mirror those in the general population, including older age, severe pain, comorbidity, use of antidepressants or benzodiazepines, and high level of disability [2▪▪,34,36]. Several studies also show an association between RA disease activity and incident chronic opioid use. The study of CORRONA participants referenced above also found a 55%-fold increase in incident chronic opioid use among patients with high RA activity [2▪▪], although opioids do not modify RA activity or effectively reduce inflammatory pain. Obesity may magnify this effect; an analysis of 19 794 participants in the FORWARD National Data Bank for Rheumatic diseases found that a body mass index $>35\,kg/m^2$ was associated with a 74% increase in the hazard of opioid use [37▪]. Over half of persistent strong opioid use at 5 years was attributable directly to obesity in this study, suggesting weight-related comorbidities like pain centralization or osteoarthritis may drive opioid use in some cases.

Analogous to trends in glucocorticoid prescribing, there is evidence of large inter-provider variation in opioid prescribing [5▪,38]. In a study of 97 859 Medicare beneficiaries, a quarter of rheumatologists prescribed opioids to more than half their RA patients, whereas another quarter prescribed opioids to fewer than a third of similar patients [34]. The same study found that patients seen by a 'high opioid prescriber' were 25% more likely to use opioids regularly than those with other providers [34].

Table 3. Practice patterns of opioid use in RA

Study	Population	Time period	Percentage using opioids
Machado-Duque *et al.* Pain Res Manag, 2020 [36]	Colombian Health System	2011	84% for at least 1 month 46.7% >12 months
Lee *et al.* Arthritis Rheumatol 2019 [2▪▪]	CORRONA	2002–2015	2002 7.4% chronic use 2015 16.9% chronic use
Kimsey *et al.* Semin Arth Rheum 2019 [43▪]	US Military TRICARE Program	2007–2012	35.5% between RA diagnosis and first DMARD
Baker *et al.* Arthritis Care Res 2020 [37▪]	FORWARD National Data Bank for Rheumatic Diseases	1999–2019	15% any use
Curtis *et al.* Arthritis Rheumatol 2017 [34]	Medicare	2014	60% any use: - 41% regular users - 19% intermittent users
Kuo *et al.* Am J Med 2016 [33]	Medicare	2012	20% any use
Zamora-Legoff *et al.* Clin Rheum 2016 [35]	Population-based cohort in Olmstead Co., Minnesota	2005–2014	Any use: - 2005: 34%[a] - 2014: 40% Chronic use: - 2005: 2%[a] - 2014: 12%

CORRONA, Consortium of Rheumatology Researchers of North America; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.
[a]Estimated from figures, exact statistics not listed.

OPIOID RISK PROFILE

We will focus on RA-specific risks of opioid use, as general risks are well described elsewhere [39]. In a study of 12 840 Medicare beneficiaries, opioid use was associated with an increased risk of myocardial infarction (HR 2.25), heart failure (HR 1.63), coronary revascularization (HR 5.34), and cardiac death (HR 1.96), as well as both overall hospitalization (HR 1.68) and all-cause death (1.87) relative to NSAID use [40]. Several other studies in both the general [41] and RA populations [40,42], also describe an association between opioid use and increased fracture risk. Potential mediators for these risks include disability level, glucocorticoid use, RA disease activity level, comorbidities, and (in the case of fractures), cognitive or motor impairment related to opioid use.

In addition to these risks, opioid use may contribute to delays in DMARD initiation. In a claims analysis of active-duty military personnel between 2007 and 2012, odds of initiating a DMARD ≥90 days after initial RA presentation were 4.74 times higher for opioid users compared to nonusers [43▪]. These odds improved over the study period, suggesting modifiable factors like provider preference and guideline awareness may partially mediate this association. Significant differences by military rank were also noted, echoing prior work showing an association between low wealth and opioid exposure [44] and suggesting opioids may be used as a stopgap in populations with limited access to specialty care or costly disease-modifying medications. Concerningly, opioid use often continues after DMARD initiation, with only 2.5–3% of patients discontinuing opioids in the subsequent 6–12 months [45,46]. Despite the absence of strong data to support the efficacy of chronic opioids for RA-related pain, the rates of use have increased and are associated.

CONCLUSIONS

Glucocorticoids are potent anti-inflammatory agents, however, even short courses or low doses are associated with harm. Reflective of this data, the 2020 ACR recommendations have shifted away from the use of glucocorticoids as bridging therapy. Randomized control trial data has revealed tapering can be safe and effective in a large population of RA patients, but more work is needed to understand candidates and strategies for glucocorticoid tapering. Use of opioids among RA patients has increased over time, which raises concern given not only their adverse risk profile in the general population, but also because they can delay the initiation of disease-modifying RA therapies. Further efforts are needed to optimize glucocorticoid and opioid prescribing in order to improve patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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Interstitial lung disease throughout the rheumatoid arthritis disease course

Gregory C. McDermott[a,c], *Tracy J. Doyle*[b,c], *and Jeffrey A. Sparks*[a,c]

Purpose of review
To summarize the current understanding of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) throughout the rheumatoid arthritis (RA) disease course from preclinical to established disease.

Recent findings
ILD is a serious extra-articular manifestation of RA. Multiple studies have demonstrated a high prevalence of both subclinical and clinical ILD throughout the RA disease course. Investigations of patients without RA have demonstrated an association between RA-related autoantibodies like anticitrullinated protein antibodies (ACPA) and interstitial abnormalities on lung imaging. A significant proportion of RA-ILD patients develop ILD prior to articular manifestations, suggesting that the lung plays a central role in RA development, perhaps through ACPA production. RA-ILD also occurs in early RA, when exuberant autoantibody production and systemic inflammation may propagate pulmonary disease activity. In patients with established RA, a high burden of subclinical and clinical ILD results in significant morbidity, mortality, and healthcare expenditure. Multiple epidemiologic and genetic risk factors, as well as serum biomarkers, have been associated with RA-ILD.

Summary
Subclinical and clinical ILD occur frequently in preclinical, early, and established RA and may play a key role in RA-related autoantibody production and disease progression. Further studies are needed to better understand the risk factors, prognosis, and potential therapies for RA-ILD.

Keywords
disease course, interstitial lung disease, pathogenesis, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects nearly 1% of adults [1]. Although the hallmark clinical manifestation of RA is a painful, destructive, inflammatory arthritis, extra-articular manifestations are common and contribute to excess morbidity and mortality [2]. RA-associated interstitial lung disease (RA-ILD) is a serious extra-articular complication of RA that involves several radiologic and pathologic subtypes. Previously considered a consequence of prolonged disease severity in longstanding RA, subclinical and clinical interstitial lung disease (ILD) are increasingly recognized throughout the entire RA disease course. In this review, we detail the pathogenesis of RA-ILD, summarize the current understanding of RA-ILD in preclinical, early, and established RA and describe the clinical importance of ILD among patients with RA.

LUNG INFLAMMATION AND RA PATHOGENESIS

Epidemiological, clinical, and molecular studies have demonstrated that the lung likely plays a central and complex role in the development of RA. According to the 'mucosal origin' hypothesis, a combination of genetic factors and environmental exposures contribute to the development of RA-related autoantibodies at mucosal sites, including the lung, oropharynx, cervicovaginal site, gingiva, and gastrointestinal tract [3]. In the lung, injury to the alveoli, airway epithelium, and mucosa occurs through smoking, microbial dysbiosis, or other environmental/inhalant exposures [4]. In a genetically susceptible individual, this damage can lead to increased protein citrullination, production of

[a]Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, [b]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital and [c]Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Jeffrey A. Sparks, MD, MMSc, Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, 60 Fenwood Road, #6016U, Boston, MA 02115, USA.
Tel: +1 617 525 1040; fax: +617 732 5766;
e-mail: jsparks@bwh.harvard.edu

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KEY POINTS

- Interstitial lung disease (ILD) is a serious extra-articular manifestation of rheumatoid arthritis (RA) and a significant driver of morbidity, mortality, and healthcare costs in RA patients.
- Subclinical and clinical RA-ILD can be seen throughout the entire RA disease course from preclinical to established disease.
- The presence of high titers of anticitrullinated protein antibodies (ACPA) in pulmonary samples, including in patients prior to RA diagnosis, suggests that the lung plays a central role in RA pathogenesis.
- Risk factors for RA-ILD include older age, smoking, male sex, longer RA disease duration, and elevated ACPA as well as the *MUC5B* promoter variant.
- Further efforts to study risk factors, prognosis, and management of RA-ILD are necessary and would be aided by standardized diagnostic criteria for subclinical and clinical RA-ILD.

neutrophil extracellular traps, generation of local RA-related autoantibodies, and, ultimately, the establishment of systemic autoimmunity [5]. Ongoing injury from repeat exposures and autoimmunity triggers chronic inflammation that can lead to airway and pulmonary interstitial remodeling [6].

Multiple studies have suggested that the lung plays a key role in RA pathogenesis. Several investigations have identified respiratory risk factors for RA disease, including cigarette smoking and silica exposure [7,8]. The central role that the lung plays in the generation of RA-related autoantibodies such as anticitrullinated protein antibodies (ACPAs) is supported by evidence of elevated titers of ACPAs in sputum samples of patients with RA, including the majority of early-RA patients [9]. Similarly, increased ACPA staining and lymphoid aggregates have been observed in transbronchial biopsies of RA patients and a recent study of ACPA-positive patients at risk of developing RA or having early untreated RA demonstrated evidence of citrulline-reactive B cells in bronchoalveolar lavage sampling, suggesting a direct link between lung inflammation and systemic RA disease progression [10,11].

Several research findings have demonstrated the importance of an underlying genetic predisposition to both RA and RA-ILD. One study identified that the human leukocyte antigen (HLA) shared epitope (*HLA-DRB1*) was associated with RA-ILD in the presence of smoking [12]. The *MUC5B* promoter variant, a known genetic risk factor for idiopathic pulmonary fibrosis (IPF), has also been identified as a risk factor for RA-ILD, specific to the usual interstitial pneumonia (UIP) subtype that is analogous to IPF [13].

ILD THROUGHOUT THE RA DISEASE COURSE

Ellmann and Ball initially noted the association between RA and ILD in 1948 when they described pulmonary lesions as part of the 'rheumatoid state' in three patients [14]. Since this initial observation, multiple investigations have estimated the prevalence of RA-ILD from 2 to 60% [12,15,16]. This wide range is due to significant variability in study design, diagnostic methods, and disease definition, but symptomatic RA-ILD likely occurs in 5–17% of patients, whereas radiologic interstitial lung abnormalities on chest high resolution computed tomography (HRCT) may be seen in up to 60% [6,17]. Despite the heterogeneity in study designs, it is increasingly apparent that this full spectrum of lung disease – ranging from subclinical interstitial lung abnormalities to clinical ILD – can be seen throughout the entire RA disease course.

ILD in preclinical RA

Investigations of lung disease in patients prior to clinical RA diagnosis (pre-RA) have typically focused on patients at risk of developing RA based on autoantibody profile. Patients with elevations in serum RA-related autoantibodies – rheumatoid factor (RF) and ACPA – have a 50% risk of progressing to clinical RA within 3 years, making them an attractive population for investigations into RA pathogenesis [18–20]. Furthermore, multiple studies have identified an association between RA-related autoantibodies and lung abnormalities on imaging, even in patients without apparent inflammatory arthritis. A large cross-sectional study of the general population showed correlations between RF and ACPA levels with ILD features detected on cardiac CT chest scans [21]. Another cohort study of patients with IPF found an increased prevalence of ACPA [22▪]. Other studies investigating patients with RA-related autoantibodies who lack clinical evidence of inflammatory arthritis have demonstrated a significant prevalence of radiologic pulmonary abnormalities. In one study of ACPA-positive patients with respiratory symptoms who lacked clinical evidence of RA, 39% had radiologically-detected ILD [23]. Similarly, 77% of patients with RF or ACPA positivity but without inflammatory arthritis had radiologic abnormalities on HRCT in a different investigation of 45 patients [24]. Finally, a study performed on patients at our center with elevated ACPA without

Table 1. Selected studies reporting ILD in preclinical RA or concurrent with articular diagnosis

Study	Country	Study period	Total patients with RA-ILD	ILD diagnosis occurred before articular RA diagnosis	Concurrent articular RA and ILD diagnoses
Hyldgaard *et al.* [27]	Denmark	2004–2016	679	14%[a]	34% (within 1 year)
Mohning *et al.* [25▪▪]	USA	2000–2014	137	10%	17% (within 1 year)
Kelly *et al.* [26]	UK	1987–2012	230	10%	7%
Zhang *et al.* [28]	China	2008–2013	237	13.5%	Not reported
Chen *et al.* [29▪]	China	2008–2017	241	17.4%	13.7%

[a]ILD diagnosis 1–5 years prior to articular RA diagnosis.
ILD, interstitial lung disease; RA, rheumatoid arthritis.

RA demonstrated that known/suspected lung disease was the second most common reason for testing after arthralgias [18].

Patients who develop ILD preceding or concurrent with RA diagnosis provide further evidence of the importance of ILD in the pre-RA period prior to clinical articular involvement (Table 1). Recent cohort studies of RA-ILD patients from Denmark, the United States, and China noted that 10–17% of patients were diagnosed with ILD prior to the articular diagnosis of RA [25▪▪,26–28,29▪]. An additional 7–34% of patients were diagnosed with RA and ILD concurrently [25▪▪,26–28,29▪]. The largest of these cohorts, a nationwide study in Denmark, noted that 14% of RA-ILD cases were diagnosed with lung disease 1–5 years prior to RA diagnosis and, overall, RA-ILD was seen in 2.2% of incident RA patients [27]. These studies show that significant lung abnormalities on a spectrum of ILD may develop prior to articular disease manifestations and provide further evidence of the importance of lung inflammation in RA disease pathogenesis.

ILD in early RA

Multiple studies have also demonstrated a high prevalence of both subclinical and clinical ILD in patients with early RA, most often defined as the 2-year period after clinical RA diagnosis (Table 2). Two investigations that examined patients with early RA using relatively comprehensive measures including radiologic imaging, functional testing, and nuclear lung scanning, showed that 44–53% of patients had lung abnormalities in at least one testing modality [30,31]. More recent studies relying on the use of HRCT imaging found evidence of clinical RA-ILD in 10–14% of RA patients with 1–2 years of disease duration [32,33]. Subclinical ILD was detected in

Table 2. Selected studies investigating RA-ILD or pulmonary abnormalities in early-RA (within 1–2 years of articular RA diagnosis)

Study	Country	Study period	Population	*n*	Methods of detection of ILD or other pulmonary abnormalities	Findings
Reynisdottir *et al.* [11]	Sweden	n/a	New RA diagnosis, no treatment	105	HRCT	63% of ACPA-positive with pulmonary abnormalities
Doyle *et al.* [31]	USA	n/a	New RA diagnosis, no treatment	18	ABG, CXR, spirometry, plethysmography, eucapneic hyperventilation	53% with at least one abnormality
Gabbay *et al.* [30]	Australia	n/a	RA <2 years duration	36	CXR, HRCT, BAL, PFTs, nuclear scan	Clinical RA-ILD in 14% Subclinical RA-ILD in 44%
Habib *et al.* [32]	Saudi Arabia	2007–2009	RA <2 years duration	40	HRCT, PFTs	Clinical RA-ILD in 10% Subclinical RA-ILD in 35%
Dong *et al.* [34▪]	USA	2011–2013	RA <1 year duration	18	HRCT, PFTs	39% with abnormalities
Mori *et al.* [33]	Japan	2003–2007	RA <1 year duration	65	HRCT, PFTs	13.8% with classic ILD pattern

ABG, arterial blood gas; ACPA, anti-citrullinated protein antibodies; BAL, bronchoalveolar lavage; CXR, chest radiograph; HRCT, high resolution computed tomography; ILD, interstitial lung disease; n/a, not available; PFTs, pulmonary function tests; RA, rheumatoid arthritis.

35–39% of early RA patients in studies from the United States and Saudi Arabia [32,34▪]. The presence of ACPA in early RA seems to be especially associated with lung imaging abnormalities as one investigation found that 63% of patients with newly diagnosed, untreated, ACPA-positive RA had abnormalities on HRCT [11].

Further evidence of the importance of the early RA period in RA-ILD comes from longitudinal studies that noted a high incidence of RA-ILD shortly after clinical (articular) RA diagnosis. A large longitudinal study of RA patients in Denmark found that 34% of RA-ILD cases received their ILD diagnosis within the first year after RA diagnosis [27]. Similarly, a retrospective, single-center study noted that 17% of patients with RA-ILD were diagnosed with ILD and RA within the same year [25▪▪]. Recently presented data from the Discus JointMan database of incident RA found that 47% of RA-ILD cases developed within 2 years of the onset of articular RA [35].

One plausible explanation for the pivotal role that early RA plays in RA-ILD pathogenesis is that this period is characterized by exuberant systemic inflammation and autoantibody production. This may lead to progressive airway inflammation and lung damage. Support for this theory comes from data suggesting that higher levels of ACPA, inflammatory markers, and disease activity are all risk factors for RA-ILD [29▪,36▪]. It is also possible that increased healthcare utilization due to newly diagnosed RA may result in earlier detection of occult or subclinical pulmonary abnormalities related to RA and/or directly related to smoking [37].

ILD in established RA

Multiple cohort studies have recognized the association between ILD and established RA (Table 3a). In Olmstead County, Minnesota, 7.7% of patients with incident RA subsequently developed RA-ILD over a lengthy follow-up of 40 years (compared to <2% of matched controls) using a stringent case definition that relied on radiologic, pathologic, and clinical diagnosis [38]. In an incident cohort of RA patients in the United Kingdom, 4% developed clinically apparent RA-ILD on HRCT imaging during 15 years of follow up [39▪]. Larger studies using billing codes found RA-ILD prevalence of 2.2% in Denmark and 4.6% in a United States Medicare database [27,40▪]. These numbers may be underestimates, as an investigation using death records suggested that up to 10% of the RA population may be affected by RA-ILD [41]. In addition to clinical RA-ILD, a high prevalence of interstitial lung abnormalities on HRCT imaging, ranging from 30 to 67%, has been described in multiple cohort studies of RA patients (Table 3b) [17,42▪,43▪,44].

The importance of established RA disease in the development of RA-ILD has also been noted in multiple cohort studies of RA-ILD patients. In one longitudinal study, 51% of patients received their diagnosis of RA-ILD more than 5 years after RA diagnosis [25▪▪]. In a smaller study of patients with

Table 3. Selected studies investigating RA-ILD in patients with established RA (>2 years after articular diagnosis)

Study	Country	Study period	*n* with ILD/*n* with RA studied	Methods of detection of ILD or pulmonary abnormalities	Finding
(a) Clinical RA-ILD prevalence					
Duarte *et al.* [39▪]	UK	2002–2018	87/1129	HRCT	4% RA-ILD prevalence
Bongartz *et al.* [38]	USA	1955–1995	45/582	HRCT, clinical, pathologic	7.7% RA-ILD prevalence
Hyldgaard *et al.* [27]	Denmark	2004–2016	679/31 333	ICD codes	2.2% RA-ILD prevalence
Sparks *et al.* [40▪]	USA	2008–2017	23 678/509 787	ICD codes	4.6% RA-ILD prevalence
Kim *et al.* [16]	Korea	2009–2012	64/3555	CXR, HRCT	1.8% RA-ILD prevalence
Huang *et al.* [42▪]	USA	2003–2017	30/190	CT	15.8% RA-ILD prevalence
(b) Radiologic abnormalities in RA					
Huang *et al.* [42▪]	USA	2003–2017	190	CT (retrospective)	30% with any clinical abnormalities
Esposito *et al.* [44]	USA	2016–2019	77	HRCT (prospective)	35% with any subclinical abnormalities
Bilgici *et al.* [17]	Turkey	n/a	52	HRCT (prospective)	67.3% abnormalities
Kawano-Dourado *et al.* [43▪]	Brazil	2014-2016	293	CT (retrospective)	44% abnormalities

CT, computed tomography; CXR, chest radiograph; HRCT, high resolution computed tomography; ICD, international classification of diseases; ILD, interstitial lung disease; n/a, not available; RA, rheumatoid arthritis.

RA-ILD in China, ILD was diagnosed subsequent to RA in 69% of cases with a median of 60 months between RA and RA-ILD diagnosis [29▪]. Finally, a recent prospective registry study noted that RF and ACPA were each associated with prevalent, but not incident, RA-ILD, suggesting that significant lung inflammation may be associated with higher ACPA concentrations both locally and systemically [45]. Alternatively, elevations in autoantibodies may be more important for RA-ILD risk soon after diagnosis whereas other mechanisms such as prolonged disease activity and medication exposure may be more important for RA-ILD development in established RA.

Progression of ILD

The progression of subclinical lung abnormalities to clinical ILD and from clinical ILD to more severe stages has been an area of intense investigation. Multiple studies have demonstrated that ILD progresses in about 30% of patients using serial imaging. In one cohort study of 923 RA patients in China who did not have RA-ILD at the time of diagnosis, over 30% subsequently had evidence of RA-ILD on HRCT imaging over 9 years of follow up and 30% of patients with serial scans showed evidence of progressive imaging abnormalities [46▪▪]. Similar findings were noted in a prospective cohort of RA patients in the United Kingdom and a retrospective study of RA patients in Brazil, where 34–38% of RA patients with HRCT abnormalities had radiologic progression over 2–4.4 years of follow up [43▪,47]. In another study of 193 RA patients who underwent cardiac CT as part of a prospective trial on cardiovascular risk, 36% had evidence of ILD on imaging and those abnormalities progressed in 39% of the patients who had repeat scans [48]. When subclinical RA-ILD was studied specifically, 57% of patients with HRCT abnormalities had progression on repeat imaging [49]. Patients who are ACPA-positive may be at particularly high risk of progression, as one study found that in ACPA-positive RA patients with baseline lung abnormalities on HRCT, 86% progressed over one year [34▪]. This finding suggests that RA-related autoantibody profiling may have utility in stratifying risk of disease progression. However, most studies investigating ILD progression have been retrospective and imaging may have been performed among patients with clinical suspicion for progression.

RA-ILD OUTCOMES AND RISK FACTORS

Studies indicate that 5–17% of patients with RA will develop clinical ILD and, despite significant advances in therapy for articular RA, the prevalence may be increasing over time [41,50▪▪]. RA-ILD is associated with increased mortality compared to both the general population and RA patients without ILD [16,40▪,41,42▪]. Median survival after diagnosis is only 2.6–8 years with a 5-year mortality around 40% noted in several studies [27,38,47,51–53]. Furthermore, one nationwide study of mortality in the United States noted that 6.6% of RA-related deaths met criteria for RA-ILD, suggesting an underascertainment of RA-ILD in clinical practice and high lifetime risk and mortality burden from this serious disease [41]. Among patients with RA-ILD, the radiologic usual interstitial pneumonia pattern, also seen in IPF, may be associated with increased mortality and worse prognosis based on results from several studies [26,51,53–55]. Other investigations, including a recent meta-analysis of 1256 patients that compared UIP to other patterns of RA-ILD, have highlighted the importance of pulmonary physiologic parameters in predicting outcomes in RA-ILD [54,56,57].

In addition to excess mortality, patients with RA-ILD have evidence of more severe RA, functional impairment, worse quality of life, and substantial healthcare costs [58]. In one study, 72% of patients had an inpatient admission and 76% had an emergency ward visit within 5 years of RA-ILD diagnosis [50▪▪]. The overall mean healthcare cost per RA-ILD patient was estimated to be $173 405 [50▪▪]. A discussion of management of RA-ILD is outside the scope of this review, but has been covered previously in this journal [59].

Although the importance of clinical ILD has long been understood, several studies have examined the relevance of subclinical RA-ILD detected by imaging. One recent investigation found that the prevalence of subclinical RA-ILD was 7.7% in several research cohorts and that these abnormalities were associated with increased all-cause mortality [60]. Among patients with RA, the presence of lung abnormalities on CT imaging has been associated with more severe RA disease [58], as well as increased mortality compared to patients with normal imaging [42▪].

Identifying risk factors and prognostication tools for development and progression of ILD are areas of active ongoing research [61]. Previously identified epidemiologic and clinical risk factors for the development of ILD include older age, male sex, elevated ACPA, high RA disease activity, and longer RA duration [26,28,36▪,38,52,62–66]. In addition, several potentially modifiable risk factors including cigarette smoking and obesity have been recognized [26,67]. Genetic risk factors associated with RA-ILD include the *MUC5B* promoter variant

[13] and, in a Japanese population, the *HLA-DR2* allele [6,68]. Novel auto-antibodies including anti-carbamylated proteins antibody and antimalondialdehyde-acetaldehyde antibody as well as serum biomarkers including matrix metalloproteinase 7, pulmonary and activation-regulated chemokine, surfactant D, and interferon-γ-inducible protein 10 have also been associated with RA-ILD [69–72].

FUTURE DIRECTIONS

There are many remaining unanswered questions about RA-ILD and its involvement throughout the RA disease course. Investigations in this area have been limited by significant heterogeneity in study methods, diagnostic approaches, and disease definitions. Consensus agreement on a research definition for both clinical RA-ILD as well as subclinical RA-ILD would be a significant advance in standardizing research in this area. Additional investigation into differences between groups, including differences between RA patients with and without RA-ILD and patients with RA-onset vs. ILD-onset RA-ILD may provide significant pathogenic and prognostic insights. Since RA-ILD is composed of several heterogenous subtypes, additional dedicated and adequately powered studies are needed to understand possible differences in etiology, natural history, and contribution to clinical outcomes. Prospective studies of patients with subclinical and clinical ILD are needed to understand the natural history and optimal treatment and monitoring for these patients. Ultimately, additional studies to better evaluate screening strategies, target populations, risk factors, and potential therapies that can reduce the incidence and disease burden of RA-ILD are major unmet needs.

CONCLUSION

Since Ellmann and Ball's initial recognition of RA-ILD nearly 70 years ago, there have been significant advances in the understanding of RA-ILD and its involvement throughout the RA disease course. Multiple studies have demonstrated the presence of both subclinical and clinical ILD in patients with preclinical RA, early RA, and established RA. RA-ILD is associated with significantly increased mortality and morbidity compared to both the general population and RA patients without RA-ILD. Further studies to better understand the risk factors, prognosis, and potential therapies for RA-ILD are needed.

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Conflicts of interest

There are no conflicts of interest.

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Impact of rheumatoid arthritis and biologic and targeted synthetic disease modifying antirheumatic agents on cancer risk and recurrence

Namrata Singh[a] *and Christopher I. Li*[b]

Purpose of review
Several new therapeutic drugs are now available for the management of rheumatoid arthritis (RA). Given that RA has been associated with an increased risk of certain cancers like lymphoma and lung cancer, concern remains about the safety of (newer) immunosuppressants used in RA management as it relates to the risk of cancer.

Recent findings
Most meta-analyses of randomized clinical trials of tumor necrosis factor inhibitors (TNFi) have not observed an association between TNFi and risk of incident cancer. Studies of non-TNFi biologic disease modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs and cancer are also reassuring but limited and of short-term follow-up. Regarding the use of DMARDs in patients with RA and a prior malignancy, retrospective studies have shown that TNFi use is not associated with recurrence.

Summary
There is a need for ongoing studies on the safety of non-TNFi bDMARDs and targeted synthetic disease modifying anti-rheumatic drugs and recurrent cancer. Further research is also needed to guide the patients, rheumatologists, and oncologists regarding the safest DMARDs to choose for patients with RA and a recent diagnosis of cancer.

Keywords
cancer recurrence, disease modifying antirheumatic drug, incident cancer, rheumatoid arthritis, tumor necrosis factor inhibitors

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a higher risk of cancer compared to the general population[1,2], with rates of lymphoma and lung cancer that are particularly elevated (standardized incidence ratio of 2.46 and 1.64, respectively) [1]. One theory is that both certain cancers and RA have shared risk factors, for example, smoking may act as a shared risk factor for both lung cancer and RA in certain individuals [3,4]. There is also evidence for the pathogenic effect of chronic immune stimulation/inflammation in lymphomagenesis, suggesting that RA itself could lead to the increased risk of certain cancers like lymphoma [5]. Immunosuppressive drugs have also been suggested to be potentially pro-carcinogenic in that they can downregulate the immune system (impairing tumor surveillance) and increase susceptibility to infection with oncogenic agents [6].

ASSOCIATION BETWEEN TREATMENTS USED IN RHEUMATOID ARTHRITIS MANAGEMENT WITH INCIDENT CANCER

Biologic disease modifying antirheumatic drugs (bDMARDs)

Over the past two decades the treatment of RA has been revolutionized by the introduction of multiple bDMARDs, starting with tumor necrosis factor inhibitors (TNFi) in 1998. The different bDMARD

[a]Division of Rheumatology, University of Washington and [b]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Correspondence to Namrata Singh, MD, MSCI; 1959 NE Pacific Street, University of Washington, Seattle, Washington 98195, USA.
Tel: +206 685 9895; e-mail: nasingh@uw.edu

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KEY POINTS

- The studies thus far provide evidence of favorable long-term safety profile of TNFi in patients with RA, even in patients with a history of cancer.
- There is a need for ongoing studies on the safety of targeted synthetic disease modifying anti-rheumatic drugs and incident cancer.
- Further research is also needed to guide the patients, rheumatologists, and oncologists regarding the safest DMARDs to choose for patients with RA and a recent diagnosis of cancer.

drug classes based on their mechanisms of action include: TNFi (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol); T-cell receptor CTLA4 (abatacept), anti-CD20 antibody (rituximab), IL-6 receptor antagonists (tocilizumab and sarilumab), and IL-1 receptor inhibitor (anakinra) [7,8]. Most of these drugs, especially TNFi, have been the focus of studies evaluating the risk of incident and recurrent cancer in patients with RA.

- Tumor necrosis factor inhibitors

The study by Bongartz *et al.* triggered concerns about the cancer risk of the TNFi's in RA. In their meta-analysis of nine randomized controlled trials (RCTs) of two TNFi's (infliximab and adalimumab) including 3493 TNFi treated versus 1512 placebo-treated patients, Bongartz *et al.* [9] reported a pooled odds ratio (OR) for malignancy of 3.3 (95% CI 1.2–9.1) for patients treated with TNFi compared to placebo. However, this study was hampered by the small number of cancer events observed in the clinical trials and limited follow-up time. A subsequent meta-analysis of 18 RCTs, including 8808 RA subjects treated over an average of 0.8 years, did not confirm these findings [10]. They observed that the treatment with recommended doses of TNFi had no increase in the odds of lymphoma (OR 1.26, 95% CI 0.52–3.06), or the composite endpoint of noncutaneous cancers plus melanomas (OR 1.31, 95% CI 0.69–2.48). Given the limitation of short follow-up times available in the RCTs, several observational studies have been done over the past two decades and they have not observed any associations between TNFi use and incident cancer risk in patients with RA [11–13].

Tumor necrosis factor inhibitors and Lymphoma

In their seminal paper, Baecklund *et al.* [5] observed that RA patients have an increased risk of lymphoma in a Swedish case-control study. Although risks of lymphoma were only modestly elevated up to the seventh decile of cumulative disease activity, they increased dramatically thereafter [OR = 61.6, 95% CI 21–181 comparing the first to the tenth decile]. The authors concluded that high inflammatory activity rather than its treatment is a major risk determinant for developing lymphoma in RA. Subsequently, utilizing the British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA), Mercer *et al.* [12] compared 11,931 TNFi-treated patients with 3,367 bDMARD-naïve patients. After adjusting for differences in baseline characteristics, no difference in the risk of lymphoma was seen for the TNFi versus the bDMARD-naive group: HR 1.00 (95% CI 0.56–1.80) with a median follow-up of 6.5 years (interquartile range, IQR 3.8, 8.0) for csDMARD and 8.6 (6.7, 9.7) for TNFi. Recognizing the heterogeneity of lymphomas, they further conducted a large collaborative analysis of data from 12 European biologic registers to determine whether treatment with bDMARDs affect the risk of specific lymphoma subtypes [14]. In their study of over 120,000 patients with RA, 533 lymphomas were identified, with diffuse large B cell lymphoma being the most frequent B-cell NHL subtype. Importantly, the study found no modification of the distribution of lymphoma subtypes in patients with RA treated with TNFi compared to bDMARD-naive patients [14]. Given the link between high systemic inflammatory activity in RA with lymphoma, and the better control of disease activity in recent years from modern therapeutics, we hypothesized that the incidence of lymphoma in patients with RA might be on the decline. Using recent data from the Veterans Affairs (VA) Corporate Data Warehouse, we actually observed a decline in lymphoma incidence in recent years among US veterans with RA, whereas there was no similar decline in patients with osteoarthritis [15▪]. Furthermore, in a recent study evaluating patients with RA initiating treatment with a bDMARD ($n = 16{,}392$), bDMARD-naïve ($n = 55{,}253$), an age- and sex-matched general population comparator cohort ($n = 229\,047$), Hellgren *et al.* concluded that treatment with bDMARDs, including both TNFi and non-TNFi bDMARDs, does not further increase the lymphoma risk in RA; instead, bDMARD treatment may actually reduce the excess lymphoma risk in RA [16▪▪].

Tumor necrosis factor inhibitors and solid organ cancers

The majority of the data regarding the association between TNFi and solid cancers comes from European registries [17]. In a meta-analysis of observational studies through March 2010, data from seven studies found the pooled estimate for all-site

malignancy in patients exposed to TNFi to be 0.95 (0.3–1.6), suggesting that treatment with TNFi was not associated with an increased risk for malignancy [18]. In a multidatabase US study including 29,555 patients with RA, the authors did not find the incidence of any solid cancer to be elevated in patients during TNFi therapy compared to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) [19]. In a large study using the British Society for Rheumatology Biologics Register (BSRBR), Mercer *et al.* compared the rates of solid cancers among 11,767 patients exposed to TNFi to those among 3249 patients treated with csDMARDs only. No difference in the risk of solid cancer for TNFi was observed compared to csDMARD treated patients (HR 0.83, 95% CI 0.64–1.07) after adjusting for differences in baseline characteristics. No difference was observed in the relative risk of cancer for any of the individual TNFi drugs. Their study had the strengths of 5 years follow-up after TNFi start, as well as the power to investigate the RR of cancer for individual TNFi compared to csDMARD, making it the largest study to date on this association [20].

- IL-6 inhibitors

Using data from the nationwide Swedish RA cohort, 1798 initiators of tocilizumab were identified, and an adjusted hazard ratio of 0.89 (95% CI 0.67–1.18) compared to the csDMARDs was observed for invasive solid or hematologic malignant neoplasms, excluding NMSC [21]. Recently, Kim *et al.* [22▪] conducted a cohort study using data from three large U.S. healthcare claims databases _ Medicare Parts A/B/D (2010–2015), IMS 'PharMetrics' Plus (2011–2015), and Truven 'MarketScan' (2011–2015) to examine the rate of incident malignancies excluding nonmelanoma skin cancer (NMSC) in patients with RA newly treated with tocilizumab versus other biologic drugs. Among 13,102 tocilizumab initiators propensity score-matched to 26,727 TNFi initiators, their risks of incident malignancies excluding NMSC were similar across all three databases, with a combined HR of 0.98 (95% CI 0.80–1.19) in tocilizumab versus TNFi.

- Other non-tumor necrosis factor inhibitors biologic disease modifying antirheumatic drugs (rituximab, abatacept)

The evidence for the association between use of abatacept and malignancy is controversial and deserves further study. Although few observational studies have found an increased risk of skin cancer – particularly NMSC [23] and squamous cell skin cancer [21] with abatacept – other cohort studies have not reported such an association [24,25]. Simon *et al.* pooled data from nine RCTs of abatacept (intravenous and subcutaneous routes) and found the incidence rates of safety events (including malignancy) to be similar in the abatacept and placebo groups [26]. However, a major limitation of this analysis is the short-term follow-up characteristic of RCTs, with mean duration of exposure to abatacept being <1 year in the included trials. Recently, de Germay *et al.* [27] performed an observational study within VigiBase, the World Health Organization's global database of individual case safety reports, from 2007 to 2017 to compare the cases of cancer reported in RA patients exposed to abatacept with those reported in RA patients exposed to other bDMARDs. Compared with other bDMARDs, the use of abatacept was not associated with an increased risk of reporting cancer overall [reporting OR, ROR 0.98 (95% CI 0.91, 1.05)]. Analyses by specific cancer sites showed a significantly increased ROR for melanoma [1.58 (95% CI 1.17, 2.08)], but not for other specific cancer sites. This is in line with prior studies suggesting a role of CTLA-4 in the development of skin cancers [28]. Ipilimumab is an immune check point inhibitor that blocks the inhibitory signals of CTLA-4 and thus, has an effect opposite to that of abatacept and is approved for the treatment of malignant melanoma [29]. Thus, with data available so far, we recommend carefully monitoring patients exposed to abatacept for skin cancer.

Xie *et al.* [30▪] conducted a meta-analysis to compare the risk of developing cancer in patients with RA exposed to non-TNFi biologics or tofacitinib therapy. The authors included a total of 10 studies and observed a small statistically significant increase in developing cancer for abatacept exposure, while no increased cancer risk for rituximab, tocilizumab, or tofacitinib, in comparison with csDMARDs or TNFi.

Studies regarding association of rituximab and incident malignancy have been consistently null. Wadstrom *et al.* observed 1074 invasive solid or hematologic malignant neoplasms, excluding NMSC, an adjusted hazard ratio of 0.86 (95% CI 0.73–1.03) compared to those patients on csDMARDs in patients initiating rituximab in their Swedish cohort [21]. In a comprehensive study of long-term malignancy reporting rates in patients treated with rituximab for RA, drawing on all spontaneously reported safety events since 2006 and RA clinical trials covering a period up to 11 years of follow-up, Emery *et al.* [31] found no increased risk of malignancies in patients treated with rituximab. Breast cancer was the most frequently reported malignant event in the rituximab safety database as well as in the clinical trial program, but the rates

did not differ from those of the general population of adults with RA. Given that rituximab was developed as a therapy for lymphoma [32,33], there has not been a concern about its association with the risk of lymphoma in RA. The 2015 American College of Rheumatology guidelines for the management of RA also recommend the use of rituximab in patients with previously treated lymphoproliferative disorders [34].

A major issue to keep in mind when interpreting data from observational studies is residual confounding. Even though most studies try to match the groups by propensity score matching, residual confounding from unmeasured factors such as disease activity, smoking, or alcohol use cannot be ruled out. Furthermore, the registries and claims databases usually lack information on important factors such as family history, diet/exercise/lifestyle factors, compliance with cancer screenings, other residential/occupational risks that are important to account for when evaluating cancer risks. Few other challenges in the research on safety of drugs with regards to association with cancer are the lag time between a drug's effect on cancer risk, the lag between cancer process initiating and it being detected/diagnosed as well as the difficulty of assessing cumulative exposures. Similarly, another challenge in studies of non-TNFi bDMARDs is the past exposure to TNFi and the ability to tease out the effect of non-TNFi bDMARD on malignancy risk from the effects of previous TNFi exposure.

tsDMARDs

One of the newer class of drugs for the treatment of RA includes the inhibitors of the Janus kinase (JAK)-signal transducers and activators of transcription signaling pathways. The JAK family consists of four members; JAK1, JAK2, JAK3, and tyrosine kinase (Tyk) 2, with each cell surface receptor requiring a pair of JAKs [35]. Tofacitinib, a JAK1/JAK3 inhibitor, was the first in this class to be FDA-approved in the US in 2012 for the treatment of RA. Baricitinib is a selective inhibitor of JAK1 and JAK 2 whereas upadacatinib is engineered for selectivity for JAK1 over the others with FDA-approved dose in the USA of 15 mg once daily.

The most safety data to date exists on tofacitinib. In the largest clinical dataset to date for a JAKi in RA, Cohen *et al.* [36] reported safety analysis of tofacitinib as of March 2017 using data from phase I, II, III, IIIb/IV and long-term extension studies in adult patients with RA. 7061 patients received tofacitinib (total exposure: 22 875 PY; median [range] exposure: 3.1 [0–9.6] years). Incidence rates (IRs) (95% CI) for malignancies (excluding NMSC), NMSC and lymphomas were 0.8 (0.7–0.9), 0.6 (0.5–0.7) and 0.1 (0.0–0.1), respectively. These rates were consistent over time with longer exposure. The IRs for malignancies (excluding NMCS) and NMSC were similar between the two doses of tofacitinib but the majority of lymphoma events occurred in the group requiring an average tofacitinib dose of 10 mg twice daily. The authors acknowledged that the estimation beyond 78 months was less precise due to small patient numbers and limited person-years of exposure.

There is a paucity of long-term safety data for baricitinib and upadacitinib. In an integrative analysis, patient-level data from 8 randomized clinical trials (4 phase III, 3 phase II, 1 phase Ib) and 1 ongoing LTE trial of baricitinib were included with data through September 1, 2016 [37]. There were 3492 patients who received baricitinib for 6637 total patient-years (PY) of exposure (median 2.1 years, maximum 5.5 years). Authors report the IR for malignancies (excluding NMSC) for overall baricitinib exposed patients to be 0.8 (95% CI 0.6–1.0) with no increased incidence over time. Smolen *et al.* performed an integrated analysis of data from five randomized, placebo- or active-controlled phase III trials of upadacitinib for patients with RA. 3834 patients received one or more doses of upadacitinib 15 mg ($n = 2630$) or 30 mg ($n = 1204$), for a total of 4020.1 patient-years of exposure. Rates of malignancies were similar among patients receiving upadacitinib, methotrexate or adalimumab [38].

Wang *et al.* conducted a meta-analysis to assess the efficacy and safety profiles of different dosing regimens of tofacitinib, baricitinib, and upadacitinib in RA [39]. Although their meta-analysis included twenty trials, the data on malignancy was available in only seven trials. The overall incidence of malignancy was similar to placebo (RR, 1.68; 95% CI, 0.57–4.95). The wide confidence intervals observed for malignancy risk highlight the fact that there were small number of patients and short follow-up period leading to a small number of events. Given that the existing evidence on safety of the JAKi is mostly from integrated analysis and meta-analyses of clinical trials, there is a need for data from observational studies with long-term follow-up to help understand the association between JAKi use and the risk of malignancies.

Recently the US Federal Drug Administration alerted the public about preliminary results from a safety clinical trial that showed an increased risk of serious heart-related problems and cancer with tofacitinib compared to TNFi [40▪▪]. Final results from this trial are awaited but in the preliminary results, HR (95% CI) of 1.48 (1.04–2.09) was observed in the combined tofacitinib doses of 5 mg and 10 mg twice

daily for adjudicated malignancies excluding NMSC relative to TNFi.

ASSOCIATION BETWEEN TREATMENTS USED IN RHEUMATOID ARTHRITIS MANAGEMENT WITH RECURRENT CANCER

The question of how to treat patients with an autoimmune disease like RA who have been diagnosed with cancer is a challenging clinical dilemma that clinicians face on a daily basis. There has been a *theoretical* concern that biologics and other immunosuppressive agents may impair immune responses to tumors making clinicians reluctant to use these therapies in patients with a history of cancer [41]. Further, existing studies on the association between DMARD use and cancer in RA [42–44,45▪▪,46–48] have been observational, based on registry data, and not randomized. Nevertheless, the results from these studies are potentially the best direct evidence to address the question posed here.

Real-world practice of biologic use in patients with RA following a malignancy diagnosis comes from two reports in the USA – one from the Corrona registry [49] and the other from patients with prevalent RA and cancer at the MD Anderson Cancer Center [50▪]. Among patients with RA in the Corrona registry, 880 patients developed an incident malignancy (excluding NMSC) and of these, 270 (30.7%) were on a b- or tsDMARD in the first (~6 months) after diagnosis of a solid malignancy. The majority of the new initiations in follow-up after cancer diagnosis was with a TNFi. Similarly, Pundole *et al.* [50▪] found in their study of the patients receiving a bDMARD, a majority (82%) received TNFi; in most cases, continuing this therapy that had been prescribed before the cancer diagnosis. Furthermore, when comparing the overall survival (OS) among patients with RA and solid malignancies receiving bDMARDs, they observed no statistically significant differences between patients who received TNFi compared to those who did not receive bDMARDs (HR 0.67, 95% CI 0.31–1.44) [45▪▪].

When studying the risk of recurrence after a primary malignancy, a very important variable to account for in the analyses is the cancer severity or stage since it independently can influence the risk of cancer recurrence. Keeping this in mind, a study using the linked national and population-based registers in Sweden investigated whether TNFi is associated with increased risk for cancer recurrence in RA, taking into account cancer stage and time between cancer diagnosis and start of TNFi treatment [47]. Their findings suggest that TNFi treatment was not associated with an increased risk (HR 1.06, 95% CI 0.73–1.54) for cancer recurrence in patients with RA and a history of cancer compared with those who had a similar cancer history and were selected to receive other RA treatments. However, as suggested by the upper limit of the CI for several risk estimates, a clinically meaningful risk could not be completely ruled out.

In the largest study to date in patients with RA and a history of a cancer, Dreyer *et al.* studied the risk of a second malignant neoplasm (SMN) and mortality in patients with RA and a history of a primary cancer using the Danish biological registry (DANBIO) and the Danish Cancer registry [42]. The authors found no increase in the risk of an SMN in RA patients with a history of cancer who had received bDMARDs compared with those non-treated (HR 1.11, 95% CI 0.74–1.67). Even in this large study, the number of deaths observed was small and so, they could not draw a clear conclusion regarding mortality in bDMARD-treated patients with RA. Also, the authors did not have data on cancer-specific mortality.

The above studies highlight the challenges in studying the risk of recurrent cancers or cancer-

Table 1. Notable observational studies in the past 3 years evaluating the association between DMARD use and lymphoma

Author/year	Country/ Registry	Study period	Study groups	Number of lymphomas observed per 100,000 PY (95% CI) in Exposed versus comparator group	aHR (95% CI)
Mercer/2017	BSRBR-RA	2001–2013	11931 TNFi-treated/ 3367 biological-naive	84/30	1.00 (0.56–1.80)
Mercer/2017	European Collaboration	N/A	47,864TNFi exposed/ 9094 rituximab exposed/ 71,088 bDMARD naive	81 (70–94) TNFi/20 (7–44) Rituximab/ 89 (79–100)	N/A
Hellgren/ 2020	Swedish RA patients	2001–2016	16,392 bDMARD exposed/55,253 bDMARD naive	76/90	1.08 (0.83–1.41)

aHR, adjusted hazard ratio; BSRBR-RA, British Society for Rheumatology Rheumatoid Arthritis Register; CI, Confidence interval; N/A, not available; PY, person years.

Table 2. Notable studies in the last 6 years of association between DMARD use and cancer outcomes in patients with RA and a history of cancer

Author/year	Country/registry/ Study period	DMARDs studied	Number of patients on bDMARDs versus no use	Cancer type studied	Major findings: HR (95%CI)	Limitations
Pundole 2020 [45▪▪]	USA/Patients from the MD Anderson Cancer Center/2002-2014	bDMARDs versus naive	111 bDMARD exposed/320 naive	Solid malignancy excluding NMSC	No difference in overall survival between TNFi exposed (HR 0.67; 0.31–1.44) or non-TNFi bDMARD (HR 1.1; 0.26–4.6) compared to bDMARD nonexposed	Small sample size
Raaschou 2018 [47]	Sweden/ARTIS/ 2001-2015	TNFi versus bDMARD naive	467 TNFi exposed/2164	Any solid, noncutaneous cancer	TNFi use is not associated with risk of cancer recurrence (HR 1.06; 0.73–1.54)	-Possible channeling bias
Dreyer 2017 [42]	Denmark/DANBIO/ 2000-2011	TNFi and rituximab	279/1203	All cancers except NMSC	Treatment with bDMARDs was not associated with increased risk of SMN; No clear conclusion could be drawn regarding mortality: Ever use of bDMARDs HR 1.11 (0.74–1.67) for SMN compared to nonuse.	-Small sample size -Could not examine cancer-specific mortality
Mamtani 2016 [48]	USA/Medicare/ 2000-2012	Methotrexate, Thiopurine and TNFi use compared to no use		Breast cancer	Risk of breast cancer recurrence with MTX (HR 1.07; 0.67–1.69), TNFi (HR 1.13; 0.65–1.97) and thiopurines (HR 2.10; 0.62–7.14) not increased, although cannot rule out greater risk with thiopurines	-Residual confounding
Phillips 2015 [44]	USA/National VA administrative database/1998–2008	TNFi versus csDMARDs	31 TNFi/149	Head and Neck Cancer (HNC)	TNFi treatment was not a risk factor for recurrence or HNC-attributable death (HR 0.75; 0.31–1.85)	-Only one cancer type -Small sample size

csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; DMARD, disease modifying antirheumatic drug; MTX, methotrexate; SMN, second malignant neoplasm; TNFi, tumor necrosis factor inhibitors; VA, Veterans Affairs.

specific mortality after exposure to TNFi in patients with RA and a prior cancer. Even among large databases, the number of patients meeting inclusion criteria for studying is relatively small. Also, due to a lack of clear guidelines on this subject, the studies might suffer from a channeling bias where only patients judged to be at low risk of cancer recurrence are prescribed bDMARDs.

CONCLUSION

The data so far do not support an association between TNFi use with solid cancer and lymphoma as well as recurrence risk in RA. Careful monitoring for skin cancer is needed among patients on abatacept. Studies regarding association of rituximab and incident malignancy have been consistently null. There is a paucity of long-term safety data on targeted synthetic disease modifying anti-rheumatic drugs. There is a need for understanding the best agents to prescribe for patients with a history of cancer since the current studies about recurrent cancer risk have the limitations of small sample sizes and lack of information on cancer-specific outcomes (Tables 1 and 2).

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Conflicts of interest

There are no conflicts of interest.

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Role of Janus Kinase inhibitors in rheumatoid arthritis treatment

Virginia Reddy[a,b] *and Stanley Cohen*[a,c,d]

Purpose of review
To review recently published articles on use of Janus Kinase inhibitors (Jaki) in the clinic for rheumatoid arthritis (RA).

Recent findings
Several Jaki have been approved for RA patients failing csDMARDS. Over the last 2 years, EULAR and ACR have published updated recommendations for the pharmacologic management of RA providing guidance on the utilization of Jaki after csDMARD failure. Clinical trials have been published addressing the efficacy of Jaki monotherapy as patients often choose monotherapy because of a desire to avoid multiple therapies and aggravating adverse events with csDMARDs. Previous clinical trials have compared the efficacy and safety of Jaki to adalimumab, and a trial comparing abatacept to upadacitinib has recently been published. An increased risk of venous thromboembolism (VTE) has been suggested with Jaki and additional information has recently become available with conflicting results.

Summary
Jaki are now standard therapy for RA patients failing csDMARDs and are being utilized frequently as an alternative to biologics in patients without risk factors for VTE. Jaki monotherapy has been demonstrated to be effective, although combination therapy has been demonstrated to be superior in clinical and radiographic outcomes. Preliminary data suggests that cycling through Jaki in patients with incomplete response to initial Jaki treatment may be an appropriate strategy.

Keywords
Janus Kinase inhibitors, targeted synthetic DMARDS, venous thromboembolism

INTRODUCTION

Janus kinase inhibitors (Jaki) have been available in the clinic for the treatment of rheumatoid arthritis (RA) since the approval of tofacitinib in 2012. Jaki are also known as targeted synthetic DMARDs (tsDMARDs). Subsequently, baricitinib, upadacitinib, peficitinib, and filgotinib have been approved for RA treatment in patients with active disease despite treatment with csDMARDs or biologics (Table 1). Baricitinib was approved in the United States in 2018 only for patients failing biologics at the 2 mg dose because of safety concerns, although the 4 mg dose is approved in the rest of the world for csDMARD-incomplete responders. Peficitinib was approved in Asia and is not available in Europe or the United States. Filgotinib was approved by the EMA in 2020 but was not approved in the United States because of concerns over impact on male fertility and safety with the 200 mg dose and recently Gilead announced they would no longer pursue approval in the United States.

All the Jaki underwent similar clinical development programs being evaluated in csDMARD/methotrexate (MTX) incomplete responders, biologic incomplete responders, and MTX-naïve patients. Efficacy was similar for all the Jaki in the clinical trials. To date, there have been no head-to-head studies conducted to confirm this observation. Jaki safety has been well delineated with similar adverse event profile to biologic DMARDs other than an increased risk for Herpes Zoster, and possibly opportunistic infections [1]. Concern over increased

[a]Rheumatology Department, THR Presbyterian Hospital, [b]Rheumatology Associates, [c]UT Southwestern Medical School and [d]Metroplex Clinical Research Center, Dallas, Texas, USA

Correspondence to Stanley Cohen, MD, Medical Director, Metroplex Clinical Research Center, Dallas, TX 75231, USA. Tel: +1 214 707 1390; e-mail: Scohen@DFWRA.com

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KEY POINTS

- Recent ACR and EULAR Recommendations recommend either biologics or Jaki in patients on csDmards with ongoing disease activity, which is a change from previous professional society recommendations based on the results from multiple clinical trials demonstrating similar or better efficacy with the Jaki compared with biologics.
- Clinical trials have demonstrated significant efficacy with Jaki monotherapy, although combination therapy has been associated with greater efficacy and slowing of radiographic progression. Observational studies have reported that about 30–40% of patients on Jak inhibitors are on monotherapy.
- Limited data suggests that patients failing one Jaki may respond to a second Jaki. Jaki cycling is occurring frequently in clinic with anecdotal reports of efficacy.
- A recent clinical trial comparing tofacitinib to biologics in RA demonstrated that patients at high risk for cardiovascular events have an increased risk of VTE events and alternative therapies should be considered for these patients, if options are available.

venous thromboembolism risk in patients with cardiovascular risk factors has recently been raised [2].

This review will focus on the use of Jaki in the clinic. Both EULAR and ACR have updated pharmacologic recommendations for the management of RA, which were recently published and provided an update on the use of Jaki in the treatment paradigm [3,4]. Data supporting the utility of Jaki monotherapy has been published along with initial reports on the success of Jaki cycling after initial nonresponse to Jaki. Previous clinical trials have demonstrated similar or better efficacy of Jaki to adalimumab and recently upadacitinib was compared with abatacept, further informing choice of DMARD therapy. Recent publications have addressed the VTE risk of Jaki with data that conflicts with the present warnings on Jaki and increased thrombotic risk.

ACR/EULAR-UPDATED RHEUMATIC ARTHRITIS RECOMMENDATIONS

EULAR updated the 2016 recommendations for use of csDMARD and biologic DMARDs for RA in 2019 [3]. In contrast to previous recommendations, the addition of tsDMARDs or biologic DMARDS to csDMARDs is strongly recommended if treatment target is not achieved in csDMARD-treated patients with poor prognostic features. Previous recommendations had preferred biologic DMARDs over tsDMARDS but the task force acknowledged the recent clinical trial data reporting similar efficacy and safety for both therapeutic classes. The task force did recommend that Jaki should be used with caution in patients with high venous thromboembolism (VTE) risk.

The ACR in their 2020 pharmacologic recommendations for RA treatment also modified the recommendations for post-csDMARD treatment.

Table 1. Janus Kinase inhibitors currently approved for clinical use

Drug	Region(s) approved	Indication(s)	Dose(s)	Jak selectivity
Tofacitinib	North America Europe Asia	Rheumatoid arthritis Psoriatic arthritis	5 mg twice daily or 11 mg XR once daily	JAK3, 1 > JAK2, TYK2
		Ulcerative colitis	10 mg twice daily or 22 mg XR once daily (induction) 5 mg twice daily or 11 mg XR once daily (maintenance)	
		Polyarticular juvenile arthritis	Oral solution 1 mg/ml: 10 to <20 kg, 3.2 mg twice daily 20 to <40 kg, 4 mg twice daily ≥40 kg: 5 mg twice daily oral solution or immediate release tablet	
Baricitinib	North America Europe Asia	Rheumatoid arthritis	2 mg once daily (U.S.) 2 or 4 mg once daily (Europe, Asia)	JAK1, 2 > TYK2
Upadacitinib	North America Europe Asia	Rheumatoid arthritis	15 mg once daily	JAK1 > JAK2
Peficitinib	Asia	Rheumatoid arthritis	100 or 150 mg once daily	JAK3 > JAK1, 2
Filgotinib	Europe Japan	Rheumatoid arthritis	100 or 200 mg once daily	JAK1

The committee conditionally recommended for patients taking maximally tolerated doses of MTX who are not at target, addition of a bDMARD or tsDMARD over triple therapy [4]. Similar to EULAR, equal weighting was given for tsDMARDs, although concerns over emerging safety signals with Jaki were raised as well.

In both the ACR and EULAR recommendations, MTX continues to be strongly recommended as the initial treatment for RA patients with moderate-to-high disease activity. Of interest in DMARD-naive patients tofacitinib monotherapy, baricitinib monotherapy/combination therapy, upadacitinib monotherapy, and filgotinib 100/200 mg as combination therapy all were demonstrated to be statistically superior in clinical response in comparison to MTX monotherapy as determined by ACR response and change in DAS28 [5–8]. For example, in the RA-BEGIN trial, baricitinib 4 mg monotherapy was statistically superior to MTX monotherapy for the primary endpoint ACR20 (baricitinib 77 versus MTX 62%, $P < 0.001$) as well as all the secondary endpoints including change in DAS28 ESR/CRP and CDAI/SDAI. Combination baricitinib/MTX was statistically superior to MTX in slowing radiographic progression (modified sharp-van der heijde score Bari/MTX 0.29, MTX 0.61, $P < 0.05$). In the Finch 3 trial in DMARD-naive patients, filgotinib/MTX and filgotinib monotherapy was statistically superior to MTX at 24 and 52 weeks in ACR response and inducing remission or LDAS.

Despite this clear difference in efficacy in DMARD-naive RA patients, neither ACR nor EULAR recommended moving Jaki up in the treatment paradigm. Jaki are costly and are not approved by payors for DMARD-naive patients, so obtaining approval for utilization is nearly impossible. This is a situation where economic/regulatory implications trump science. With previous studies, such as TEAR trial demonstrating no harm to the patient with delay of introduction of biologics, the present approach is appropriate [9]. In the future, as the Jaki become generic and hopefully cost reductions are realized, rethinking this approach will need to be considered.

JANUS KINASE INHIBITOR MONOTHERAPY

Additionally, the EULAR task force confirmed their previous recommendation for combination therapy with biologic DMARDs or tsDMARDs over monotherapy but did recommend that in patients who could not use concomitant csDMARDs, IL6 inhibitors and tsDMARDs may have advantages compared with other biologic DMARDs. Studies have demonstrated significant benefit with tsDMARD monotherapy and being small molecules, there are no issues with anti-drug antibodies as seen with monoclonal antibodies [10]. Upadacitinib was evaluated as monotherapy in RA patients with active disease despite MTX and rather than the addition of upadacitinib to MTX patients were randomized to switch to upadacitinib 15 or 30 mg daily monotherapy or to continue MTX [11]. Upadacitinib monotherapy at both doses were statistically superior to MTX in ACR20 response (Upa 15 mg 71%; Upa 30 mg 68%; MTX 41%) and change in DAS28CRP (Upa 15 mg −2.3; Upa 30 mg −2.7; MTX −1.2). Of interest, patients randomized to receive upadacitinib, discontinued MTX rather than tapering which is the usual practice, and flares were not seen in the patients transitioning to upadacitinib monotherapy.

Tofacitinib monotherapy was compared with combination tofacitinib/MTX and adalimumab/MTX in a phase 3b/4 clinical trial [12]. The primary endpoint in this trial was ACR50 at 24 weeks, and this was a noninferiority trial. At 6 months, ACR50 response was attained in 147 (38%) of 384 patients who received tofacitinib monotherapy, 173 (46%) of 376 patients who received tofacitinib/MTX, and 169 (44%) of 386 patients who received adalimumab/MTX. Noninferiority was observed for tofacitinib/MTX in comparison to adalimumab/MTX but tofacitinib monotherapy did not achieve noninferiority. Nevertheless, substantial improvement was seen for tofacitinib monotherapy not only in ACR response but also change in secondary endpoints – DAS28ESR/CRP and CDAI/SDAI – that persisted through week 52.

COMBINATION JANUS KINASE INHIBITORS/CONVENTIONAL SYNTHETIC DMARD TREATMENT WITHDRAWAL

The issue of treatment withdrawal with Jaki/csDMARDs was evaluated in the Oral Shift trial [13▪]. Five hundred and thirty RA patients in low disease activity (LDAS) as determined by CDAI 10 or less after tofacitinib/MTX treatment at 24 weeks underwent blinded MTX withdrawal and were followed for an additional 24 weeks. The primary endpoint was the least squares mean (LSM) change from week 24 to week 48 in DAS28(ESR) in patients who received at least one dose of study treatment in both phases. Noninferiority of tofacitinib monotherapy versus tofacitinib/MTX was declared if the upper bound of the 95% confidence interval (CI) for the difference in DAS28(ESR) between treatment arms was less than 0.6. LSM change from week 24 to week 48 in DAS28-4(ESR) was greater with tofacitinib monotherapy versus tofacitinib/MTX, yet the

difference between treatment arms was 0.30 (95% CI 0.12–0.48), demonstrating that tofacitinib monotherapy following MTX withdrawal was noninferior to continued tofacitinib with MTX. Patients on combination therapy frequently prefer to withdraw therapy if under adequate disease control. The recent ACR guidelines conditionally recommend tapering or withdrawal of the csDMARD in patients in LDAS, rather than the biologic or tsDMARD. This study supports that recommendation and observational studies have suggested that ~30–40% of patients on Jaki in clinic are on monotherapy [14].

COMPARATIVE EFFECTIVENESS OF JANUS KINASE INHIBITORS TO BIOLOGIC DMARDS

During the development program, all of the approved Jaki were compared with adalimumab in RA patients with active disease despite MTX [15–18]. All of the Jaki demonstrated similar clinical response to adalimumab with baricitinib and upadacitinib demonstrating superiority to adalimumab in ACR 20 response (Table 2). These results informed both the EULAR and ACR task forces to modify their recommendations for treatment for RA patients on MTX with active disease.

Recently results of a comparative effectiveness trial was reported in RA patients with active disease despite biologic DMARD treatment. Rubberts-Roth *et al.* [19▪▪] reported the results from a 24 week phase 3 clinical trial comparing upadacitinib 15 mg to abatacept 10 mg/kg intravenously in RA patients with active disease despite previous biologic treatment. All patients continued background csDMARDs, primarily MTX. The primary endpoint was noninferiority of upadacitinib to abatacept as determined by the change in DAS28(CRP) at week 12. Superiority of upadacitinib to abatacept in change in DAS28(CRP) was also evaluated at week 12.

Six hundred and thirteen RA patients were enrolled with mean 11–12 years of disease with baseline DAS28(CRP) 5.7–5.9. 51–55% were on concomitant corticosteroids and ~30% had failed more than one biologic. Ninety percent of patients completed the 24-week study. At week 12, upadacitinib met the primary endpoint of noninferiority versus abatacept for change from baseline in DAS28(CRP) and was shown to be superior to abatacept for change from baseline in DAS28(CRP) (Upa-2.52, Aba-2.00) ($P < 0.001$). Thirty percent of upadacitinib-treated patients achieved DAS28(CRP) less than 2.6 compared with 13% on abatacept at week 12 ($P < 0.001$). A significant difference in the proportion of patients achieving DAS28(CRP) less than 2.6 was also maintained at week 24 ($P < .01$). Similar response was seen in CDAI and Boolean-defined remission, which do not require CRP, which may be impacted to a greater degree by upadacitinib because of Jak1 inhibition of IL6.

ACR response was evaluated at week 12 with a significantly higher proportion of patients receiving upadacitinib achieving ACR20 compared with those receiving abatacept ($P = 0.01$). ACR20 response rates were similar at week 24. Significantly greater proportions of patients achieved ACR50 and ACR70 with upadacitinib versus abatacept from week 2 through week 24 (P values between <0.001 and <0.05). The differences between abatacept and upadacitinib narrowed by week 24, although most endpoints continued to demonstrate statistical superiority. For the patient-reported outcome HAQ-DI the proportion of patients achieving clinically meaningful change in HAQ-DI −0.22 or less ($P = 0.02$) was significantly greater with upadacitinib (76%) versus abatacept (65%) at week 12 but not at week 24. Similar improvement favoring upadacitinib was reported for FACIT-F scores at week 12 but no difference was noted at week 24.

Over 24 weeks, the rates of serious adverse events, adverse events leading to discontinuation of study drug, and severe adverse events were numerically higher with upadacitinib compared with abatacept. Herpes zoster was reported in 1.3% of patients in both the upadacitinib and abatacept groups. 4.6% of upadacitinib-treated patients withdrew from the study because of an adverse event compared with 2.9% of abatacept patients and severe adverse events were reported in 3.3% of upadacitinib patients and 1.6% of abatacept-treated patients. Two VTEs occurred in upadacitinib-treated patients and none on abatacept.

This study supports the findings from the registration trials and clearly Jaki are equally as effective, and in some trials superior to biologics in RA treatment. Data from these trials provided the evidence to both ACR/EULAR committee members to recommend biologics and Jaki as interchangeable options for csDMARD incomplete responders. However, as noted in this trial, Jaki are associated with a numerical increase in adverse events compared with biologics and in patients with comorbidities with increased cardiovascular risk, biologics remain the preferred option.

JANUS KINASE INHIBITOR CYCLING

Limited information regarding cycling through the approved Jaki is available and no clinical trials have addressed this issue to date. Each of the Jaki has selectivity for particular Jak isoforms in preclinical studies with modest differences on the impact on

Table 2. Comparative effectiveness trials, Janus Kinase inhibitors versus biologics

Study	Comparator	Key inclusions	Key exclusions	Primary endpoint(s)	Main findings
Van Vollenhoven 2012 (ORAL Standard)	Tofa 5 mg twice daily + PBO Tofa 5 mg twice daily + MTX Tofa 10 mg twice daily + MTX ADA 40 mg EOW + MTX	6+/68 tender joints 6+/66 swollen joints ESR>28 or CRP>7 mg/l On MTX 7.5–25 mg	Prior TNF failure Prior use of ADA	% ACR20 (week 24) Mean change baseline to month 3 HAQ-DI % patients with DAS28–4[ESR] < 2.6 at month 6	All active study arms met primary endpoints. $P<0.001$ for ACR20 and HAQ-DI. DAS28–4[ESR] $P<0.05$ for tofa 5 mg and ADA; $P<0.0001$ for tofa 10 mg. Study not designed to assess noninferiority
Fleischmann 2017 (ORAL Strategy)	Tofa 5 mg twice daily + PBO Tofa 5 mg twice daily + MTX ADA 40 mg QOW + MTX	4+/28 tender joints 4+/28 swollen joints hsCRP≥3 mg/dl On MTX 15–25 mg	Prior TNF failure Prior use of tofa or ADA	Noninferiority of % ACR50 (week 24)	Primary endpoint met 6 months ACR50 tofa monotherapy 38%, tofa + MTX 46%, adalimumab + MTX 44%. Tofa + MTX determined noninferior to ADA + MTX Superiority not found
Taylor 2017 (RA-BEAM)	PBO + MTX Bari 4 mg + MTX ADA 40 mg QOW + MTX	6+/68 tender joints 6+/66 swollen joints hsCRP≥ 6 mg/l MTX 15–25 mg or lower if clinically indicated 3+ joint erosions or 1+ joint erosions plus +RF or CCP	Prior biologic DMARD use	Superiority of % ACR20 (week 12)	Primary endpoint met PBO 40%, bari 4 mg + MTX 70%, ADA + MTX 61%. Bari versus placebo $P<0.0001$ Bari versus ADA Is Superior ($P=0.01$)
Fleischmann 2018 (SELECT-COMPARE)	PBO + MTX Upa 15 mg + MTX ADA 40 mg QOW + MTX	6+/68 tender joints 6+/66 swollen joints hsCRP≥5 mg/l 3+ joint erosions or 1+ joint erosions plus +RF or CCP Mtx 15–25 mg or ≥ 10 mg if intolerant	Prior JAKi or ADA exposure Prior bDMARD inadequate response, except up to 20% patients could be exposed to one bDMARD if less than 3 months. Exposure or discontinued because of intolerance	Superiority of % ACR20 (week 12)	Primary endpoint met ACR20 placebo 36%, upa 71%, ADA 63%. Upa versus placebo $P\leq0.001$ Upa versus adalimumab is superior ($P\leq0.05$) Also met superiority for ACR50
Combe 2019 (FINCH 1)	PBO + MTX Fil 100 mg + MTX Fil 200 mg + MTX ADA 40 mg QOW + MTX	6+/68 tender joints 6+/66 swollen joints ≥ 1 joint erosion AND + RF or CCP OR ≥ 3 erosions if RF/CCP neg OR CRP≥ 6 mg/L	Prior JAKi exposure Prior bDMARD failure (exception if <3 months exposure to bDMARD) Prior ADA exposure	% ACR20 at week 12 Secondary assessment of noninferiority Fil versus ADA in DAS28-CRP at week 12	Met primary endpoint of %ACR20 Fil 200 mg 76.6%, 100 mg 69.8%, ADA 70.8%, PBO 49.9%, $P<0.001$ versus PBO Noninferiority of Fil 200 mg to ADA was met based on DAS28-CRP ≤3.2, (49.7 versus 43.4%), $P<0.01$
Rubbert-Roth 2020 (SELECT-CHOICE)	Upa 15 mg once daily Abatacept i.v. 500 mg (weight <60 kg); 750 mg (weight 60–100–kg); 1000 mg (weight >100 kg)	6+/68 tender joints 6+/66 swollen joints hsCRP ≥ 3 mg/l Treatment failures of 1 or more bDMARD or unacceptable side effects with 1 or more bDMARD On csDMARD for at least 3 months	Prior JAKi exposure Prior abatacept exposure	Non inferiority of primary end point (change from baseline DAS28-CRP week 12) Secondary endpoint superiority Upa over Aba in DAS28-CRP change from baseline and DAS28-CRP remission (<2.6)	Met primary endpoint Upa superior to Aba in change from baseline DAS28-CRP (−2.52 versus −2.00, $P<0.001$) Upa superior to aba in percent remission (30 versus 13.3%, $P<0.001$) SAEs Upa 3.3%, Aba 1.6%; SIEs Upa 1.0%, Aba 0.3% Upa 2 VTEs, Aba zero

Comparative effectiveness trials, JAKi versus biologics. All studies were conducted in methotrexate nonresponders, except SELECT-CHOICE, which was in biologic failures. aba, abatacept; ADA, adalimumab; bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; Fil, filgotinib; hsCRP, high-sensitivity C reactive protein; i.v., intravenous; MTX, methotrexate; PBO, placebo; QOW, every other week; Tofa, tofacitinib; Upa, upadacitinib; VTE, venous thromboembolism.

inflammatory cytokine production [20,21▪]. Metabolism and clearance differs between the therapies. For example, all the Jaki other than filgotinib are metabolized through the cytochrome p450 pathway and baricitinib is primarily cleared through renal excretion. Additionally, in contrast to the other Jaki filgotinib does not have an impact on natural killer (NK) cells [22]. On the basis of these subtle differences, one would expect that as with TNF inhibitors, switching Jaki in patients with nonresponse or adverse events might be an appropriate strategy.

A recent abstract reported on 28 RA patients who failed either tofacitinib or baricitinib [23]. These patients had high disease activity and had failed a mean of 3.9 biologic DMARDs. Half the patients received baricitinib or tofacitinib first and the mean survival on the initial Jaki was 7.6 ± 6.1 months. Sixty-one percent discontinued the initial Jaki because of lack of efficacy and 39% for adverse events. Mean survival on the second Jaki was 9.6 ± 5.6 months. 20/28 remained on treatment at the time of study completion. The eight discontinuations were all because of lack of efficacy. Mean DAS28CRP improved at month 12 from 5.4 to 2.1. Response rate to the second Jaki was similar in patients with inefficacy or with toxicity to the first Jaki. Jak cycling is becoming more frequent in the clinic, and data from observational registries and claims-based data should be available in the near future to confirm if this is an appropriate strategy.

VENOUS THROMBOEMBOLISM

Increased VTE risk has been suggested for tofacitinib and baricitinib, and as a class, all Jaki carry a warning about thrombosis risk. In the phase lll placebo-controlled trials of baricitinib, an imbalance of the incidence of VTE with 4 mg dose (1.4/100 patient-years) was reported compared with the 2 mg dose and placebo (0/100 patient-years) [24]. A VTE/pulmonary embolism (PE) signal was noted in an Food and Drug (FDA)-mandated phase IV study evaluating RA patients with at least one cardiovascular risk factor comparing tofacitinib 5 or 10 mg twice daily to adalimumab/etanercept with the primary endpoints major adverse cardiovascular events or malignancy events [2]. The 10 mg tofacitinib demonstrated a statistically significant increase in PE events and numerical increase for the 5 mg twice daily dose compared with tumor necrosis factor (TNF) inhibitor-treated patients and nonsignificant numerical increase in VTEs with both doses of tofacitinib.

Conflicting data on this issue has been presented as well. A recent meta-analysis of the phase ll/lll placebo-controlled clinical trials of the approved Jaki in immune-mediated inflammatory diseases including RA, psoriatic arthritis, spondyloarthritis, psoriasis, and inflammatory bowel disease examined this issue [25]. Twenty-nine of 42 studies evaluated were in patients with inflammatory arthritis. There were 6542 Jaki patient-exposure years compared with only 1578 placebo patient exposure years as expected as the duration of placebo exposure in these trials was generally 8–12 weeks. There were 15 VTE events in the Jaki group and four in the placebo group with an incidence rate for Jaki (0.23/100 patient-years, 95% CI 0.12–0.38) compared with patients on placebo (0.25/100 patient-years, 95% CI 0.07–0.73). The authors concluded that based on this analysis the pooled VTE risk is unlikely to be increased compared with placebo.

Mease *et al.* [26▪] reported data from the tofacitinib RA clinical trial program, which demonstrated no increased risk of VTE, with similar incidence rate for 5 mg twice daily (0.29/100 patient-years) and 10 mg twice daily (0.28/100 patient-years), similar as rates in published observational studies of RA patients. Patients with cardiovascular or VTE risk factors had higher rates of VTEs. They also reported data from the CORRONA registry as well as FAERS and compared incidence rates to biologics and no increase in VTE rates was observed for tofacitinib. Data from the clinical trials for both upadacitinib and filgotinib have not demonstrated an increased risk of VTEs and the few patients with VTEs frequently had baseline risk factors [27,28].

How does the healthcare provider assess this conflicting information? In RA patients, the incidence of VTE is increased approximately two-fold over matched control population, and VTE risk is associated with greater disease activity [29]. There is at present no mechanistic explanation as to how Jaki may increase VTE risk, and by decreasing inflammation, one would think risk might be decreased. Ruxolitinib (Jak1/2 inhibitor) has been reported to decrease risk in polycythemia vera patients where VTE risk is increased [30]. RA patients with risk factors for VTE have greater risk of VTEs and possibly Jaki increase the risk in these patients. It is also possible that the modified VTE risk may also be seen in patients treated with biologics or csDMARDS, although exposure in the registration trials to these comparators was too limited to address this question.

It seems appropriate presently to follow regulatory recommendations to avoid Jaki in patients at higher risk for VTEs if alternative therapies are an option. If not, a proper benefit/risk discussion with the patient is indicated. This is an area where additional mechanistic and observational data will be necessary to confirm or refute the role of Jaki on VTE risk.

CONCLUSION

Jaki have fulfilled the hope rheumatologists had for an oral small molecule with efficacy and safety similar to biologic DMARDs. The data from multiple clinical trials over the last several years has confirmed the efficacy and safety of Jaki for RA patients. These therapies are now standard options for RA patients with active disease despite csDMARDS. Concerns persists over utilization in patients with VTE risk and in patient with comorbidities.

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Conflicts of interest

There are no conflicts of interest.

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