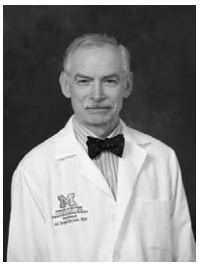
Editorial introductions

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



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.

Joshua F. Baker

Dr Joshua F. Baker is a faculty member appointed within rheumatology and epidemiology at the University of Pennsylvania, funded by a Merit Award though Veterans Affairs Clinical Science Research & Development. Through this support he has focused on identifying modifiable risk factors with the goal of improving clinical care of chronic forms of arthritis, particularly rheumatoid arthritis. Specifically, Dr Baker conducts observational and interventional studies with a focus on skeletal muscle health, obesity, bone, and joint health, cardiovascular disease, and other long-term outcomes in patients with arthritis.

Recent advances in the diagnosis and management of giant cell arteritis

Naomi Serling-Boyd and John H. Stone

Purpose of review
Giant cell arteritis (GCA) has classically been diagnosed by temporal artery biopsy and treated with high-dose, long-term glucocorticoid therapy. Noninvasive imaging increasingly is employed for diagnostic purposes, but further studies are needed to determine the role of imaging in monitoring longitudinal disease activity. Glucocorticoid-sparing therapy mitigates the numerous adverse effects of glucocorticoids. This review addresses new developments in these areas.

Recent findings
For diagnosis, when performed at a center with expertise in its use, temporal artery ultrasound has an estimated sensitivity and specificity of 78 and 79%, respectively. State-of-the-art time-of-flight positron emission tomography/computed tomography (PET/CT) has an estimated sensitivity and specificity of 71 and 91%, respectively. The sensitivities of both imaging modalities decrease following glucocorticoid administration. Tocilizumab is an effective glucocorticoid-sparing therapy, demonstrating sustained glucocorticoid-free remission in 56% of patients receiving weekly tocilizumab compared with 18% of patients receiving a 52-week prednisone taper. The traditional acute phase reactants are of no value in patients treated with interleukin-6 receptor (IL6-R) blockade, and thus, the development of new biomarkers is an important priority in the field.

Summary
Noninvasive imaging techniques are increasingly used in the absence of temporal artery biopsy to confirm diagnostic suspicions of GCA. Tocilizumab reduces the cumulative glucocorticoid exposure and increases the rate of sustained remission. Ongoing efforts are directed towards new methods to identify disease flares.

Keywords
giant cell arteritis, large vessel vasculitis, tocilizumab

INTRODUCTION

Giant cell arteritis (GCA) is a form of large vessel vasculitis. It affects patients older than 50 years of age and is approximately three times more common among women than men. Symptoms include headache, jaw claudication, scalp tenderness, fevers, weight loss, and symptoms of polymyalgia rheumatica (PMR). In addition, ocular symptoms, such as transient or permanent vision loss or stroke may occur. No diagnostic laboratory test exists for this disease. Temporal artery biopsy has traditionally been considered the 'gold standard' for diagnosis, though the sensitivity of biopsy may be as low as 50%. More recently, imaging modalities have been employed with increasing frequency to establish the diagnosis without a positive temporal artery biopsy. The prompt institution of treatment is important once the diagnosis of GCA is considered as failure to initiate therapy in a timely manner may lead to unfortunate clinical outcomes, such as blindness. Although glucocorticoids are effective at controlling GCA and preventing vision loss, they can be poorly tolerated, and multiple attempts have been made through the years to identify effective glucocorticoid-sparing agents. Most recently, tocilizumab, an interleukin-6 (IL-6) receptor alpha inhibitor, has been identified as an effective agent. This review will focus on recent updates in the diagnosis and management of GCA.

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KEY POINTS

- Noninvasive imaging techniques can allow for a diagnosis of GCA without a temporal artery biopsy.
- Glucocorticoids remain a mainstay in the treatment of GCA, though are associated with numerous toxicities.
- Tocilizumab helps to reduce the rate of flare, increase remission, and reduce the cumulative dose of glucocorticoid.

ESTABLISHING THE DIAGNOSIS: ULTRASOUND OF THE TEMPORAL ARTERY AND OTHER ARTERIES

The European League Against Rheumatism (EULAR) recommendations for imaging in large vessel vasculitis regard temporal artery ultrasound as the first-line imaging study for patients suspected of having GCA [1▪▪]. A positive ultrasound study is considered adequate to establish the diagnosis of GCA in the absence of a temporal artery biopsy if suspicion for the diagnosis is high. Findings consistent with mural inflammation and GCA include a hypoechoic 'halo sign' (Fig. 1), occlusion, or stenosis of the temporal artery. The test characteristics of the finding of a hypoechoic halo are estimated to be 68% for sensitivity and 81% for specificity. These estimates increase to 78 and 79%, respectively, if any ultrasonographic abnormality is considered (Table 1) [2▪▪]. Of note, most studies examining temporal artery ultrasound were performed in academic medical centers with expertise in ultrasound imaging of the temporal arteries. Whether ultrasound should be used to guide the temporal artery biopsy site is unclear. One study randomized patients with suspected GCA to ultrasound-guided temporal artery biopsy or standard temporal artery biopsy, in which the ophthalmologist attempted to select a segment of temporal artery that was either tender or nodular on examination when possible and found no improvement in the sensitivity of temporal artery biopsy in the ultrasound-guided group [3]. There has been some suggestion that a 'directional' biopsy (i.e. biopsy ipsilateral to where the halo sign was present) may increase the sensitivity in patients with a unilateral halo sign [4]. The sensitivity of ultrasound decreases following the use of glucocorticoids, from 92% after 0–1 days of glucocorticoid treatment to 80% after 2–4 days of glucocorticoids, and to 50% after more than 4 days of glucocorticoids [5].

Compared with the change in sensitivity of temporal artery biopsy with glucocorticoid treatment, the sensitivity of the halo sign on ultrasound

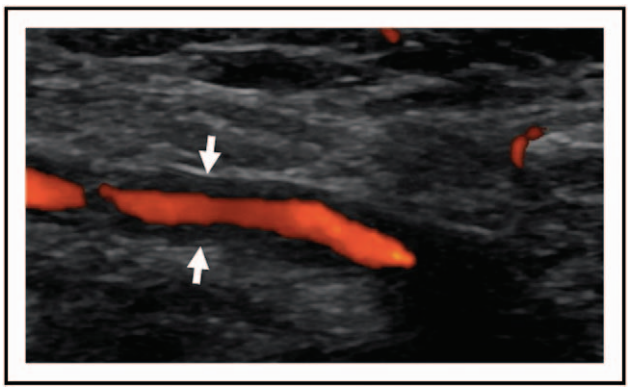

FIGURE 1. Temporal artery ultrasound with doppler demonstrating the halo sign. Ultrasound demonstrating a longitudinal view of the left superficial cutaneous temporal artery. The halo sign is indicated by the white arrows and is demonstrated as a hypoechoic lining around the artery.

Table 1. Sensitivity and specificity of different imaging modalities for the diagnosis of giant cell arteritis

Imaging type	Sensitivity	Specificity	Findings on imaging	Recommendations for use
Temporal artery ultrasound	68–78%	79–81%	Noncompressible hypoechoic halo sign, occlusion, or stenosis of the temporal artery	Recommended as first line imaging to establish a diagnosis of GCA
Routine PET/CT	71%	64%	Uptake throughout eight different vascular territories	Not recommended as first line imaging in diagnosis, less effective for imaging of cranial arteries
Time of flight PET/CT	71–92%	85–91%	Uptake in temporal artery	Has not been addressed in recommendations because of being newer
High resolution MRI	85–90%	67–100%	Mural enhancement of temporal artery	Can be considered for diagnosis if ultrasound not available, less preferable because of cost as well as limited availability and adverse effects of contrast

Data from [1▪▪,2▪▪,5,11▪]. GCA, giant cell arteritis; PET/CT, positron emission tomography/computed tomography.

may decrease more rapidly, whereas the histopathologic changes on biopsy subside more slowly. An early study showed no decrease in positive temporal artery biopsies in patients treated with glucocorticoids prior to biopsy, though more recent work has shown a decrease in sensitivity over time. One study showed that temporal artery biopsy was positive in 78% of patients treated with less than 2 weeks of glucocorticoids prior to biopsy, compared with 65% treated for 2–4 weeks, and 40% treated for more than 4 weeks [6,7]. Another study evaluated patients with GCA and assigned them to repeat temporal artery biopsy at varying time points and found that after 3 months, 70% were still positive; after 6 months, 75% were still positive; after 9 months, 44% were still positive; and after 12 months, 44% were still positive [8].

Of note, US has very limited value in evaluating the thoracic aorta and should not be used as a reliable method of detecting aortitis or other large vessel involvement. Whether ultrasound is helpful in confirming or excluding a flare of GCA in a patient with an established diagnosis is still under investigation [1▪▪]. Overall, ultrasound is an excellent diagnostic tool, though is subject to operator dependence, and thus it is important that it be utilized in centers where those performing and interpreting the studies are well versed in its use for the assessment of giant cell arteritis. Its sensitivity and specificity may further vary outside of academic centers, and further studies evaluating its utility in a variety of clinical practices will be helpful moving forward.

ESTABLISHING THE DIAGNOSIS: PET/COMPUTED TOMOGRAPHY AND MRI

EULAR has developed a set of guidelines for imaging in large vessel vasculitis. Positron emission tomography/computed tomography (PET/CT) is not recommended as part of the first-line imaging approach to diagnosis. PET/CT, however, is particularly helpful in assessing aortitis, which is detected most commonly in the ascending aorta. Data are increasingly emerging that PET/CT has a reasonable sensitivity in identifying vasculitis not only in the extracranial large blood vessels but also in the cranial vessels. A recently developed method that employs 1 mm tomographic cuts, for example, improves the ability of PET/CT to evaluate the temporal arteries [9▪].

A recent study evaluated 64 patients who underwent time of flight PET/CT. Compared with temporal artery biopsy, sensitivity was 92% and specificity was 85% for diagnosing temporal arteritis. Compared with clinical diagnosis, the sensitivity of this PET/CT procedure was 71% and its specificity was 91%. PET/CT also had a negative predictive value of 98%, demonstrating its great utility in excluding GCA in lower risk patients. Aortitis is detected on PET/CT in almost half of patients with a positive temporal artery biopsy, and among patients with large vessel vasculitis detected on PET/CT, an average of four vascular territories are involved (Fig. 2) [9▪,10].

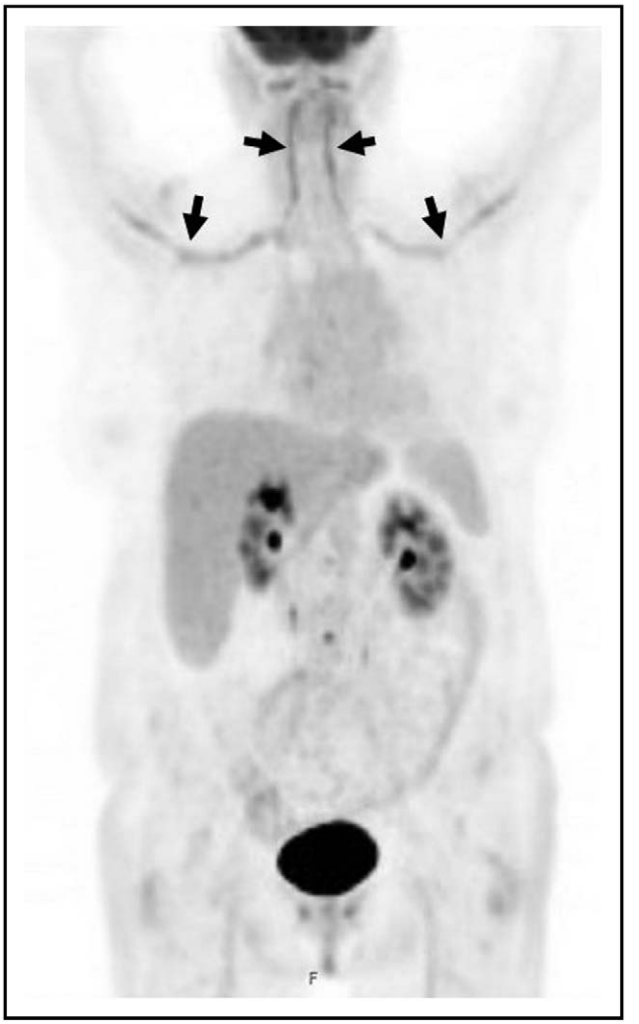

FIGURE 2. Large vessel vasculitis on positron emission tomography/computed tomography (PET/CT). PET/CT in a patient with giant cell arteritis demonstrating intense fluorodeoxyglucose avidity in the bilateral vertebral and subclavian arteries, indicated by the black arrows.

Disadvantages of using PET/CT include high cost, radiation exposure, and lack of widespread availability of the newer generation imaging [9▪]. In addition, as is true for other imaging modalities, fluorodeoxyglucose (FDG) uptake, and consequently the test's sensitivity decrease significantly after glucocorticoid exposure. It is recommended, therefore, that PET/CT be performed within 72 h of initiating glucocorticoids for the most accurate

diagnosis [11▪]. An additional potential shortcoming is that many patients maintain some degree of FDG uptake in the large vessels even after treatment; thus, its role in monitoring disease activity remains uncertain [11▪].

MRI has also been used to evaluate the cranial arteries, with a pooled sensitivity of around 73% and specificity of 88%. Because of the cost and limited availability of MRI, however, as well as the possible adverse effects of contrast reagents, MRI is not recommended for first-line use in imaging [1▪▪].

GLUCOCORTICOIDS AND THEIR TOXICITIES

Glucocorticoids were first-line therapy – and the monotherapy – for GCA for nearly 70 years. Conventional wisdom dictated the importance of high initial doses of prednisone, typically on the order of 1 mg/kg/day, or pulse-dose methylprednisolone 1 g intravenously daily for 3 days in the setting of imminent vision impairment or frank vision loss. Treatment with glucocorticoids generally consisted of a minimum of 1 year of prednisone or another glucocorticoid, tapering from high to low doses over many months without a specified endpoint. The majority of patients treated with prednisone alone ultimately require additional dosing because of flares or refractory symptoms, particularly if attempts are made to stop glucocorticoids entirely within 1 year [12▪▪].

Despite this unquestioned efficacy of high-dose prednisone for quelling active GCA and preventing vision loss, the toxicities of conventional glucocorticoid dosing for the treatment of GCA are daunting. Up to 90% of patients have at least one adverse event while taking glucocorticoids, with the most frequent occurrences being cataracts and bone mineral disease. For each 1000 mg increase in glucocorticoid exposure, the hazard ratio for adverse events increases by 3% [13]. A series of nested case–control analyses evaluated numerous complications as well as the dose-dependent nature of the risk. Among GCA patients taking prednisone 30 mg daily or more compared with those on lower daily prednisone (5 mg daily or less), the odds ratios for complications were: diabetes (4.7), osteoporosis (1.9), fractures (2.6), glaucoma (3.5), serious infection (3.3), and death (2.1), with many complications occurring after years [14].

Another study showed similar rates of osteoporosis and fractures among male and female individuals despite the fact that female individuals have more risk factors at baseline for fracture [15]. The possibility of weight gain is also a particular concern to many patients and may contribute to poor adherence. Prior studies in vasculitis have shown mixed results regarding the effect of glucocorticoids on weight gain. Improvement in disease activity, for example, is associated with weight gain regardless of cumulative prednisone dose, and patients who fail to achieve disease control may not experience weight gain despite receiving larger doses of glucocorticoids [16,17].

TREATMENT WITH TOCILIZUMAB

The first reported randomized controlled trial to assess the efficacy of tocilizumab in GCA randomized 20 patients to either tocilizumab 8 mg/kg intravenous monthly or placebo infusions in addition to glucocorticoids and found a higher relapse-free survival in the tocilizumab group (85 versus 20%, $P = 0.001$) at week 52 [18]. The Giant Cell Arteritis Actemra (GiACTA) trial enrolled 251 patients, randomized to one of four arms: tocilizumab 162 mg weekly or every other week (combined with a 26-week prednisone taper), or a prednisone taper alone (either 26 or 52 weeks). The primary endpoint – the rate of sustained glucocorticoid-free remission at week 52 – was achieved in 56% of the weekly tocilizumab group and 53% of the every other week tocilizumab group compared with 14% in the 26-week prednisone group and 18% in the 52-week prednisone group. The cumulative prednisone dose was significantly lower in both tocilizumab groups compared with both prednisone groups. Serious adverse events were seen more frequently in the prednisone groups [12▪▪]. The effects of tocilizumab on glucocorticoid-sparing were observed in both relapsing and newly diagnosed GCA.

TREATMENT WITH USTEKINUMAB

Ustekinumab has also been studied as a potential glucocorticoid-sparing agent in GCA, but with less consistently positive results and is not Food and Drug Administration (FDA)-approved for treatment. The investigators in one open-label study of 25 patients with refractory GCA treated all patients with ustekinumab in addition to glucocorticoids and demonstrated that no patients relapsed while on ustekinumab. Over 52 weeks, the median daily prednisolone dose decreased from 20 to 5 mg. In addition, CT angiography demonstrated improvement in large-vessel vasculitis in all patients [19]. However, a subsequent open-label study evaluating ustekinumab in combination with a 6-month prednisone taper was terminated early because of the observation of disease flares in 7 out of the first 11 (63.6%) patients enrolled. Only two patients (18%) achieved the primary outcome of prednisone-free

remission with normal inflammatory markers at 52 weeks [20]. The fundamental difference in these two open-label experiences with ustekinumab appears to be the maintenance of glucocorticoid therapy in one, and the discontinuation of glucocorticoid treatment completely in the other.

OTHER TREATMENT MODALITIES

Abatacept, a CTLA-4 immunoglobulin that acts as a negative regulator of T-cell costimulation, was studied in a randomized withdrawal trial design. The relapse-free survival rate in the abatacept group was 48% compared with 31% in the placebo group (one-sided P-value = 0.049). There was also a longer median duration of remission in the abatacept group (9.9 versus 3.9 months) and no increase in adverse events though abatacept is not FDA approved for GCA treatment [21].

HOW LONG SHOULD TOCILIZUMAB BE CONTINUED?

Although tocilizumab has shown encouraging results as a glucocorticoid-sparing treatment for GCA, the optimal duration of treatment remains unknown. A follow-up study of 17 patients who had received 1 year of tocilizumab treatment and were in treatment-free remission at the time of tocilizumab cessation showed that eight patients (47%) relapsed after a mean of 6.3 months. The patients in that study who relapsed following the discontinuation of tocilizumab were younger and had a greater degree of vessel wall enhancement on MRI at baseline compared with those who did not flare. All of the patients in the study, however, had persistent MRI abnormalities at follow-up [22]. The proper interpretation of persistent MRI enhancement in GCA remains uncertain.

A long- term, 2-year extension of the GiACTA trial followed patients who had received either tocilizumab with glucocorticoids or glucocorticoids alone, with treatment at the discretion of the provider. Forty-nine percent of the patients in the weekly tocilizumab group and 39% of the patients in the every other week tocilizumab group maintained complete remission during the entirety of part 2, and 65% of these patients were treatment free. The highest proportion of patients who maintained complete remission while not on any treatment was 68% in the weekly tocilizumab group. Forty-two percent of the patients who achieved sustained disease remissions on weekly tocilizumab and a 26-week prednisone taper maintained treatment-free remissions for 2 years after tocilizumab discontinuation, underscoring the point that although vigilance for the possibility of disease flares remains crucial in GCA, not all patients require continuous treatment with immunosuppressive medications [23▪].

RISK FACTORS FOR TREATMENT FAILURE OR RELAPSE

Despite treatment with glucocorticoids and even tocilizumab, a substantial portion of patients still experience flares either during or after the discontinuation of these immunosuppressive medications. A study of 149 tocilizumab-treated patients showed that 24% experienced a flare, and 64% were still receiving prednisone at the time of the flare. Approximately 25% of the disease flares occurred while patients were taking greater than 10 mg daily [24]. Inflammatory markers are not reliable indicators of flare, particularly in patients receiving IL6-R blockade treatment. Ninety-two percent of patients receiving tocilizumab had normal C-reactive protein (CRP) levels at the time of flare. Moreover, 34% of patients treated with prednisone alone had normal CRP levels at disease flare. This highlights the need for the discovery of additional biomarkers.

The study described above that reported a higher degree of mural enhancement on MRI among patients who relapsed after stopping tocilizumab treatment found no differences in sex, presence or absence of cranial symptoms, presence or absence of a positive temporal artery biopsy, or other factors that predicted posttreatment relapse [22].

A follow-up analysis from the GiACTA trial, however, showed that female sex, worse patient-reported outcomes at baseline, and treatment with prednisone alone (as opposed to tocilizumab) were independent predictors of treatment failure [25]. In a multivariate analysis, women with GCA were more than five times more likely than men to fail treatment if treated with prednisone alone. The two strongest risk factors for GCA flare were the absence of treatment with tocilizumab and female sex.

Although it has been hypothesized that patients with GCA who have involvement of the aorta and its primary branches as opposed to cranial GCA have a disease phenotype that is more difficult to treat, to date the outcomes of patients with GCA and large vessel involvement have not been proved different compared with those with cranial disease only [10].

USE OF BIOMARKERS TO IDENTIFY FLARE

Attempts have been made to identify biomarkers that could be useful in monitoring disease and identifying a flare. This is especially important as

tocilizumab suppresses the erythrocyte sedimentation rate (ESR) and CRP, thus rendering them unreliable as markers of disease activity. Despite the role of IL-6 in GCA, IL-6 levels have not been shown to correlate with disease activity [24].

One study found that matrix metalloproteinase-3 (MMP-3), pentraxin-3, and soluble tumor necrosis factor receptor 2 (sTNFR2) were significantly elevated in GCA patients compared with age-matched and sex-matched controls, and that tocilizumab resulted in normalization of these levels. MMP-3 levels also had a weak association with MRI signal intensity on MRA of the aortic wall [26]. Two studies recently evaluated the role of serum amyloid A in evaluating disease activity. One study found that the serum amyloid A (SAA) levels were significantly higher in GCA patients with active disease compared with inactive disease [27▪]. Another study analyzed the profiles of healthy blood donors and patients with GCA and found that levels of SAA as well as interleukin-23 (IL-23) and IL-6 were significantly higher in patients with GCA compared with healthy controls. Changes in the SAA levels also correlated with relapses of disease as well as visual disturbance [28]. Though these serum markers are not currently used in clinical practice, these studies may pave the way for studies of therapy targeted toward SAA.

MONITORING WITH SERIAL IMAGING

Longitudinal MRI, PET/CT, and ultrasound have been studied in GCA patients with mixed results. One study showed that all patients in lasting remission still had enhancement on MRI with low intensity vessel wall signal at the time of follow-up [22]. Another study also showed that MRI vessel wall signal does not parallel clinical disease activity [29▪]. Similarly with PET/CT, the majority of patients still have some degree of vascular uptake after 1 year, though the level of maximal uptake can potentially help to distinguish patients in remission from those with active disease [11▪,30]. For temporal artery ultrasound, one group described two patients in whom the halo sign was significantly diminished with tocilizumab treatment, and further studies are ongoing to evaluate this [31]. The use of imaging to confirm or exclude a flare is not known though is recommended for long-term monitoring of patients with known large vessel involvement [1▪▪].

CONCLUSION

In summary, the diagnosis and treatment of GCA have evolved substantially in recent years. Temporal biopsy was once regarded as the only definitive way to diagnose GCA, whereas noninvasive imaging studies can now be used. Furthermore, some noninvasive imaging studies are also helpful for detecting large vessel or aortic involvement. Their role in the longitudinal monitoring of disease activity requires further evaluation. Similarly, long-term treatment with glucocorticoids was regarded as the only reliable therapeutic option for patients with GCA for decades. Tocilizumab has emerged recently as an agent that substantially increases the rate of glucocorticoid-free remission and reduces the cumulative glucocorticoid doses required to maintain disease control. Further studies are necessary to identify other novel treatment options as well as other biomarkers that can accurately identify flares.

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Conflicts of interest

N.S.-B. has no conflicts of interest to report. J.H.S. has received grants from and performed consulting for Roche and has received a grant from Bristol-Myers Squibb.

REFERENCES AND RECOMMENDED READING

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

- ▪ of special interest
- ▪▪ of outstanding interest

1. ▪▪ Dejaco C, Ramiro S, Duftner C, *et al.* EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018; 77:636–643.

These recommendations, published by EULAR, discuss that in patients with a high pretest probability, a GCA diagnosis can be made with imaging alone. They recommend temporal artery ultrasound as the first line, with high-resolution MRI as a second line. They do not recommend that CT, PET CT, or conventional angiography be used for diagnosis.

2. ▪▪ Rinagel M, Chatelus E, Jousse-Joulin S, *et al.* Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. Autoimmun Rev 2019; 18:56–61.

This was a meta-analysis that compared the sensitivity and specificity of temporal artery ultrasound to that of temporal artery biopsy and overall found sensitivity of 68% and specificity of 81% for the hypoechoic halo, or sensitivity of 78% and specificity of 79% for any ultrasonographic abnormality.

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This prospective study evaluated 64 patients with newly suspected GCA who underwent time of flight PET CT to evaluate the temporal arteries. They found that compared with temporal artery biopsy, the sensitivity of PET CT was 92% and specificity was 85%, and compared with clinical diagnosis, the sensitivity was 71% and specificity was 91%. Additionally, the negative predictive value of 98% indicates that it can be helpful in ruling out GCA in patients with a low pretest probability. Additionally, aortitis was seen in 42% of patients with a positive temporal artery biopsy.

10. de Boysson H, Liozon E, Lambert M, *et al.* Giant-cell arteritis: do we treat patients with large-vessel involvement differently? Am J Med 2017; 130:992–995.
11. ▪ Braun J, Baraliakos X, Fruth M. The role of 18F-FDG positron emission tomography for the diagnosis of vasculitides. Clin Exp Rheumatol 2018; 36(Suppl 114):S108–S114.

This review discussed the use of PET CT for the diagnosis of vasculitis. Several of the main points were that the diagnosis is most accurate in the first 3 days after glucocorticoid administration, that supra-aortic arteries provide the best identification of GCA patients. The ascending aorta and axillary arteries had the highest uptake. The value of PET CT in follow-up imaging and disease flares is less clear.

12. ▪▪ Stone J, Tuckwell K, Dimonaco S, *et al.* Trial of tocilizumab in giant-cell arteritis. NEJM 2017; 377:317–328.

This landmark trial randomized 251 patients to tocilizumab (weekly or every other week) with a 26-week prednisone taper or placebo with either a 26 or 52 week prednisone taper. The primary endpoint of sustained glucocorticoid-free remission at week 52 was obtained in 56% of the weekly tocilizumab group and 53% of the every other week tocilizumab group compared with 14% in the 26 week taper prednisone group and 18% in the 52 week prednisone group. The cumulative prednisone was significantly reduced in the tocilizumab groups compared with the prednisone groups.

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22. Adler S, Reichenbach S, Gloor A, *et al.* Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis. Rheumatology (Oxford) 2019; 58:1639–1643.
23. ▪ Stone J, Bao M, Han J, *et al.* Long-term outcome of tocilizumab for patients with giant cell arteritis: results from part 2 of a randomized controlled phase 3 trial (abstract 808). American College of Rheumatology's Annual Meeting. 2019.

This study was a long-term, 2-year extension of the GiACTA trial and showed that 49% of patients in the weekly tocilizumab group remained complete remission for the 2 years following discontinuation.

24. Stone JH, Tuckwell K, Dimonaco S, *et al.* Glucocorticoid dosages and acute-phase reactant levels at giant cell arteritis flare in a randomized trial of tocilizumab. Arthritis Rheumatol 2019; 71:1329–1338.
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Treatment of cutaneous lupus erythematosus: current approaches and future strategies

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Purpose of review
Cutaneous lupus erythematosus (CLE) is a highly heterogeneous autoimmune disease. No specific Federal Drug Administration-approved therapies for CLE-alone are available, and resistance to conventional treatments is common. This review will summarize current treatment approaches and pending treatment strategies.

Recent findings
Research into the pathogenesis of CLE is accelerating. A skewed type I interferon production and response contribute to CLE lesions. The pathophysiology of lesions may be similar among the lesional subtypes, and patients with a more TLR9-driven disease mechanism may have more benefit from hydroxychloroquine. Case reports continue to support the use of dapsone for CLE, especially bullous lupus erythematosus. Rituximab and Belimumab have efficacy in patients with systemic lupus erythematosus and severe active CLE. The significant role for type I interferons in CLE and encouraging clinical data suggest anifrolumab as a very promising agent for CLE. Dapirolizumab, BIIB059, Ustekinumab and Janus kinase inhibitors also have supportive early data as promising new strategies for CLE treatment.

Summary
Continued research to understand the mechanisms driving CLE will facilitate the development and approval of new targets. The pipeline for new treatments is rich.

Keywords
antimalarials, biologic therapies, cutaneous lupus, interferon

INTRODUCTION

Cutaneous lupus erythematosus (CLE) manifests in about 70% of all patients with systemic lupus erythematosus (SLE) and also can occur without associated SLE. Beyond generalized autoimmunity, more cases are now also being seen secondary to drug-induced CLE, especially as a side effect of novel cancer therapies [1,2]. CLE is divided into four different subsets: acute CLE (ACLE), subacute CLE (SCLE), intermittent CLE and chronic CLE (CCLE) including discoid lupus erythematosus (DLE), chilblain lupus erythematosus and lupus erythematosus panniculitis [3]. The most common subset is CCLE, followed by SCLE and other subsets; 1/3 of patients have two or more different subsets [4]. The cause for CLE is still under investigation, but a skewed type I interferon production [5▪▪] and response [6] are contributing factors. Intriguingly, the pathophysiology of lesions may be similar among the lesional subtypes [5▪▪,7▪▪]. Although there are many management strategies available for CLE, the degrees of efficacy are varied. Resistance to conventional treatments is common, leading to an increased risk of scarring, disfigurement and poor quality of life. Thus, our review aims to summarize current treatment approaches and the evolution of future strategies based on advances in the understanding of CLE pathogenesis. These will include topical treatment, antimalarials, synthetic disease modifying anti-rheumatic drugs (DMARDs) and novel biologic therapies.

CURRENT TREATMENT OPTIONS

Although SLE has a meager 3 Food and Drug Administration (FDA)-approved medications [corticosteroids, hydroxychloroquine (HCQ) and belimumab], no specific FDA-approved medications for CLE itself have yet been approved. Despite this, established standard treatment of CLE includes pharmacological therapy

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KEY POINTS

- Topical corticosteroids, calcineurin inhibitors, antimalarials and systemic steroids remain the first-line treatment for CLE.
- Some targeted agents such as anifrolumab, ustekinumab, rituximab and belimumab show promise for CLE and systemic lupus erythematosus patients with skin manifestations.
- Future research and ongoing clinical studies are needed for better, more targeted therapies for patients with refractory skin lesions.

ranging from topical to systemic therapy. Preventive measures, including sun protection, smoking cessation, elimination of photosensitizing drugs and vitamin D supplementation, are also important adjuncts for disease management [3]. Of note, a recent maximum usage trial demonstrated that all four chemical-based sunscreens tested showed systemic absorption more than 0.5 ng/ml, which is above FDA recommended limits [8]. The FDA has since recommended only barrier sunscreens containing zinc oxide or titanium dioxide as safe and effective. Because of the white residue from barrier sunscreens, tinted formulations can help adherence in patients with darker skin. Consideration of these changes when recommending sunscreen to patients should be made.

Topical treatments

Recent European League Against Rheumatism (EULAR) guidelines recommended topical agents as the first-line treatment for CLE which mostly include topical corticosteroids and calcineurin inhibitors [9]. Multiple randomized controlled trials (RCTs) highlight that topical steroids are the mainstay treatment for CLE; high potency topical steroids are typically more effective (refer to Table 1 for steroid potency and body part recommendations). Because of well known side effects such as atrophy, telangiectasias and steroid-induced rosacea-like dermatitis, topical corticosteroids should be intermittent and not exceed an application of more than a few weeks [3]; a common recommendation is use for 2 weeks then on weekends only for maintenance. Prolonged use of topical steroid may be necessary in patients with scalp DLE lesions. Intralesional injections of triamcinolone may be beneficial in patients with refractory localized DLE [10].

Topical calcineurin inhibitors (CNIs) can be used as an alternative to, or in combination with if more efficacy is needed [11], topical corticosteroids, especially for thin skin areas or in skin damaged by chronic topical steroids. There are two available commercial preparations (pimecrolimus 1% cream and tacrolimus 0.03 or 0.1% ointment) [12]. A recent systematic review examined 13 studies (five RCTs, three noncontrolled clinical trials, one observational study and four case series) for topical CNI in patients with CLE. Six studies included only patients with DLE, whereas seven studies included patients with a mixture of different subtypes of CLE. Among them, eight studies used topical tacrolimus (0.03 or 0.1%), four studies topical pimecrolimus (1%) and one study a mixture of both. 6/13 studies involved a comparison group (mostly topical steroids). All studies demonstrated moderate improvement with topical

Table 1. Potency ranking of commonly used topical steroids

Potency	Class	Example	Sites
Super-potent	*I*	Clobetasol propionate 0.05% Halobetasol 0.05%	Palms, soles, acral sites, trunk
High potency	*II*	Bethamethasone dipropionate 0.025% Desoximetasone 0.25% Halcinonide 0.1%	Palms, soles, acral sites, trunk
	III	Bethamethasone valerate 0.1% Fluticasone propionate 0.005%	Acral sites, trunk
Medium potency	*IV*	Triamcinolone 0.1% Desoximetasone 0.05%	Acral sites, trunk
	V	Hydrocortisone valerate 0.2% Hydrocortisone butyrate 0.1%	Acral sites, trunk
Low potency	*VI*	Fluocinolone acetonid 0.01% Desonide 0.05%	Face, intertriginous areas
	VII	Hydrocortisone acetate 1%	Face, intertriginous areas

Topical steroids come in many different formulations (ointments, creams, lotion, foam, solution and gels) and potency may vary depending on the carrier vehicle. An ointment formulation is considered more potent than the same molecule in a cream or lotion base as it enhances percutaneous absorption. Most patients favor creams as they tend to be a more tolerable form of application. Foams and solutions are appropriate for lesions on the scalp.

CNI therapy with statistically significant improvement in patients with DLE, tumid lupus and ACLE. In a study of case series, those patients on topical tacrolimus lotion 0.3% achieved hair regrowth. Benefit was equivalent to topical steroids and the side effects were minor [13].

Other topical agents with reported use in CLE include topical R-Salbutamol 0.5% cream, retinoids, R333, clindamycin and topical Janus kinase (JAK) inhibitors. Two studies (one RCT and one case series) investigated the use of topical R-salbutamol cream in 46 patients with CLE. The RCT only included patients with DLE lesions although the case series included patients with mixed subtypes. Both studies showed improvement [10]. Case reports of effective use of topical retinoids (tretinoid and tazarotene) and clindamycin have also been reported [14,15]. JAK1 is overexpressed in the dermis of CLE patients and is critical to type I interferon signaling, which suggests JAK1 inhibitors, including topical formulas, may benefit CLE [16].

Systemic treatments

Antimalarials and systemic steroids are recommended as first-line systemic treatment of CLE [9]. Other immunosuppressive and immunomodulating agents that can be considered for refractory disease or for minimizing systemic steroid exposure. These agents include methotrexate, azathioprine, mycophenolate sodium, mycophenolate mofetil, dapsone, thalidomide and lenalidomide.

Antimalarials

Antimalarials include HCQ, chloroquine and quinacrine and are administered according to actual body weight. HCQ is typically the treatment of choice, and it may have better efficacy than chloroquine [17]. A systematic review by Shipman *et al.* [18▪] included a total of 852 patients treated with HCQ from 10 studies (five retrospective studies, three prospective, two case series and two RCTs). It identified that a HCQ dosage up to 400 mg/day is effective for most CLE patients (range of effectiveness: 50–97%), with few adverse effects, but the response rate (RR) declines over time such that long-term HCQ RR drop to 45%. More recently, in a retrospective study investigating the efficacy of HCQ on Japanese patients with CLE, complete improvement was observed at high rates for ACLE; partial or nonimprovement rates were higher for CCLE at 16 weeks. Several patients with alopecia without scarring achieved complete improvement at 32 weeks. CCLE tended to take more time to improve than ACLE. Overall, 87% of patients had at least some beneficial response at 16 weeks. However, there were wide variations in complete improvement rates and duration for improvement among CLE subtypes [19]. Intriguingly, patients with a more TLR9-driven disease pathology may have more benefit from HCQ [20▪]. Currently, biomarkers are lacking to predict HCQ treatment response.

Retinal toxicity remains the most concerning complication of antimalarial use, especially HCQ and chloroquine; the risk of which is under 1% after 5 years but rises to ~20% after 20 years of antimalarial use [21]. More recent studies suggest that toxicity rates may be lower than previously thought: One recent study showed ~5% patients developed retinal complications over an average of 12.8 years [22], although another study demonstrated the prevalence of retinopathy was only 4.3% [23]. The elderly, high BMI, duration of HCQ intake, renal insufficiency, concomitant use with tamoxifen and previous macular damage are major risk factors for retinal toxicity [22,23]. Compared with HCQ, there was increased retinopathy risk with chloroquine and chloroquine-quinacrine, but no retinopathy was seen with quinacrine alone [24].

How to properly dose HCQ to mitigate side effects but maintain efficacy is a topic of debate. Monitoring of HCQ blood concentrations can be used to assess treatment compliance, with low blood levels indicative of poor adherence and very low blood HCQ concentrations (<200 ng/ml) indicating nonadherence to the treatment. This is an important consideration as blood levels of HCQ (>750 ng/ml) positively correlate with a significant decrease in CLE disease area and severity index (CLASI) [25]. Risk of retinal toxicity according to blood levels of HCQ is not known, but higher doses are associated with increased risk [26]. Thus dosing recommendations have been placed at 5 mg/kg/day, but how this impacts efficacy of the drug requires further study. If additional drug is needed once HCQ has been maxed out, one recommended strategy [3] is to add quinacrine to HCQ in declining responders to achieve a synergic effect [17,27]. On the contrary, a shortage of quinacrine has made this approach difficult in the United States.

Evolving therapeutic approaches of other DMARDs

Use of other DMARD therapies are supported primarily by case reports, which can lead to reporting bias for efficacy. Case reports continue to support the use of dapsone for CLE [28], and a recent literature review identified up to 90% efficacy for bullous lupus [29▪]. Similarly, a meta-analysis of 548 patients from 21

studies found the overall rate of response of multiple CLE subtypes to thalidomide was 90%. However, toxicity limits thalidomide use: the pooled rate of thalidomide withdrawal due to adverse events was 24% (peripheral neuropathy in 16% and thromboembolic events in 2%) and the pooled rate of relapse after thalidomide withdrawal was 71% [30]. Lenalidomide is a promising drug for severe refractory CLE with a lower frequency of nerve-related side effects [31]. In a translational study, iberdomide (CC-220), a related cereblon modulator, significantly reduced Ikaros and Aiolos protein levels in inflammatory cells and limited autoantibody production [32]. How iberdomide impacts CLE remains to be determined [33].

Emerging novel biologic therapies

Recent advances in the pathogenesis of CLE link environmental factors, most notably ultraviolet light, with activation of innate immune responses, leading to subsequent generation of adaptive immune responses and the development of CLE skin lesions; this process is a self-amplification loop orchestrated by a large number of interferon-regulated cytokines and chemokines [34]. All these findings have led to the testing of novel biologic agents targeting either immune cells (B cells, T cells and plasmacytoid dendritic cells) or pro-inflammatory mediators, such as type I interferons, in SLE. Few recent trials are specific for CLE outcomes [35]. Thus, we summarize data from CLE and SLE trials with available data for CLE responses from the past 2 years.

Targeting B cells

Rituximab is a chimeric mAb against the protein CD20. Two phase III studies, LUNAR and EXPLORER investigated the efficacy of rituximab in SLE patients and did not meet the primary endpoints. However, a systematic review of efficacy and safety of rituximab in nonrenal SLE patients included results from seven cohort studies in which SLE mucocutaneous manifestations were analyzed and found partial or complete response rates from 33 to 71%, (four cohorts with SLE mucocutaneous manifestation in general; three cohorts with specific manifestations like urticarial vasculitis, small vessel vasculitis or rash); in addition, this study suggested that rituximab may benefit ACLE patients [36]. A retrospective study on 26 SLE patient with active mucocutaneous manifestations treated with rituximab identified improvement in British Isles Lupus Assessment Group Index (BILAG) mucocutaneous domain scores in 42.9 and 50% of patients with ACLE and SCLE respectively; no response was seen in CCLE [37]. In another retrospective cohort study, a total of 50 SLE patients with CLE were included (21 ACLE, six SCLE, 10 CCLE, 11 nonspecific SLE including two with concurrent ACLE and CCLE). 76% improvement was noted at 6 months and 61% of patients maintained this response at 12 months. Complete response was seen in 2/6 (33%) with SCLE at 6 and 12 months and 5/12 (42%) and 5/11 (45%) with CCLE at 6 months and 12 months respectively; 15 patients (30%) required further rituximab therapy within 12 months for cutaneous involvement. Thus, rituximab may have efficacy in patients with SLE and severe active CLE; however, outcomes were variable in those with SCLE and CCLE subtypes and may reflect the variation in comedications, including administration of Cytoxan, in the various retrospective studies [36,37,38▪]. Prospective studies in which coadministered medications and steroid doses are controlled may be more useful for understanding the role of Rituximab in CLE treatment.

Belimumab

Belimumab is a fully humanized mAb against B-cell activation factor (BAFF, also known as BlyS) which is the only biologic drug currently approved for SLE; no clinical trials have formally studied the effects of belimumab on cutaneous disease. In a post-hoc analysis of combined data from two phase III trials (BLISS-52 and BLISS-76), belimumab and standard therapy showed significant improvement according to BILAG and SELENA-SLEDAI dermal component [39]. A retrospective study by Iaccarino *et al.* [40] analyzed 188 active SLE patients from 11 Italian cohorts that were treated with belimumab; 62 patients had cutaneous lesions including 48 patients with refractory, prominent skin lesions. CLASI scores were low (average of 4 at baseline) but improved after 6, 12 and 18 months of follow-up (1.5, 0 and 0 respectively). Thus, active SLE patients with acute mucocutaneous lesions may have improvement with belimumab [41].

Targeting T cells

Beyond generalized immunosuppressive measures, targeting T cells has not been successful or well studied thus far for CLE. Abatacept, a fusion protein composed of the Fc region of the IgG1 fused to the extracellular domain of CTLA-4, inhibits costimulatory T-cell activation. Results from three studies (two retrospective and one case series) showed that it may have some effects on non-specific cutaneous lupus lesions (oral ulceration, facial erythema ad alopecia), but no effect on CCLE, and the efficacy was not assessed on ACLE and SCLE [42]. Another targeting approach with lupuzor (rigerimod), a synthetic

phosphopeptide (P140) that modulates the activation of autoreactive T-cells by targeting MHC class II receptors, had a failed phase III trial in which there was a superior RR over placebo in 202 patients including withdrawals who were considered nonresponders, but did not reach statistical significance for the primary end point. No specific assessment of CLE was done in the trial [43]. Other T-cell approaches, such as the use of calcineurin inhibitors, have been used in SLE; a recent trial of voclosporin showed positive results for lupus nephritis, but skin metrics were not included in the trial [44▪].

Targeting plasmacytoid dendritic cells and interferon signaling

BIIB059 is a humanized IgG1 mAb that binds blood DC antigen 2 (BDCA2), a pDC-specific receptor that inhibits the production of type I interferons and other inflammatory mediators when ligated. In a recent phase I, randomized, double-blind, placebo-controlled clinical trial, eight CLE patients were treated with one dose of BIIB059 (four ACLE, one SCLE and three DLE); a reduction in CLASI-A scores was observed in 5/6 patients at week 4 and maintained at week 12, although no improvement was seen in three of four patient in the placebo group. In addition, decreased CLASI-A score was correlated with reduced level of interferon-response genes in blood, normalization of MxA expression and reduced immune infiltrates in skin lesions [45▪▪]. A phase 2 trial for the treatment of SLE and CLE is ongoing (NCT02847598) [46].

Anifrolumab is a fully humanized, IgG1κ mAb that binds to IFN-α/β/ω receptor and prevents signaling by all type I interferons. A post-hoc analysis of a phase IIb, comparing IV anifrolumab vs. placebo on rash and arthritis measures demonstrated significant improvement of cutaneous involvement in the high interferon gene signature subgroup [47]. Recently, results of the second phase 3 RCTs of anifrolumab demonstrated improvement vs. placebo for multiple efficacy endpoints [overall disease activity, skin disease and oral corticosteroids (OCS) tapering], with CLASI response 49 vs. 25%, $P = 0.039$ [48▪▪]. In another phase II study on the efficacy of subcutaneous anifrolumab in SLE with type I interferon test-high and active skin disease, greater reductions in CLASI activity score were observed in anifrolumab groups [49]. These results suggest anifrolumab is a promising agent for CLE.

AMG 811 is a human anti-IFNγ antibody (IgG1 isotype) that selectively targets human IFNγ. A phase I RCT compared 15 DLE patients treated with AMG 811 with placebo group; there was no significant difference in CLASI score, but there were changes in biomarkers associated with IFNγ in the blood and skins of DLE patients [50]. Given that only a subset of CLE lesions demonstrates IFNγ overexpression [7▪▪], further subsetting of patients should be considered prior to additional treatment studies with AMG 811.

Targeting the Janus kinase-signal transducer and activator of transcription (STAT) pathway

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2 that blocks type I interferon, IL-21 and IL-6 signaling. Results of a phase 2 trial in SLE of baricitinib met its primary endpoint and several secondary end points, but no difference in CLASI score was observed [51▪]. Overall CLASI scores were low at enrollment for this trial, so the performance of baricitinib in CLE remains debatable. Baricitinib, however, has shown significant improvement of skin lesions in patients with familial chilblain lupus and *TREX1* mutation [52] and complete remission of a refractory papulosquamous rash in an SLE patient [53]. In addition to baricitinib, case reports support efficacy of tofacitinib for CLE [54▪] and several ongoing phase I and II clinical trials are investigating this [55,56].

Other therapies targeting cytokines and their receptors

Consistent with previous results [57▪▪], a post-hoc analysis of a phase II RCT of ustekinumab, an IL-12/23 mAb, demonstrated reduced the skin disease activity of patients with SLE who had a high CLASI score. The proportion of patients with at least 50% improvement in CLASI activity score stabilized at week 28 (67.7%) and then maintained through week 48 (68.6%) in the ustekinumab group [58]. Phase III trials are ongoing.

CONCLUSION AND PERSPECTIVE

CLE encompasses several cutaneous diseases with common and unique pathogenesis. Current treatment approaches can improve CLE, but there are still several unmet needs, including more effective less toxic medications and a reliable supply of quinacrine. Ongoing research is driving the pipeline of possible therapies. Consideration of CLE as a disease entity worthy of individual study will be important for patients who suffer from CLE without associated SLE and for SLE patients with fairly good disease control but refractory skin lesions.

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Conflicts of interest

J.M.K. has served on advisory boards for AstraZeneca, Eli Lilly and Bristol-Myers Squibb. J.M.K. and J.E.G. have grant funding from Celgene. J.E.G. has served on advisory boards for Novartis and MiRagen, and he has received additional research support from AbbVie, SunPharma and Genentech. No industry funds were used to complete this study. H.S. has no relevant conflicts.

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Treatment of thrombotic antiphospholipid syndrome in adults and children

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Purpose of review
Antiphospholipid syndrome (APS), more common than once believed, is an autoimmune disease best known for its high risk of incident and recurrent thrombotic events. The approach to treatment potentially differs from treatment of thrombosis in the general population, and this article endeavors to review the latest updates on this topic.

Recent findings
The epidemiology of APS is being increasingly elucidated by large population-based studies, with APS perhaps affecting as many as 1 in 2000 individuals. Vitamin K antagonists, aspirin, and heparinoids continue to have obvious roles in the management of patients with APS. There has recently been intensive study of direct oral anticoagulants in APS, with the most recent randomized studies raising concerns about their inferiority to vitamin K antagonists, at least in some subgroups. Other approaches to treating APS beyond anticoagulants and antiaggregants are also receiving increased attention in mechanistic and preclinical studies with an eye toward future roles in patients with refractory and/or microvascular disease. Pediatric APS is identified as an area in desperate need of additional prospective research.

Summary
Progress continues to be made in pursuit of improving the lives of individuals afflicted with APS. The most important future directions would seem to involve leveraging modern molecular technologies in order to improve subphenotyping of antiphospholipid antibody-positive individuals. This will help personalize risk profiles and ideally define the optimal approach to therapy based on future risk, rather than past morbid events.

Keywords
antiphospholipid, antiphospholipid syndrome, direct oral anticoagulants, pediatric, thrombosis

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune, thromboinflammatory disorder characterized by an increased risk of thrombotic events and pregnancy morbidity – in the setting of persistently positive antiphospholipid antibodies (aPL) [1]. For research purposes, classification of APS should utilize the Sapporo criteria (last updated in 2006), which require the presence of at least one clinical event and one durably positive (over at least 12 weeks) aPL laboratory test [2]. Clinical events that fulfill updated Sapporo criteria include proven vascular thrombosis in arteries, veins, or small vessels, along with certain types of pregnancy morbidity (Table 1). Beyond thrombosis and pregnancy complications, patients with APS are also at risk for myriad autoimmune, inflammatory, and microvascular manifestations including thrombocytopenia, hemolytic anemia, cardiac valve dysfunction, nephropathy, livedo reticularis/racemosa, and cognitive dysfunction, among others.

Laboratory tests included in the updated Sapporo criteria include the lupus anticoagulant (a functional assay that screens for clinically relevant aPL); anticardiolipin IgG or IgM in medium or high

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KEY POINTS

- Antiphospholipid syndrome (APS) may be more common than previously appreciated with a prevalence as high as 1 in 2000.
- The first-line therapy for both children and adults with APS is anticoagulation with vitamin K antagonists.
- Direct oral anticoagulants (DOACs) are not first-line therapy, and the approach to their second-line use needs to be cautious and individualized to a patient's history and antiphospholipid antibody profile.
- The treatment of catastrophic APS (CAPS) consists of a combination of anticoagulation, corticosteroids, and either plasmapheresis or IVIG.
- Hydroxychloroquine and statins can be considered as adjunctive therapies in APS.
- Study is underway of other emerging therapies in APS, such as antioxidants and adenosine receptor agonists.

titer (>40 GPL/MPL or >99th percentile); and anti-beta-2 glycoprotein I (β_2GPI) IgG or IgM in titer greater than 99th percentile (Table 1). Some 'non-criteria' laboratory tests, such as antiphosphatidylserine/prothrombin and antiβ_2GPI domain I, continue to be characterized and may one day find a role in routine clinical practice [3].

The concept of 'pediatric APS' is typically applied when APS presents in children under the age of 18 years [4,5]. The updated Sapporo criteria were developed with adults in mind, and there are no specific criteria for pediatric APS. As will be discussed in more detail below, potential limitations of these criteria in children include the fact that most individuals under the age of 18 years will not have experienced pregnancy (and therefore, have no opportunity to meet that aspect of the criteria). Furthermore, certain neurologic and hematologic manifestations of APS (chorea, thrombocytopenia, etc.) that are not part of the updated Sapporo criteria may be particularly common in children.

EPIDEMIOLOGY

Although the initial descriptions of APS were made more than three decades ago, our understanding of its epidemiology is still far from complete. In a recent population-based study, it was determined that the incidence of APS is approximately 2 per 100 000, whereas the prevalence is 50 per 100 000 [6▪▪]. This study was done in a predominantly white population; therefore, it is still unknown if APS has a different burden in other racial groups, as is the case for lupus. Potentially separable from APS, the prevalence of aPL themselves also remain to be fully defined. For example, one classic study measured aPL in a random sample of 552 healthy blood donors and detected aCL IgG and IgM in 6.5 and 9.4%, respectively. However, it is important to note that none of the positive individuals developed a thrombotic event after 1 year of follow-up, and for most, the titers decreased over time [7].

As for many autoantibodies, the prevalence of aPL in the general population likely increases with age [8]. aPL are also significantly more common in individuals with other autoimmune conditions. In individuals with lupus, the prevalence of lupus anticoagulant ranges from 15 to 34%, aCL from 12 to 44%, and antiβ_2GPI from 10 to 19% [9]. When considering the prevalence of aPL in individuals who have presented with a thrombotic event, studies have found 9% positive in the setting of

Table 1. Classification criteria for antiphospholipid syndrome

Clinical criteria	Vascular thrombosis	≥1 clinical episode of arterial, venous, or small-vessel thrombosis
	Pregnancy morbidity	(a) ≥1 unexplained death of a morphologically normal fetus at ≥10 weeks of gestation
		(b) ≥1 premature delivery of a morphologically normal fetus at <34 weeks gestation because of:
		(i) Severe preeclampsia or eclampsia defined according to standard definition
		(ii) Recognized features of placental insufficiency
		(c) ≥3 unexplained consecutive miscarriages at <10 weeks gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded
Laboratory criteria	The presence of antiphospholipid antibodies on ≥2 occasions ≥12 weeks apart (a) Presence of lupus anticoagulant in plasma (b) Medium- to high-titer anticardiolipin antibodies of IgG or IgM isotypes (c) Medium-titer to high-titer antibeta-2 glycoprotein-I (antiβ_2GPI) antibodies of IgG or IgM isotypes	

Data from [2]. APS is present if one of the clinical criteria and one of the laboratory criteria are met. APS, antiphospholipid syndrome.

unprovoked venous thromboembolism, 17% in the setting of stroke under age 50 years, and 11% in the setting of myocardial infarction [10▪,11,12▪]; studies addressing this particular question are of course burdened by variability in antibodies tested, positive/negative cutoffs, and typically a lack of repeated measurements.

PRIMARY PREVENTION IN ANTIPHOSPHOLIPID ANTIBODY-POSITIVE INDIVDUALS

A significant challenge in APS management is how to approach asymptomatic aPL-positive individuals. The first important step is to confirm the durability of aPL positivity as transient positivity has been reported among adult patients in the setting of viral infections (particularly parvovirus B19) [13]; patients in ICUs (positive lupus anticoagulant in 52.9% of patients, which resolved spontaneously in 63% of these patients) [14]; critically ill cancer patients (70% of patients had initial positivity, but only 33% of those available for reassessment remained positive at least 12 weeks later) [15]; and even healthy blood donors (positive anticardiolipin IgG in 6.5% of 552 blood donors, 78% of whom did not remain positive after 9 months) [7]. Although it is well known that persistently positive aPL are associated with an increased risk of arterial and venous thrombosis [16], quantification of such risk in an individual person remains difficult because of inconsistent application of aPL laboratory criteria in many studies, the multifactorial nature of thrombosis risk, and potential confounding factors, such as underlying autoimmune diseases and medication effects [16,17]. As such, how to approach primary thrombosis prophylaxis among asymptomatic aPL carriers remains largely unknown because of limited and low-quality data [17,18]. For example, aspirin's role in the primary thrombosis prophylaxis of individuals with persistently positive aPL remains debatable [17,18]. The APLASA study is the only randomized trial to evaluate the effectiveness of aspirin ($n = 48$) versus placebo ($n = 50$) in preventing a first thrombotic event among asymptomatic aPL-positive carriers. With the caveat that the study had a very low event rate overall, daily low-dose aspirin was no better than placebo at preventing thrombosis (hazard ratio = 1.04, 95% CI = 0.69–1.56) [19]. Although prospective data to broadly support the use of aspirin for primary thrombosis prophylaxis are lacking, some point to retrospective literature to argue that persistent aPL carriers with lupus, high-risk aPL profiles, or other cardiovascular risk factors may benefit from aspirin to lower the risk of first thrombosis [18,20–22]. The risk of bleeding from aspirin should always be considered when making a decision about primary thrombosis prophylaxis [23].

Whenever considering primary prophylaxis with aspirin or other medications in aPL-positive, asymptomatic children, for example, with lupus, there is only adult data, described above, to guide decisions regarding potentially lifelong therapy. It is especially important, then, to confirm the durability of aPL, which have frequently been reported as transiently positive in children because of infectious exposures, such as upper airway infections, vaccinations, and exposure to nutritional antigens in atopic dermatitis [24–28]. The SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative, a project to identify best practices for diagnosis and management of pediatric rheumatic diseases, developed a set of evidence-graded recommendations; in pediatric patients with lupus, they suggested that antiplatelet agents could be considered for primary prevention in addition to hydroxychloroquine, and they made no comment on other asymptomatic aPL-positive children [29].

SECONDARY PREVENTION AFTER A THROMBOTIC EVENT (VENOUS OR ARTERIAL)

Heparinoids

In a patient with acute venous thrombosis regardless of underlying cause, the mainstay of treatment is anticoagulation with unfractionated heparin or low-molecular-weight heparin (LMWH) followed by bridging to a long-term anticoagulation strategy, usually with a vitamin K antagonist (VKA), such as warfarin. This strategy also applies to patients with APS, who will often be diagnosed with thrombosis first and tested for APS later. The latest EULAR recommendations for managing APS in adults recommend this strategy as a first-line approach [30▪▪]. These recommendations also include LMWH as an option when recurrent thrombosis occurs despite use of VKA with target international normalized ratio (INR) of 2–3. Two small studies evaluating the use of LMWH in APS patients both concluded that LMWH is a well tolerated and effective alternative to warfarin based on lack of recurrent thrombotic events or significant adverse effects with follow-up of an average of 309 days and 36 months [31,32]. An additional small study of 11 patients with APS nephropathy found that treatment with LMWH led to improvement of proteinuria, arterial pressure, and glomerular filtration rate [33].

Vitamin K antagonists

In patients with definite APS and a first episode of venous thrombosis, the recommended treatment

from EULAR guidelines is a VKA with INR goal of 2–3 [30▪▪]. Two randomized controlled trials (RCTs) evaluating a higher INR goal of 3–4 did not show any additional benefit, albeit it with the caveat that it was difficult for study participants to consistently achieve the higher INR target [34,35]. In one of the studies, there was an increased rate of minor hemorrhagic complications but no other difference in adverse effect [35].

In the setting of an unprovoked venous thrombotic event associated with APS, there is consensus that long-term anticoagulation is recommended [30▪▪]. In comparing long-term versus 3–6 months of oral anticoagulation in APS patients with venous thrombosis (both provoked and unprovoked), an RCT and a retrospective cohort study both showed a lower risk of recurrent thrombosis in the group on long-term anticoagulation [36,37]. Although some case series have suggested that patients may tolerate discontinuation of anticoagulation once aPL testing becomes persistently negative, a more recent study demonstrated a high rate of recurrent thrombosis (45.8% at 5 years' follow-up since negative aPL) despite persistently negative aPL [38–40]. In our opinion, a randomized VKA-withdrawal trial is very much needed, specifically to study whether select patients who technically meet criteria for APS can safely discontinue anticoagulation, especially in the setting of obvious provocation of the venous event, low-risk aPL profiles, or aPL profiles that normalize.

In patients with APS who experience an initial arterial thrombosis, treatment with a VKA is again recommended [30▪▪]. EULAR recommendations suggest weighing a patient's risks of thrombosis and bleeding and then deciding on an individualized treatment strategy that might include a VKA with INR goal 2–3 with or without aspirin or a VKA with INR goal 3–4 [30▪▪]. Again, INR goals were compared previously, and there was no benefit with a higher goal, but the studies included only a minority of patients with arterial events and achievement of target INR 3–4 was relatively low [34,35].

Aspirin

Low-dose aspirin (LDA) has been studied in APS as both primary and adjunctive therapy. There are observational studies comparing VKA monotherapy with LDA monotherapy in patients with APS, and there is a decreased risk of recurrent thrombosis in those treated with a VKA [41,42]. In a small RCT, APS patients with ischemic stroke were randomized to either LDA or LDA with a VKA, and the patients receiving combination therapy had a lower incidence of stroke; there was not an arm receiving a VKA alone [43]. Therefore, in most circumstances, LDA should not be used in place of a VKA.

Our opinion is that strong consideration should be given to the use of LDA in addition to a VKA in most patients who have experienced arterial thrombosis. One interesting retrospective cohort study looked at multiple treatment approaches and how they affected recurrent thrombosis. In this study, there was a significant decrease in recurrence among patients on warfarin alone as well as warfarin with LDA; additionally, there were no recurrent arterial events at all among patients on warfarin with LDA, but the difference between the groups with and without LDA was not significant because of an insufficient number of patient-years in follow-up [44]. On the basis of large studies in the general population, LDA is recommended by the American Heart Association as secondary prevention for all patients with noncardioembolic ischemic stroke or TIA [45]. Again, our opinion is that APS patients with history of stroke or TIA, and perhaps even other forms of arterial thrombosis, may benefit from taking LDA in addition to a VKA (or other form of anticoagulation).

Dual antiplatelet therapy

Though VKAs are the standard of care for secondary prevention of thrombosis in APS, other therapy options have been considered including dual antiplatelet therapy, a strategy used for secondary prevention of myocardial infarction and stroke. In a retrospective cohort study of 90 APS patients with a high rate of recurrent thrombosis (40 of 90 patients had recurrent thrombosis, and 35 of the 40 had a recurrent arterial thrombotic event) [46]. When analyzing outcome stratified by treatment received, the authors found that patients on dual antiplatelet therapy had a recurrence rate (per 100 patient-years) of 1.8, which was statistically similar to those receiving warfarin with aspirin (3.7), and significantly lower than those receiving warfarin alone (11.6, $P = 0.001$) [46]. This study is the first to examine dual antiplatelet therapy specifically for APS patients and highlights its potential benefits. Though additional study is warranted, it does seem that dual antiplatelet therapy might be an option for some APS patients at risk for recurrent arterial thrombotic events.

APS patients may sometimes be prescribed dual antiplatelet therapy for other indications. For example, dual antiplatelet therapy is standard of care for patients with myocardial infarction (MI) who are treated with a drug-eluting stent based on recommendations from the American College of Cardiology and American Heart Association [47]. If an APS

Table 2. Characteristics of key clinical trials regarding the use of direct oral anticoagulants in patients with antiphospholipid syndrome

Trial	*N*	Length of trial	Thrombosis type	INR goal of VKA patients?	Triple-positive aPL profiles	More thrombosis on DOACs[a]?
RAPS by Cohen *et al.* [51]	116	6 months	V	2–3	28%	No
TRAPS by Pengo *et al.* [52▪▪]	120	569 days[b]	A, V, M	2–3 or 3–4	100%	Yes
Ordi-Ros *et al.* [53▪▪]	190	3 years	A, V, M	2–3	61%	Yes

A, arterial; DOAC, direct oral anticoagulant; INR, international normalized ratio; M, microvascular; V, venous; VKA, vitamin K antagonist.
[a]Primary outcome for RAPS was a laboratory surrogate, but no thrombotic events were seen in either the VKA or DOAC arm. Primary outcome of TRAPS was a summative incidence of thromboembolic events, major bleeding, and vascular death.
[b]TRAPS ended early because of excessive events in DOAC group.

patient has an MI and a stent placed, the approach to treatment will have to be individualized. The study discussed above might lead one to consider using dual antiplatelet therapy without a VKA [46], whereas others would argue for the use of dual antiplatelet therapy in addition to a VKA [48] because of the high rate of re-thrombosis after percutaneous coronary intervention in APS patient [49]. We would tend to follow the latter approach unless we felt that a particular patient was at especially high risk of bleeding.

Direct oral anticoagulants

Treatment with VKAs has drawbacks including the need for frequent laboratory monitoring, difficulty maintaining the target INR goal (at least for some individuals), and many interactions with diet and other medications. The direct oral anticoagulants (DOACs) are an attractive group of anticoagulants, given the absence of a requirement for regular laboratory monitoring, relative ease of administration, and lack of dietary restrictions. DOACs have been approved for treatment and secondary prevention of venous thromboembolism (VTE), VTE prophylaxis in certain settings, stroke prevention in nonvalvular atrial fibrillation, and stable coronary and peripheral artery disease for selected patients. In the large clinical trials of DOACs for VTE, patients with APS were almost certainly included as evidenced by the relatively high prevalence of aPL in DVT (estimated at 10%) [50], but aPL were not systematically documented and so subgroup analyses are not possible [51].

There have been three large RCTs comparing warfarin to rivaroxaban in patients with APS (Table 2); all three included both primary and secondary APS patients. The first was the RAPS trial, a randomized, controlled, open-label, phase 2/3, noninferiority trial of 116 patients with a history of only venous, not arterial, thrombosis [51]. They also excluded patients who previously had a recurrence on standard-intensity warfarin. The trial included patients with any Sapporo-qualifying aPL profile. This 6-month trial had as primary endpoint a laboratory surrogate of thrombosis, the endogenous thrombin potential. Although the trial did not meet the primary endpoint, there were neither thrombotic events in either group over the 6 months of the trial nor was there any difference in bleeding events. Overall, within the fairly homogenous study population (as defined by clinical history), the trial results suggested optimism towards the use of rivaroxaban for patients with a history of VTE and without previous recurrence on warfarin.

The next large RCT examining DOACs in APS was TRAPS, a large randomized, open-label, multicenter phase 3 noninferiority study comparing rivaroxaban to warfarin (INR goal 2–3) in 120 APS patients defined as 'high-risk' with a triple-positive aPL profile. The patients could have a history of any type of prior thrombosis: arterial, venous, or biopsy-proven microvascular thrombosis [52▪▪]. The primary endpoint was the cumulative incidence of thromboembolic events, major bleeding, and vascular death. The trial was terminated early because of a significant excess of thrombotic events in the rivaroxaban group. Indeed, there were seven arterial thrombotic events in the rivaroxaban group (including three patients who only had a history of venous thrombosis), as compared with no arterial thrombotic events in the VKA group. There were no venous thrombotic events in either group. In summary, this trial provides evidence that among triple-positive APS patients with any type of prior thrombosis, there appears to be an increased risk for thrombosis with the use of rivaroxaban as compared with VKA. Of note, use of LDA was not systematically controlled in the trial and used in less than 20% of patients.

The third large trial was another randomized, open-label, phase 3 noninferiority clinical trial with a larger and more heterogeneous patient population, again comparing rivaroxaban to a vitamin K

antagonist [53▪▪]. The trial included patients with either arterial or venous thrombosis, a current INR target of either 2–3 or 3–4 (the latter selected if there was a history of prior recurrent thrombosis), and any combination of Sapporo-qualifying aPL profile. In this study, the primary efficacy endpoint was the proportion of patients who had a new thrombotic event during the study. Rivaroxaban failed to meet the noninferiority threshold, and there was a significant increase in the proportion of patients on rivaroxaban who developed a stroke. Again, some of these patients who developed an arterial event only had past history of venous thrombosis. Of note, LDA was used in just 12.6% of patients with no difference between the two groups. In subgroup analysis, the possibility was raised of increased events in patients with previous arterial thrombosis, livedo reticularis/racemosa, and APS valvular disease, but no definite conclusions could be drawn.

Finally, we can briefly mention a prospective cohort study of 176 APS patients, including 82 patients on DOACs because of either patient preference or unstable anticoagulation with VKAs, again showed increased risk of recurrent thrombotic events in patients on DOACs compared with those on VKAs (hazard ratio 3.98 with 95% CI 1.54–10.28, $P = 0.004$) [54▪]. This study included patients with a history of venous and/or arterial thrombotic events and followed them for a median 51 months. There was no difference between single/double-positive aPL profiles as compared with triple-positive. However, increased risk was predicted by older age and higher global APS score (GAPSS). Of note, in 40% of the patients on DOACs who had a thrombotic event, it occurred around the time of an interruption of therapy.

To summarize this emerging body of evidence [55▪,56▪], two large RCTs have raised concerns about the use of rivaroxaban, as compared with VKAs, in APS. One of these studies focused on patients with triple-positive aPL profiles, and the other a more heterogeneous group of patients with any aPL profile and any type of prior thrombosis. The RAPS trial was more encouraging that perhaps in patients with only a history of venous thrombosis, and no prior recurrence, DOACs might still be considered; having said that, recurrent thrombotic events did occur in the other two RCTs even in patients with history of venous thrombosis only. At this time, rivaroxaban should certainly not be considered first-line therapy in APS, and the available evidence does not support its use in patients with triple-positive aPL profiles or history of arterial thrombotic events. Whether there is a role for DOACs as second-line therapy in patients with history of venous thrombosis may still warrant further study. Given the heterogeneity of APS clinical profiles, our opinion is that the clinician may still consider DOACs as second-line therapy in select patients, but should certainly make those patients aware of the risks. The EULAR recommendations do include DOACs as a possible treatment for patients with either contraindications to VKA or difficulty achieving the goal INR despite compliance to VKA [30▪▪]. Our opinion is that DOACs may eventually require a regular place in the APS clinic, but this will require implementation of molecular sub-phenotyping that goes beyond patient history and aPL profiles.

Secondary prevention after a thrombotic event in children

The general treatment strategy used in adults is the same as that recommended for children per the SHARE initiative recommendations [29]. For venous thrombotic events and durable aPL positivity, long-term anticoagulation is recommended. Data from the largest pediatric APS registry showed a high rate of recurrence of thrombosis at 19%, and a review of 17 cases at Mayo showed an even higher rate of recurrence of 58.8%, 80% of whom were not on therapeutic levels of anticoagulation [5,57]. Even in patients whose aPL become negative, adult data suggest recurrence of thrombosis in almost half of patients who discontinue anticoagulation by 5 years follow-up [40]. For APS with an arterial thrombotic event, the SHARE initiative recommends either anticoagulation or combined anticoagulation and antiaggregant therapy [29]. In considering aspirin therapy specifically in children, a study of seven children with aPL and acute cerebral infarction found that when treated with aspirin, there were no recurrent events over 15.7 months of follow-up [58]. For recurrent thrombosis, despite VKA with target INR 2–3, the SHARE initiative suggests increasing the target INR to 3–4 or using an alternative therapy, such as LMWH; these strategies have not been specifically studied in children [29].

At this time, DOACs are not Food and Drug Administration (FDA)-approved for patients less than 18 years of age and the trials using DOACs in APS were only done in adults. In a retrospective review of 17 pediatric APS patients seen at the Mayo Clinic in Rochester, Minnesota, none of the patients were treated with DOACs [57]. In another retrospective review of APS in pediatric patients in China, rivaroxaban was used in one patient without recurrence during 5 months of follow-up [59▪]. The largest published series, an international registry of 121 patients, made no mention of treatment with any DOACs [5]. Expert opinion with the SHARE initiative also makes no mention of the use of DOACs

[29]. There have been no studies specifically evaluating the use of DOACs in children with APS, and we therefore, cannot comment on their efficacy or safety beyond extrapolating adult data to children. Our opinion is that DOACs should be avoided in children with APS pending additional study.

SMALL-VESSEL THROMBOSIS

Over the years, it has been recognized that APS not only causes large-vessel thrombosis (e.g. venous thromboembolism, stroke, myocardial infarction), but also may affect the microcirculation. Examples of microvascular manifestations (many of which are being considered for the next round of APS classification criteria) include livedo reticularis and racemosa; skin ulcers including livedoid vasculopathy; adrenal hemorrhage; cardiac microvascular disease; pulmonary hemorrhage; acute or chronic aPL nephropathy; and others [60]. However, unless accompanied by definitive biopsy results (thrombotic microangiopathy), these manifestations do not fulfill the updated Sapporo criteria (Table 1) [2], and as such they are often referred to as 'non-criteria' manifestations. That terminology should not, however, distract from the fact that these features often bring with them significant morbidity and pose a clinical challenge as many occur despite otherwise adequate anticoagulation. Indeed, other approaches to treatment may be required, which – based on case reports and series – can include immunomodulatory strategies [61▪]. Some options for treatment beyond anticoagulation will be discussed below (Table 3).

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Catastrophic APS (CAPS) is the rapid (≤1 week) onset of widespread microvascular thrombosis in multiple organs – often with an identifiable trigger, such as infection, surgery, or anticoagulation withdrawal [62]. The approach to treating catastrophic APS has been reviewed in detail by our group [63] and others [62]. Despite the absence of prospective data, there is relative consensus that patients do best when treated with so-called triple therapy – heparin, corticosteroids, and either IVIG or plasmapheresis. Future studies in the area of CAPS should continue to assess the extent to which complement inhibition may be effective as add-on therapy [64,65]. Presently, complement inhibition may be considered in refractory cases, but there are insufficient data to make firm, proactive recommendations.

Catastrophic antiphospholipid syndrome in lupus patients

If CAPS were to occur in a patient with secondary APS, especially in the context of concomitant lupus,

Table 3. Medications beyond anticoagulants that may be considered in patients with 'microvascular antiphospholipid syndrome' or other refractory cases

Therapy	Evidence base	Potential therapeutic use
Hydroxychloroquine	Preclinical mechanistic data, large cohort studies	Primary and secondary thromboprophylaxis in all patients with lupus. May also be used as adjunctive therapy in refractory cases with recurrent thrombosis despite adequate anticoagulation
Statins	Preclinical mechanistic data, a few cohort studies	Consider in all patients with history of arterial thrombosis. May also be used as adjunctive therapy in refractory cases with recurrent thrombosis despite adequate anticoagulation
Rituximab	Open-label clinical trial, case reports	Consider in patients with difficult-to-control microvascular manifestations, such as skin ulcers and diffuse alveolar hemorrhage. May also be used as adjunctive therapy for refractory CAPS
Belimumab	Case reports	Very limited evidence to support use in patients at this point
Eculizumab	Case reports	May be used as adjunctive therapy for refractory CAPS
Antioxidants	Preclinical mechanistic data, small clinical trial of reduced coenzyme Q10	May consider as adjunctive therapy given good safety profile
Adenosine receptor agonists[a]	Preclinical mechanistic data, case reports	Need prospective clinical trials with mechanistic endpoints
Depletion of antibody-producing cells	Preclinical mechanistic data only	Need prospective clinical trials with mechanistic endpoints
Antiinterferon therapies	Preclinical mechanistic data only	Need prospective clinical trials with mechanistic endpoints

[a]Such as dipyridamole, dilazep, and defibrotide.

there may be a role for additional immunosuppression with cyclophosphamide. We recommend strongly considering the use of cyclophosphamide (typically administered intravenously at a dose of 500–700 mg/m^2 adjusted based on renal function, as has been used for other organ-threatening and life-threatening manifestations of lupus) based on data from the CAPS registry; there are no prospective studies to guide management [63]. In the registry, 103 patients with lupus-CAPS were analyzed, and the use of cyclophosphamide given to 47% of patients led to a decreased mortality (odds ratio 0.20, range 0.06–0.71, $P = 0.013$) [66]. Among 126 CAPS patients without lupus, 15% of patients also received cyclophosphamide and actually had increased mortality (odds ratio 8.5, range 1.91–37.83, $P = 0.005$), though these were also patients with more organs involved and so their poor outcomes were likely at least somewhat attributable to disease severity [66]. At this time, cyclophosphamide should be strongly considered in CAPS patients with a history of lupus, but typically not in CAPS patients without lupus.

Catastrophic antiphospholipid syndrome in children

In pediatrics, the same approach with triple therapy has been recommended [29]. Within the international CAPS registry, 45 pediatric patients were included, and there was a trend towards increased use of triple therapy among patients who survived (8/33 versus 0/12 patients who died), but the difference was not statistically significant ($P = 0.087$) [67]. In pediatric patients, four case reports of the use of rituximab for CAPS have been summarized with all four recovering [68]. The SHARE recommendations include the consideration of rituximab and other immunosuppressive therapies as treatment options [29]. Additional study is needed to solidify treatment recommendations in pediatric CAPS. It may also be particularly important to identify and treat any underlying infections, as infection is more often the inciting event leading to CAPS in children as compared with adults [67].

EMERGING/FUTURE THERAPIES

Hydroxychloroquine

Hydroxychloroquine is an important disease-modifying agent for the treatment of systemic autoimmune diseases, particularly lupus. Interestingly, its use as a prophylactic agent against venous thrombosis was regularly reported in the orthopedic literature in the 1970s; however, in contrast to treatment of lupus, hydroxychloroquine was used in this context at relatively high doses (>500 mg/day) and for short periods of time [69]. A number of mechanistic and preclinical studies have suggested a protective role of hydroxychloroquine in the context of aPL-mediated thrombosis [70–72]; hydroxychloroquine use may also be associated with reduction in aPL titers [73,74]. Hydroxychloroquine clearly protects against thrombosis in lupus patients, a finding that has been observed in different cohorts across the world [21,75,76]. A clinical trial of hydroxychloroquine in aPL-positive but thrombosis-free individuals without systemic autoimmune diseases enrolled 20 patients; however, there were no thrombotic events during trial follow-up in either group [77]. In a small nonrandomized clinical trial of patients with primary APS, study subjects on oral anticoagulation and hydroxychloroquine had less thrombotic events than those on oral anticoagulation alone [78]. The use of hydroxychloroquine in all aPL-positive patients with lupus was recommended by the 14th International Congress APS Treatment Trends Taskforce [79]. Although there are no solid data to support hydroxychloroquine's use in all patients with primary thrombotic APS, our opinion is that it should certainly be considered in refractory cases [30▪▪,80].

Statins

Statins, which function as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, have been widely used for primary and secondary cardiovascular disease prevention because of their cholesterol-lowering, anti-inflammatory, and antithrombotic effects [81,82]. Fluvastatin-treated APS mice have significantly smaller thrombi, decreased inflammatory molecules, and reduced leukocyte adhesion to endothelial cells as compared with controls [83]. Administration of fluvastatin to aPL-positive individuals reduces tissue factor expression in monocytes [84] along with other circulating proinflammatory and prothrombotic biomarkers [85]. Furthermore, simvastatin appears to reduce aPL levels in patients with lupus [86]. Only a few studies have assessed the relationship between aPL status, statin use, and clinical outcomes. In a retrospective cohort study from Japan, lupus patients without a history of thrombosis (both with and without aPL) were followed to estimate the incidence of thrombosis and factors affecting it. Eighty patients were aPL-positive, including criteria and noncriteria antibodies. The investigators reported that after adjusting for several risk factors, statins were protective for thrombosis onset; however, in the subset of patients with only criteria aPL, this effect did not reach statistical significance [87]. Given the limited clinical data available, statins can

only definitively be recommended in APS when an accompanying indication, such as hyperlipidemia is present. However, our opinion is that their use should be strongly considered in all APS patients with history of arterial thrombosis, as well as in cases that are resistant to standard anticoagulant approaches [30▪▪].

B-cell modulation (rituximab and belimumab)

It is widely believed that aPL themselves drive thrombosis through a variety of mechanisms, and therefore, play a central role in disease pathogenesis. This and other observations have pointed to targeting B cells as a potential therapeutic strategy in APS. Rituximab, a chimeric monoclonal antibody targeting CD20-positive cells is regularly used in the treatment of various autoimmune diseases including small-vessel vasculitis and rheumatoid arthritis. The use of rituximab in lupus is somewhat more controversial although another B-cell agent, belimumab (an antibody directed against B-cell activating factor) is approved for treatment of lupus [80,88].

The data available for the use of rituximab in the treatment of thrombotic APS is drawn from case reports and case series. For example, in one small retrospective study, rituximab decreased thrombotic events in individuals with lupus and APS who were refractory to treatment with warfarin [42]. In primary APS, just a handful of case reports are available describing successful use of rituximab in the treatment of thrombotic APS [89]. It should be noted though that a small pilot open-label phase II trial administered rituximab to 20 patients with primary APS, demonstrating a favorable safety profile as well as potential clinical effectiveness in microangiopathic manifestations, such as skin ulcers and aPL nephropathy [90]. Case series and reports also support its use in diffuse alveolar hemorrhage and in cases of CAPS that are unresponsive to traditional triple therapy [91,92]. Regarding belimumab, a few case reports and series have demonstrated that it may decrease the titers of aPL, with some patients even becoming seronegative. Not surprisingly, these reports have typically been in individuals with both lupus and APS [93]. One case report describes a possible therapeutic response of aPL-associated skin ulcers to belimumab [94]. Our opinion is that these agents (especially rituximab) can be considered in individuals with refractory microvascular disease, such as skin ulcers, alveolar hemorrhage, and CAPS.

Complement inhibitors (eculizumab)

The complement system likely plays an important role in APS pathogenesis. Indeed, in preclinical models of APS, C3 and C5 activation are required for aPL-induced thrombosis, increased leukocyte adhesion to endothelium, and release of tissue factor and other procoagulant substances from activated neutrophils [95–98]. Eculizumab is a humanized monoclonal antibody that binds to the C5 protein, blocking its cleavage, and thereby preventing the assembly of the membrane attack complex. Eculizumab is used for the treatment of paroxysmal nocturnal hemoglobinuria as well as atypical hemolytic uremic syndrome. Successful trials have also been reported in neuromyelitis optica spectrum disorders [99–101]. Most of the current available clinical reports are based on its use as rescue therapy in refractory cases of CAPS. Successful treatment or prevention of thrombotic microangiopathy in APS patients undergoing renal transplantation has also been described [102–104]. Given the limited clinical data but the life-threatening situation that CAPS often entails, eculizumab may be considered in cases refractory to traditional treatment.

Others

Coenzyme Q10 (CoQ10) participates as an electron carrier in mitochondrial and other membranes, with adequate CoQ10 levels protecting cells from protein oxidation and lipid peroxidation. In the general population, CoQ10 supplementation decreases the production of proinflammatory cytokines in the context of heart failure and coronary disease [105]. In a small clinical trial, 36 patients with APS received ubiquinol (reduced CoQ10, 200 mg/day) or placebo for 1 month; ~90% of subjects completed the study [106]. Among other positive effects, ubiquinol improved endothelial function and decreased monocyte expression of prothrombotic mediators [106]. The authors suggested that in the absence of clinically significant side effects, ubiquinol might act as a well tolerated adjunct to standard therapies in APS [106].

APS neutrophils have a reduced threshold for the release of neutrophils extracellular traps (NETs) – prothrombotic tangles of DNA, histones, and granule-derived proteins expelled from dying neutrophils [107,108] that potentiate thrombosis in human/mouse chimeric models of APS [109,110]. Given evidence that intracellular cyclic AMP (cAMP) suppresses NET release [111,112], a recent preclinical study hypothesized that activation of surface adenosine receptors (which trigger cAMP formation in neutrophils) might mitigate the thrombotic manifestations of APS [113▪▪]. Indeed, selective agonism of the adenosine A_{2A} receptor reduced NET release and thrombosis in the inferior vena cava of both

control mice and mice administered aPL [113▪▪]. Interestingly, the antithrombotic medication dipyridamole (which increases extracellular concentrations of adenosine) also suppressed aPL-mediated NETosis and mitigated venous thrombosis in APS mice [113▪▪]. Although dipyridamole has never been systematically studied in patients with APS, other drugs with adenosine-amplifying properties, such as defibrotide [114] and dilazep [115] have been reported as effective in case reports and preclinical models.

The potential utility of agents that directly target plasma cells (for example, anti-CD38, as is currently employed for multiple myeloma) was recently emphasized by a preclinical study characterizing lymphocyte subsets of patients with primary APS [116▪]. Although aPL were still robustly produced *ex vivo* by peripheral-blood leukocytes depleted of CD20-positive B cells, aPL production was eliminated by depletion of CD38-positive plasmablasts [116▪]. Another area to watch is the development of antiinterferon therapies, as are being pursued for treatment of lupus. Indeed, a number of groups have recently detected elevated levels of type I interferons in primary APS [110,117], including potential associations with triple positivity and pregnancy morbidity [118▪]. Whether neutralization of interferon pathways might mitigate any of the thrombotic – or perhaps more likely nonthrombotic – manifestations of APS awaits further study.

CONCLUSION

APS is more common than once believed, perhaps affecting as many as 1 in 2000 individuals. Vitamin K antagonists, aspirin, and heparinoids continue to have obvious roles in the management of patients with APS. There has recently been intensive study of direct oral anticoagulants in APS with the most recent randomized studies raising concerns about inferiority to vitamin K antagonists, at least in some subgroups. Other approaches to treating APS beyond anticoagulants and antiaggregants are also receiving increased attention in mechanistic and preclinical studies with an eye toward future roles in patients with refractory and/or microvascular disease. Overall, the most important future directions would seem to involve leveraging modern molecular technologies in order to improve subphenotyping of antiphospholipid antibody-positive individuals. This will help personalize risk profiles and ideally define the optimal approach to therapy based on future risk, rather than past morbid events.

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Conflicts of interest

There are no conflicts of interest

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This interesting study puts forth low interferon lambda gene expression as a new biomarker that potentially provides additional context to traditional type I interferon scoring in APS.

Management of systemic sclerosis: the first five years

David Roofeh and Dinesh Khanna

Purpose of review
This review provides a risk-stratified and evidence-based management for subsets of systemic sclerosis (SSc) patients in the first five years from disease onset.

Recent findings
Cardiopulmonary disease remains the primary cause of mortality in SSc patients. Morbidity and mortality in SSc-associated pulmonary arterial hypertension have improved with combination treatment, in either an upfront or sequential treatment pattern. Traditional therapies for interstitial lung disease (SSc-ILD) have targeted those with clinically significant and progressive ILD with immunosuppression. New data suggest a possible paradigm shift, introducing immunosuppressive therapy to patients before they develop clinically significant or progressive ILD. The year 2019 saw the approval of the first FDA-approved therapy for SSc-associated interstitial lung disease, using an antifibrotic agent previously approved for idiopathic pulmonary fibrosis. To date, only autologous hematopoietic stem cell transplant has demonstrated a mortality benefit for SSc-ILD, albeit in a narrow spectrum of SSc-ILD patients.

Summary
SSc is a highly heterogeneous autoimmune disease typified by varying clinical trajectories. Its management may be stratified within the first five years by subclassifying patients based on factors that have important prognostic significance: skin distribution and autoantibody status.

Keywords
management, systemic sclerosis, treatment

INTRODUCTION

Systemic sclerosis

Systemic sclerosis (SSc) is a chronic, heterogeneous autoimmune disease characterized by a triad of immune dysregulation, vasculopathy, and overproduction of collagen leading to skin and internal organ fibrosis [1]. This clinical heterogeneity may be codified into disease subsets, a critical insight allowing the provider to anticipate internal organ involvement and disease progression. Classification based upon the distribution of affected skin areas and autoantibody status informs the management of disease-related complications.

This article focuses on disease stratification and management in the first five years from onset of SSc. We support algorithmic approaches to management of disease subsets using recently published data.

EARLY SYSTEMIC SCLEROSIS

Early disease

The majority of internal organ involvement in SSc will occur within the first two to five years from the disease onset (typically defined as the appearance of the first non-Raynaud's phenomenon symptom). Classifying SSc patients into an early disease subset allows for tailored screening and management strategies, with an aim to institute therapeutic intervention to prevent irreversible organ damage.

Classification

Patients with SSc may be classified based on the extent of skin involvement: limited cutaneous (affected skin is distal to the elbows and knees, and may include the face), diffuse cutaneous (affected skin is both distal and proximal to the elbows and knees and may include the face, chest, trunk, and thighs), or absent (SSc sine scleroderma).

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KEY POINTS

- Identifying patients within the first five years and subclassifying patients based on skin distribution and autoantibody status allow practitioners the best opportunity to intervene before advanced fibrosis sets in and cannot be reversed.
- All patients should be screened with HRCT for SSc-ILD and routinely monitored for the development of dyspnea, cough, or exercise limitation alongside pulmonary function testing.
- Early detection and prompt initiation of therapy for PAH is essential.
- Those with RNA polymerase III antibody positivity should be counseled for risk of renal crisis and remain up-to-date on age-appropriate cancer screening.
- Enrollment in clinical treatment trials provides an option for investigational use of medications not yet approved by the FDA for SSc.

The 2013 ACR/EULAR classification criteria improved upon the performance of the 1980 classification criteria in terms of recognition of the disease, especially in limited disease and the early stages when skin fibrosis is less advanced: the sensitivity improved (91%, from 75%), as well as the specificity (90%, from 72%) [2].

Patients may also be classified based on autoantibody status: antibodies are detected in more than 95% of patients with SSc, rarely found in healthy populations, and are mutually exclusive (the presence of one generally precludes the presence of another). These serological markers precede the onset of symptoms and are useful in making an early diagnosis [3]. Table 1 provides an overview of the likelihood of clinical feature development of SSc stratified by autoantibody status. Anticentromere antibody has a high specificity for limited cutaneous SSc (95%) [4,5]. Anti-SCL-70 (anti-topoisomerase I antibody) is typically associated with diffuse cutaneous SSc; however, up to one-third of patients with antitopoisomerase I antibodies may have limited cutaneous SSc [6]. Commercially available ELISA-based assays for this antibody have been associated with high false positivity [7]. Anti-RNA polymerase III antibodies are associated with diffuse cutaneous SSc (90%) [8].

Prognostication

Factors present in the first five years of disease are predictive of development of major outcomes in SSc (e.g., development of interstitial lung disease, pulmonary hypertension, scleroderma renal crisis, death) [6,9–14].

Patients with limited cutaneous SSc typically have a burden of nonlethal signs and symptoms, notably a longstanding course of Raynaud's phenomenon, digital ulcerations, gastrointestinal involvement, and later-stage development of pulmonary arterial hypertension. Compared with patients with diffuse cutaneous SSc, they have a lower mortality rate and incidence of developing severe interstitial

Table 1. Organ involvement within the first five years, stratified by autoantibody status

	Anticentromere	Anti-SCL-70	Anti-RNA polymerase III	ANA positive, ENA negative
Skin				
Limited cutaneous	++	+	+	Unclear
Diffuse cutaneous	–	+++	+++	Unclear
Cardiopulmonary				
Pulmonary arterial hypertension	+*	+/–	+	+
Clinically significant interstitial lung disease	+/–	+++	++	++
Cardiomyopathy	+/–	+	+/–	+
Renal				
Scleroderma renal crisis	+/–	+	+++	++
Malignancy				
Presence	–	+	+++	Unclear

–Very rare.
+/–Rare.
+*Rare within the first five years.
+Less common.
++Common.
+++More common.

lung disease [15,16]. Those with diffuse cutaneous SSc, particularly in the early stage, will have rapid progression of skin thickening, musculoskeletal involvement, higher frequency of clinically significant interstitial lung disease, renal disease, and mortality.

Autoantibody status has better predictive value, compared with the extent of skin distribution, in predicting scleroderma organ involvement [6,17▪▪]. Patients with anticentromere antibody positivity have a favorable prognosis compared with those with anti-SCL-70 antibody; they are more likely to develop ulcerations, gangrene, and tuft resorption of the digits, calcinosis, and are lower risk for arthritis or myositis. This antibody is associated with a higher risk for pulmonary arterial hypertension [18,19]. Patients with anti-SCL-70 antibody have a higher prevalence of arthritis, tendon friction rubs, severe pulmonary fibrosis, severe cardiac disease, and scleroderma renal crisis. The risk of interstitial lung disease in anti-SCL-70 positive patients is similarly independent of the extent of skin involvement [20]. RNA polymerase III antibody-positive patients have a high prevalence of scleroderma renal crisis (25%) [21].

MANAGEMENT

Table 2 provides a screening strategy for internal organ involvement by skin and autoantibody status, noting areas of high priority.

Interstitial lung disease

All patients should be screened with high-resolution chest CT (HRCT) and routine use of pulmonary function testing for monitoring purposes. The majority (55–65%) of scleroderma patients will have HRCT-positive interstitial lung disease; that number increases to 96% of those with abnormal pulmonary function testing [22,23]. Routine pulmonary testing (spirometry and diffusion capacity of carbon monoxide [DLco]), especially in the first five years, is critical to identify those patients developing progressive interstitial lung disease [24,25]. Patients with only minor impairment in the forced vital capacity (FVC) after more than five years of disease duration are much less likely to develop severe fibrotic lung disease later in their disease course. Reduced FVC within four years of the onset of symptoms is an important predictor of the eventual development of severe lung disease (FVC $\leq$ 50%) [4]. The greatest risk of progression for SSc ILD appears to be early in the disease course, particularly in those with diffuse SSc, male gender, African-American race, and positive anti-SCL-70 antibodies [26].

Traditional management focuses on treating those with significant baseline impairment in FVC, extensive involvement on HRCT, or evidence of progressive disease. Proposed definitions identifying those with clinically significant disease include an FVC less than 70%, and extensive ILD on baseline HRCT of greater than 20%, and a decline of FVC by at least 5–10% and/or DLco of more than 10–15% within a 12-month period [27,28]. The goal of treatment is disease attenuation and retardation of progression with the use of cyclophosphamide or mycophenolate mofetil, as demonstrated in the Scleroderma Lung Study I and II trials [29,30]. Importantly, SLS-II demonstrated that mycophenolate mofetil with a target dose of 3 g/day was comparable in efficacy to one year of oral cyclophosphamide was better tolerated with fewer adverse hematological events. In patients with early diffuse SSc, a recent open-label single-institution study showed promising evidence of lung and skin benefit with rituximab therapy [31].

Table 2. Screening stratified by skin involvement and autoantibody status

	Limited SSc		Diffuse SSc		
	Anticentromere	Anti-SCL-70	Anti-SCL-70	Anti-RNA polymerase III	ANA positive, ENA negative
Cardiopulmonary involvement screening					
Electrocardiogram	++	++	++	++	++
Transthoracic echocardiogram	++	++	++	++	++
Pulmonary function testing	++	++	++	++	++
High resolution chest CT	+	++	++	++	++
Blood pressure monitoring for scleroderma renal crisis	+	+	+	++	+
Age-appropriate cancer screening	+	+	+	++	+

+Routine clinical care.
++High priority.
SSc, systemic sclerosis.

The landscape of treatment is showing signs of changing in terms of targeted populations and mechanisms of action. Within the last year, clinical trials in SSc-ILD have shown data to suggest benefit of tocilizumab in reducing the rate of FVC decline compared with placebo in those with mild impairment on pulmonary function testing in early diffuse SSc patients, with elevated inflammatory markers and positive SCL-70 antibody [32,33]. A landmark phase III, randomized, double-blind, placebo-controlled trial showed an antifibrotic medication, nintedanib, to slow the rate of decline in FVC decline in SSc-ILD [34▪▪]. This medication has demonstrated efficacy in those with progressive fibrotic lung disease despite being on immune suppression and those with a usual interstitial pneumonia pattern deriving significant benefit from antifibrotic therapy [35].

There are no universally agreed-upon treatment algorithms at this time, but several have been proposed [33,36,37]. A recent European consensus statement, achieved through a modified Delphi process, yielded a clinical management algorithm for SSc-ILD. Nintedanib may be appropriate for treatment initiation or escalation and used as monotherapy or in combination with mycophenolate mofetil 3 g/day [38,30,34▪▪]. We recommend stratifying on the basis of disease severity (subclinical versus clinical ILD) and tailoring therapy based on risk of progression and the burden of disease (e.g., if lung predominant or multiorgan involvement). Figure 1a outlines a recommended treatment strategy based on this approach.

The use of autologous hematopoietic stem cell transplantation should be reserved for those with early diffuse scleroderma, less than 65 years of age, with severe visceral organ involvement (e.g., SSc-ILD) but without cardiac disease [39]. The experience of the treating medical team is considered to be of high importance when considering this modality [40]. Lung transplant should be considered in patients with progressive ILD despite aggressive medical therapy.

Pulmonary arterial hypertension

All patients with SSc are risk for developing of pulmonary arterial hypertension (PAH); however, there is increased risk in those with longer disease duration, male gender, the number of telangiectasias, reduced capillary nail-fold density, and anticentromere antibody positivity. It is important to differentiate between precapillary pulmonary hypertension [because of PAH vs. pulmonary hypertension (PH)-ILD] and postcapillary PH. PAH accounts for 17–30% of deaths among SSc patients [41,42]. Early detection and prompt initiation of therapy for PAH is essential; those with early diagnosis have more pronounced benefit with therapy [43,44]. In 2018, a revised definition of PH was proposed, lowering the threshold of right heart catheterization-derived mean pulmonary arterial pressure from at least 25 mmHg to more than 20 mmHg [45]. This shift was in accord with data showing those with an elevated mPAP have an increased risk for morbidity and mortality compared with normal mPAP [46,47]. Its implementation did not significantly impact the diagnosis of PH of those in two different screening cohorts [48].

Patients with longer duration of disease and limited cutaneous involvement are more likely to develop this complication [49,50]; however, patients within their first five years [51] and those with diffuse cutaneous involvement may also be affected, largely because of PH-related ILD. A recent single-center review of SSc showed a high rate of coexisting interstitial lung disease (>20% extent of lung involvement) and WHO Group III PH [52]. As a result, all patients should receive electrocardiogram, pulmonary function testing, echocardiography, and N-terminal pro b-type natriuretic peptide screening for this complication at the time of diagnosis. A screening algorithm, as proposed by recent 6th World Symposium on Pulmonary Hypertension, should be performed annually [53]. Any new symptoms or signs should prompt consideration for referral for right heart catheterization.

Treatment for patients with PAH includes use of phosphodiesterase 5 inhibitors (e.g., sildenafil, tadalafil), endothelin receptor antagonists (e.g., bosentan, macitentan, ambrisentan), and prostacyclins (iloprost, epoprostenil, and treprostinil), with a goal to achieve New York Heart Association functional class II or higher (mild shortness of breath) and slight limitation during ordinary activity [54]. Recent data from three large clinical trials (AMBITION, SERAPHIN, GRIPHON) suggest benefit of targeting multiple pathways in treatment of PAH [55–57]. The AMBITION trial showed ambrisentan and tadalafil combination therapy was superior to monotherapy for either medication [58]. The SERAPHIN trial showed the addition of macitentan (compared with placebo) and patients in the GRIPHON study receiving the addition of selexipag to combination therapy reduced the risk of morbidity/mortality [55,56,59,60]. Treatment of PH-ILD includes management of underlying ILD and 02 therapy, although many patients may have an overlap for PAH and PH-ILD [52].

Scleroderma heart involvement

The majority of cardiac involvement in early SSc is subclinical [61–63]. Cardiac involvement may be

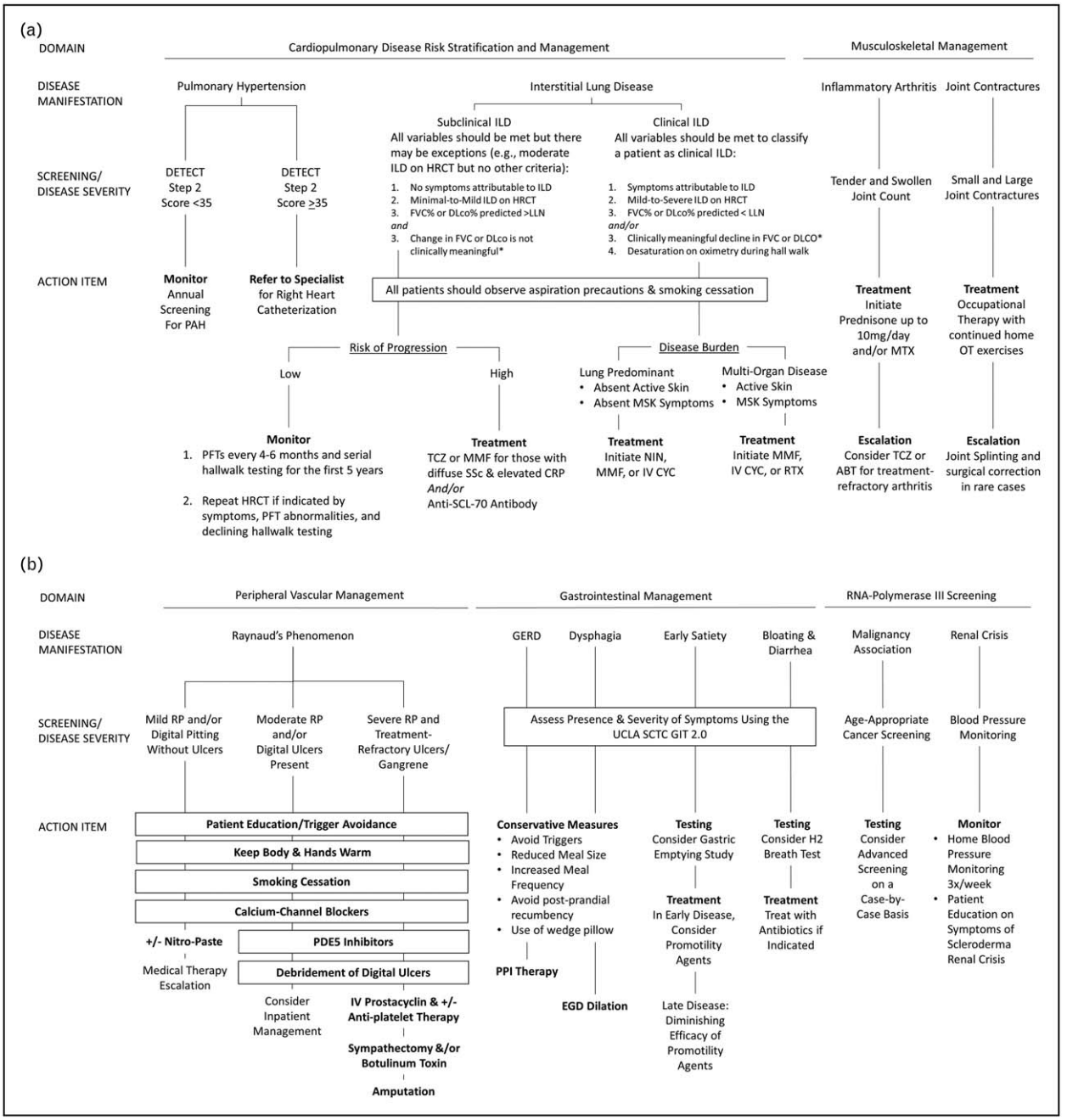

FIGURE 1. (a) General management of early systemic sclerosis. Clinically meaningful change: *if more than 1 PFT available, a clinically meaningful decline is defined as FVC levels of more than 10% from baseline or decline in FVC more than 5% to less than 10% and more than 15% relative decline in DLCO. Medication/treatment acronyms: ABT, abatacept; CYC, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; NIN, nintedanib; OT, occupational therapy; RTX, rituximab; TCZ, tocilizumab. Testing acronyms: Anti-SCL-70; anti-topoisomerase I antibody; CRP, C-reactive protein; DLco, diffusion capacity of carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution chest CT; LLN, lower limit of normal; PFT, pulmonary function testing. Disease acronyms: ILD, interstitial lung disease; MSK, musculoskeletal; SSc, systemic sclerosis. (b) General management of early systemic sclerosis. Medication/treatment acronyms: EGD, esophagogastroduodenoscopy; PDE5, phosphodiesterase 5; PPI, proton pump inhibitor. Testing acronyms: H_2, hydrogen; UCLA SCTC GIT 2.0, UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Questionnaire. Disease acronyms: GERD, gastroesophageal reflux disease; RP, Raynaud's phenomenon.

separated into fibrotic disease that can affect any component of the heart (pericardium, myocardium, conduction system, and less commonly the valves) and secondary involvement because of other sites of SSc involvement (e.g., PAH, SSc-ILD, renal disease) [64,65]. Myocardial involvement may present in early disease; it presents more commonly with diastolic (rather than systolic) dysfunction as heart failure with preserved ejection fraction [66–68].

Cardiac assessment should include considerations of myocardial fibrosis, coronary artery disease, co-occurring pulmonary hypertension, arrhythmias, and myocarditis. Hung *et al.* [65], provide a diagnostic algorithm that includes an initial workup of cardiac involvement including electrocardiogram, chest X-ray, transthoracic echocardiogram, troponin, creatine kinase isoenzyme MB, and N-terminal pro b-type natriuretic peptide measurements. If abnormal or symptomatic, an appropriate workup should include a Holter monitor and appropriate referral to cardiology should be made. Speckle tracking echocardiography is a technique recently shown to detect left ventricle and right ventricle dysfunction not detected by conventional 2D echo [69]. Cardiac MRI is a noninvasive, radiation-free, operator-independent technique for identifying myocardial fibrosis and perfusion defects even in early disease. Those patients with modifiable risk factors for coronary artery disease (e.g., hypertension, dyslipidemia, diabetes, smoking) should be counseled.

Scleroderma renal crisis

Scleroderma renal crisis is the new onset of accelerated arterial hypertension and/or rapidly progressive oliguric renal failure during the course of scleroderma [70]; this is significantly more likely in diffuse SSc (12%) compared with limited SSc (2%) [71]. Features predictive of scleroderma renal crisis include disease symptoms less than four years, diffuse cutaneous skin involvement, rapid progression of skin thickening, the presence of anti-RNA polymerase III antibody, new anemia, new pericardial effusion or congestive heart failure, and antecedent high-dose corticosteroids.

Providers should become concerned for renal crisis if the SSc patient has an elevated BP of more than 150/85 mmHg or if there is an increase of at least 20 mmHg from baseline systolic blood pressure on two occasions in a 24-h period [72]. These patients should be directed to the emergency department immediately. A decline in renal function (increase of 50% from baseline creatinine or an absolute increase of 0.3 mg/dl, even if within normal range) and/or presence of proteinuria (>2+) and/or hematuria 1+ should prompt initiation of an angiotensin converting enzyme (ACE) inhibitor [73]. A small proportion of patients may develop normotensive renal crisis, especially in those with background ACE inhibitor. Supportive features of this diagnosis include a microangiopathic hemolytic anemia, retinopathy typical of an acute hypertensive crisis, new onset of urinary red blood cells, flash pulmonary edema, and oliguria/anuria [70,72]. Clinical features include dyspnea, headache, blurred vision, encephalopathy, and seizures.

Management includes education for those at high risk regarding the importance of routine blood pressure monitoring and close communication of new symptom development (headache, dyspnea, dizziness, syncope). Patients with scleroderma renal crisis should be hospitalized and prompt initiation of ACE inhibitor with close monitoring to avoid hypotensive nephropathy [74]. Other antihypertensive agents may be used if the blood pressure remains unacceptably high, with the exception of β-blockers. The use of ACE inhibitors in a prophylactic role has been found to be detrimental; and one study, exposure to ACE inhibitors prior to the onset of scleroderma renal crisis was associated with a greater than two-fold increased risk of mortality [75].

Gastrointestinal disease

Gastrointestinal involvement is the most common site of internal organ involvement, and may affect anywhere in the tract: gastroesophageal reflux disease, dysphagia because of altered contractility of the esophagus, delayed gastric emptying, delayed motility with resulting postprandial bloating and small intestinal bacterial overgrowth, chronic constipation, and vascular complications like gastric antral vascular ectasia [76].

Management is based on symptom development. Immunosuppression and stem-cell transportation have not demonstrated correction of the underlying gastrointestinal dysmotility associated with SSc. Education about silent aspiration and precautions to avoid choking should be instituted early on. We recommend conservative measures like remaining upright during meals, using liquids between swallowing solid foods, and avoiding recumbency for at least 4 h following a meal to allow gravity to facilitate bolus transit.

Treatments include proton pump inhibitor for esophageal reflux disease, serial esophageal dilatation for persisting dysphasia, nutritional supplementation for those with a restricted diet and/or malabsorption, antibiotics for bacterial overgrowth, and photocoagulation for those patients with

gastric antral vascular ectasia. We recommend comanagement with a gastroenterologist when considering use of promotility agents or Botox injections into the esophagus. There are data to suggest sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement [77]. Use of phosphodiesterase inhibitors and calcium channel blockers can impair the lower esophageal sphincter from functioning, and make esophageal reflux worse. Care should be taken to avoid pill esophagitis with common culprits (e.g., bisphosphonates, doxycycline), and consider common infections like candida as a source of esophageal discomfort.

Musculoskeletal/cutaneous involvement

SSc may affect several structures of the musculoskeletal system. Inflammatory arthritis (occurring in 16% [1191 of 7286] of a large European registry) and tendon friction rubs (occurring in 11% of patients [802 of 77,286]) are commonly found in dcSSc, affecting the hands, wrists, elbows, knees, and ankles [78]. In addition to skin thickening, cutaneous disease involves the presence of calcinosis, occurring in 20–40% of SSc patients and seen more frequently in those with limited SSC with positive anticentromere antibody positivity. Pruritus results as a consequence of small fiber neuropathy.

Patients with inflammatory arthritis may be treated similarly to those with rheumatoid arthritis [79]. Use of nonsteroidal antiinflammatory drugs should be conducted with caution, given the risk of gastroesophageal abnormalities, gastric antral vascular ectasia in a small subset of patients, and those with impaired renal function. Low-dose corticosteroids (less than 10 mg/day) may have value for symptomatic treatment of inflammatory arthritis. Providers should be cautious not to give doses above 15 mg/day to those patients with early diffuse SSc and especially those with RNA polymerase III positivity for fear of induction of scleroderma renal crisis. RA-approved therapies may be considered, including abatacept and tocilizumab for treatment-refractory arthritis, although this recommendation is based on expert opinion [80].

Treatment options for skin involvement appear to have modest benefit; efficacy in treatment is confounded by a treatment-independent regression of skin thickening (typically by five years past the first non-Raynaud's phenomenon onset). Treatments include methotrexate, mycophenolate mofetil, with recent trials of tocilizumab and abatacept failing to show significant differences in modified Rodnan skin score compared with placebo, but significant improvements in global assessment of disease with abatacept [81]. The role of intravenous immunoglobulin therapy on skin manifestations in SSc remain unclear, but promising [82]. Hematopoietic stem cell transplant may be an option for a narrow spectrum of patients with early, rapidly progressive diffuse SSc with poor prognosis but an absence of advanced organ involvement.

Hand therapy includes paraffin wax treatments, resistance training, home therapy exercises as directed by an occupational therapist, and splinting [83]. Hand surgery is reserved for those with severe fixed deformities with functional limitations, ulcerations, and calcinosis refractory to treatment. The focus of surgery is to reposition digits and fuse the joints, immobilizing them to reduce pain and further digital complications of severely flexed proximal interphalangeal joint.

The efficacy of treatment of calcinosis remains disappointing. To date, there are little data to support the use of calcium channel blockers, bisphosphonates, minocycline, warfarin, and elective surgical excision. Gabapentin may have therapeutic role in treating small-fiber neuropathic pruritus.

Screening for malignancy

There are data to suggest that SSc may be a paraneoplastic syndrome [84,85]. Maria *et al.* [86] provide a comprehensive review of the subject to date. In one cohort of 2383 patients with scleroderma, 205 or 8.6% had a diagnosis of cancer. Patients with RNA polymerase III antibody positivity had a standardized incidence ratio of 2.84 (95% confidence interval 1.89–4.10); those who did not have scleroderma specific autoantibody positivity had a standardized incidence ratio of 1.83 (95% confidence interval 1.1–2.86). Those who were anticentromere antibody-positive had a lower risk of cancer during follow-up, with a standardized incidence ratio of 0.59 (95% confidence interval 0.44–0.76) [87].

APPROACH TO CLINICAL CARE

Management of early systemic sclerosis

For patients with early SSc, we begin by counseling and educating the patient on his/her disease, the expected distribution, and severity of organ involvement based on their skin and autoantibody profile and reinforce the varied trajectories of clinical outcomes depending on development of disease progression. Figure 1a and Figure 1b outline the general management of early SSc.

All patients should be screened for cardiac disease, interstitial lung disease, and pulmonary arterial hypertension; we recommend baseline

electrocardiogram, echocardiogram, pulmonary function testing, and HRCT for all patients. Pulmonary arterial hypertension is rare to develop within the first five years, but the onset of shortness of breath is insidious and a screening algorithm such as the DETECT algorithm [88] is advocated; echocardiogram is insufficient as a screening tool for PAH. High-resolution chest CT is the gold standard in diagnosing ILD. Those patients with clinically significant ILD, high risk for progression, or evidence of progressive disease should be initiated on immunosuppressive or antifibrotic therapy [33]. It is unclear if mild or subclinical ILD with limited SSc and anticentromere antibody should be offered therapy. For those with positive anti-SCL-70 antibody status or elevated C-reactive protein levels in the setting of mild ILD on HRCT and mild deficits on FVC% predicted, we recommend initiation of tocilizumab or mycophenolate mofetil [32] as these patients are at an increased risk of progression. For those with symptomatic ILD, mild-to-severe ILD on HRCT, FVC% predicted or DLco% predicted less than the lower limit of normal and/or clinically meaningful decline in FVC or DLco (if >1 pulmonary function testing is available) accompanied by desaturation on oximetry during hall walk, we recommend mycophenolate mofetil. For those with progressive disease or nontolerability to mycophenolate mofetil, we add/replace with nintedanib [30,89]. Those with extensive skin, musculoskeletal, and lung disease receive mycophenolate mofetil, cyclophosphamide, or rituximab [29,30,90].

Nearly all patients will have gastrointestinal symptoms at the time of initial contact with rheumatology; patients should institute reflux/aspiration precautions, increase the frequency and decrease food consumption size per meal, and initiate proton pump inhibitor for GERD symptoms. Symptoms of small intestinal bacterial overgrowth should be screened for at each visit; we administer University of California at Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Questionnaire 2.0 to every patient to assess for symptoms and severity of gastrointestinal involvement (https://umich. qualtrics.com/jfe/form/SV_3eBP4A4umBwnSvj). We refer patients to gastroenterology who continue to have symptoms despite pharmacologic therapy.

Inflammatory arthritis and advancing skin thickening may simultaneously be treated with escalating immune suppressive therapy [32,81,79] but continues to lead to considerable morbidity and remains a focus in the unmet needs of this subset of patients [91]. Patients with dcSSc and anti-SCL-70 antibody positivity are more likely than others to develop digital ulcerations; vasodilation, pain management, and prevention of/treatment for osteomyelitis remain a top priority [92,93]. Patients should be evaluated for the severity and frequency of Raynaud's phenomenon, with particular attention paid to the presence and monitoring of digital ulcerations; tobacco abstinence should be a top priority for several health benefits, in addition to its detrimental vasoconstriction effect [94].

Those with RNA polymerase III antibody positivity should be counseled as above for risk of renal crisis. Those patients and those with triple-negative antibody screening (negative anticentromere, SCL-70, and RNA polymerase III) should achieve up-to-date age-appropriate cancer screening [87].

Finally, enrollment in clinical treatment trials provides an option for investigational use of medications not yet approved by the FDA for SSc. Clinical research trials are advancing the goal of improving outcomes for SSc patients and stratifying therapies for SSc subsets [95].

CONCLUSION

Systemic sclerosis is a highly heterogeneous autoimmune disease, with varying clinical trajectories. Identifying patients within the first five years and subclassifying patients based on skin distribution and autoantibody status allow practitioners the best opportunity to intervene before advanced fibrosis sets in and cannot be reversed. Patients should be educated on the challenges ahead, limitations to treatment, and empowered to optimize their participation in maintaining their health. We encourage all our patients to explore their disease and management options at www.selfmanagescleroderma.com and scleroderma.org. Depending on the patient's SSc subset, risk stratification allows for timely follow-up and close monitoring for the development of and response to therapy.

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Conflicts of interest

D.K.'s financial conflicts of interest: Actelion, Abbvie, Bayer, Boehringer-Ingelheim, Chemomab, Corbus, CSL Behring, Genentech/Roche, Gilead, GSK, Mitsubishi Tanabi, Sanofi-Aventis, UCB Pharma. He reports grants from Bayer, Boehringer-Ingelheim, Genentech/Roche, Pfizer, Sanofi-Aventis and has stock options in Eicos Sciences, Inc. D.R. has no conflicts of interest.

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Antirheumatic medications in pregnancy and breastfeeding

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Purpose of review
As active rheumatic and musculoskeletal disease during pregnancy increases the risk for pregnancy loss, preterm birth, and maternal illness, ongoing management with pregnancy-compatible medications can improve these outcomes. Selecting and taking these medications can be challenging for rheumatologists and patients due to limited knowledge about potential risks and benefits.

Recent findings
Fortunately, the American College of Rheumatology, American College of Obstetrics and Gynecology, British Rheumatology Society, and the European League Against Rheumatism have each published recommendations to guide the use of antirheumatic medications in pregnancy and lactation. Each of these groups endorsed the use of hydroxychloroquine, azathioprine, sulfasalazine, corticosteroids, NSAIDs, and tumor necrosis factor inhibitors in pregnancy. They also agreed that methotrexate, mycophenolate, cyclophosphamide, and leflunomide should be avoided in pregnancy. New medications, including small-molecules and biologics, have limited data to support safety in pregnancy and are not currently recommended during this period. Most antirheumatic medications are compatible with lactation.

Summary
Because many patients are hesitant to use antirheumatic medications during pregnancy, honest and accurate discussions about pregnancy planning and management are important to help women make decisions that are in their and their offspring's best interest.

Keywords
lactation, medication safety, pregnancy, rheumatic disease

INTRODUCTION

Rheumatic and musculoskeletal disorders (RMD) disproportionately affect women, many of whom are diagnosed while they are of reproductive age [1]. Advances in the treatment of RMDs have enabled women to live longer and healthier lives, and therefore to consider the potential for pregnancy and childrearing [2]. Treatment decisions between patients and providers may thus require consideration of women's plans for pregnancy, current pregnancy, or desire to breastfeed. Fortunately, several sets of guidelines and recommendations have been published by national and international organizations that provide needed guidance for the use of medications to manage RMDs [3▪▪–6▪▪]. In this review, we summarize the current data and these guidelines to facilitated the safe use of medications during pregnancy and lactation.

GENERAL PRINCIPLES

Women with RMDs who achieve disease quiescence at the time of conception and throughout pregnancy have better pregnancy and perinatal outcomes than women with active rheumatic disease [7–10]. *Therefore, medical treatment, if safe and compatible with pregnancy, may be necessary to facilitate healthy pregnancy and perinatal outcomes among some women with RMDs.*

Medication safety must also be considered in the context of breastfeeding. Eighty percentage of infants born in the United States are breastfed at least initially [11], with benefits that include bonding between mother and child; maternal protection against hypertension, diabetes, and cardiovascular disease; as well as reduction in their risk of obesity,

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KEY POINTS

- Medications that are compatible with pregnancy include hydroxychloroquine, azathioprine, sulfasalazine, corticosteroids, NSAIDs, and tumor necrosis factor inhibitors.
- Medications that should be avoided in pregnancy include methotrexate, mycophenolate, cyclophosphamide, and leflunomide should be avoided in pregnancy.
- New medications, including small-molecules and biologics, have limited data to support safety in pregnancy and are not currently recommended during this period.
- Most antirheumatic medications are compatible with lactation.
- Honest and accurate conversations about medication use in pregnancy and breastfeeding are required to assist women in making decisions that can improve the health of their offspring.

asthma, and sudden infant death syndrome [12]. Many women with RMD want to breastfeed: 80.5% of women with lupus initiated breastfeeding in Argentina and 87% in a US-based cohort; only 5% were taking a medication postpartum that was not compatible with breastfeeding [13,14]. Women with rheumatoid arthritis (RA) in a separately study were significantly less likely to breastfeed than were healthy controls [15]. Patients' and providers' concerns about the safety of medications while breastfeeding are one reason why women with RMDs are less likely than other women to breastfeed [16].

The placenta provides a complex and active barrier between the maternal and fetal circulation. The extent to which a drug may cross the placenta depends on placental biology and the drug's pharmacokinetic properties. The timing of drug exposure to the fetus is critically important to our conceptualization of drug safety. Organogenesis, which is complete by around 12 weeks' gestation, is the highest risk period for birth defects [17]. Some drugs diffuse across the placental barrier, whereas others, including the biologics, require active transport [18]. The Fc portion of IgG binds to a neonatal Fc receptor (FcRn) on the placenta, which facilitates its transfer across the synctiotrophoblast and into the fetal circulation. Biologic disease-modifying anti-rheumatic drugs (DMARDs) that are constructed with Fc portions may similarly enter the fetal circulation via the FcRn (e.g, adalimumab, golimumab, infliximab, rituximab, tocilizumab). The FcRn on the syncytiotrophoblast is nearly undetectable until 14 weeks' gestation, but immunoglobulin transfer increases steadily throughout the second and third trimesters of pregnancy. Thus, the fetus may be exposed to high concentrations of biologic DMARDs, immunosuppressing the fetus when it is born and theoretically increasing the risk for infection.

As a general principle, medications that are compatible with pregnancy are also compatible with breastfeeding [4▪▪]. As the concentrations of drugs found in breastmilk are generally 1% or less of the concentrations of drug found in maternal sera, most breastfeeding infants are exposed to exceptionally low levels of medications.

SAFE DRUGS IN PREGNANCY AND LACTATION

The following section reviews DMARDs and other drugs routinely used in rheumatology that are generally considered compatible with pregnancy and breast-feeding.

NSAIDs

While widely used, caution is warranted for NSAID use in the first trimester of pregnancy, as NSAIDs may potentially increase time to pregnancy among women who are trying to conceive [19], possibly by inhibiting ovulation [20]; and risk of miscarriage, as described inconclusively in studies of the general population [21,22]. At present, there is no contraindication to use of NSAIDs in the first or second trimesters of pregnancy. However, providers may consider discontinuation of NSAIDs among women who are trying unsuccessfully to conceive a pregnancy. In the third trimester of pregnancy, NSAIDs should be avoided altogether, as they can cause premature closure of the fetal patent ductus arteriosus, a risk that has been long-described in population-based studies [23]. Few studies have evaluated the safety of Cox-2 inhibitors in pregnancy, so classic NSAIDs are preferred during pregnancy [24–26].

Classic NSAIDs also appear to be compatible with breastfeeding based on consensus recommendations, with ibuprofen preferred due to limited cross-placental transfer and shorter half-life compared with other NSAIDs [27]. Given the absence of safety data for Cox-2 inhibitors, providers should consider switching patients to classic NSAIDs if possible [5▪▪].

Corticosteroids

Corticosteroids, particularly at relatively low doses (e.g., prednisone less than 10 mg or an equivalent dose), are considered compatible with pregnancy in

oral, intraarticular, and/or intramuscular forms. Prednisone, prednisolone, and methylprednisolone are converted to inactive forms by the placental enzyme 11β-hydroxysteroid dehydrogenase [28]. Thus, activated prednisone and other nonfluorinated steroids have more limited fetal exposure than fluorinated steroids [29,30], and therefore are preferred during pregnancy. An exception is in congenital heart block, observed among some mothers with Ro antibodies, in which case fluorinated steroids may be used to try to reverse this rare fetal conduction abnormality [31].

While corticosteroids are widely used in pregnancies of women with RMDs, they also have been inconsistently associated with preterm birth and orofacial clefts in studies of RA, antiphospholipid antibody syndrome, and asthma, particularly at prednisone-equivalent doses greater than 20 mg daily [19,32–35]. Corticosteroids may be necessary to control active disease during pregnancy, but it should be noted that some pregnancy-compatible DMARDs appear to have fewer fetal risks than moderate or high doses of corticosteroids.

Corticosteroids are generally considered safe for breastfeeding. At prednisone-equivalent doses greater than 20 mg a day, breastmilk might be discarded or delayed 4 h after steroid administration to reduce infant exposure. Lower doses of steroids are considered compatible with breastfeeding without need for specific timing intervals.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial medication with anti-inflammatory properties that is widely considered compatible with pregnancy. Hydroxychloroquine does cross the placenta, which is why it can protect against adverse perinatal outcomes such as congenital heart block associated with maternal Ro antibodies [36,37]. When taken daily at doses of 400 mg or less, hydroxychloroquine is not associated with increased risk of adverse perinatal outcomes [38,39]. Hydroxychloroquine also improves maternal outcomes, and has been found to prevent disease flares among pregnant women with lupus [40,41]. As disease flares are associated with adverse perinatal outcomes, maternal hydroxychloroquine could potentially be protective toward fetal health as well.

Hydroxychloroquine is safe to use while breastfeeding. Among 13 infants of mothers with systemic lupus erythematosus who were breastfed, all had normal development and visual function [42]. A review of 251 infants exposed to hydroxychloroquine during pregnancy revealed that these children had no greater risk of visual function abnormalities than unexposed children [43].

Sulfasalazine

Sulfasalazine, a DMARD composed of a sulfa antibiotic and salicylate, is compatible with pregnancy. Most safety data about sulfasalazine has been extrapolated from pregnant women with inflammatory bowel diseases [24,44]. As sulfasalazine is a dihydrofolate reductase inhibitor, folic acid supplementation may be considered for women who use sulfasalazine and who are considering pregnancy [4▪▪]. There are no guidelines that specify a dose of folic acid, although the standard dose in multivitamins and prenatal vitamins appears to be sufficient to reduce the risk for oral clefts, cardiovascular and urinary tract defects among pregnancy women who use sulfasalazine or other dihydrofolate reductase inhibitors [45].

Sulfasalazine is compatible with breastfeeding. Sulfasalazine was found to cause bloody diarrhea in one infant whose mother used 3 g/day, and thus, women could be counseled to consider discontinuation of sulfasalazine if their infants develop intractable diarrhea [46].

TNF-α inhibitors

TNF-α inhibitors are biologic antirheumatic drugs composed of immunoglobulins or immunoglobulin fragments; this class of medications appears to be safe to use during pregnancy and lactation. TNF-α inhibitors are generally too large to cross the placenta by simple diffusion, and active cross-placental transport does not begin until approximately after 14 weeks' gestation [47]. Multiple studies suggest that pregnancy and fetal outcomes do not differ between users and nonusers of TNF-α inhibitors [48–51].

A concern about TNF-α inhibitors use during pregnancy is that they may immunosuppress the neonate, increasing the risk of infection. In a term delivery, the infant may have a circulating concentration of adalimumab or infliximab that is 60% higher than drug levels in the mother [47]. TNF-α inhibitor levels can be detected in the neonatal circulation up to 12 months postdelivery, particularly infliximab and adalimumab [47]. Despite this degree of transfer, maternal TNF-α inhibitor use does not appear to predict increased neonatal infections [52]. Given concerns about immunosuppression of the newborn, consensus recommendations generally recommend discontinuation of TNF-α inhibitors in the second or third trimesters. Only women with ongoing disease activity should continue treatment through delivery. However, certolizumab, a biologic TNF-α inhibitor, does not have an Fc portion, and therefore is not actively transferred across the placenta during pregnancy [53];

this medication is therefore not expected to cause neonatal immunosuppression, even with dosing in the later third trimester.

As a precaution, most consensus guidelines suggest that live virus vaccines are avoided among infants who were exposed to TNF-α inhibitors in the late second or third trimesters (i.e., rotavirus in the United States), but an otherwise normal vaccination schedule may otherwise be used [54▪▪]. One European study described a neonate who was exposed to infliximab in utero and developed disseminated tuberculosis in the setting of a bacille Calmette–Guerin (BCG) vaccine [55]; thus, BCG vaccines, which are not routinely administered to neonates in the United States, should be avoided by tumor necrosis factor-exposed children. The rotovirus vaccine is the primary live vaccine administered in the first months of life.

Studies also suggest that there is minimal transfer of TNF-α inhibitors with lactation, and breastfeeding neonates have not been found to have increased risk of infections [5▪▪,56]. We recommend restarting TNF-α inhibitors within 1–2 weeks after delivery to avoid the expected postpartum flare in women with inflammatory arthritis.

Azathioprine, tacrolimus, cyclosporine

Azathioprine, tacrolimus, and cyclosporine have been used for several decades in pregnant women with solid organ transplants and each has a solid basis of data demonstrating compatibility with pregnancy [57–59].

Azathioprine, an immunosuppressive antimetabolite, is not associated with fetal defects or spontaneous abortion. Among women with systemic lupus erythematosus, fetal and neonatal outcomes in one study were similar among women who did and did not use azathioprine [60]. While early animal studies reported fetal anomalies related to azathioprine exposure, the human fetal liver lacks the enzyme inosinate pyrophosphorylase, which converts azathioprine into active metabolites and may potentiate fetal anomalies; thus, the human fetus has limited exposure to active form of azathioprine [61]. Some studies suggest that preterm birth is more likely among women with renal transplants or systemic lupus erythematosus who use azathioprine, but future studies are needed to assess if this is a reflection of maternal disease activity and/or disease burden [60,62,63].

Tacrolimus is a calcineurin inhibitor that is widely used among pregnant women with solid organ transplants. Although it is not associated with birth defects, it has been associated with hyperkalemia and renal insufficiency among exposed infants [64]. Thus, renal laboratory monitoring is suggested for exposed neonates. Cyclosporine reduces the expression of IL-II receptors and production of IL-II [65]. Cyclosporine is not associated with birth defects among women with solid organ transplants, although it is associated with maternal hypertension, gestational diabetes, and preeclampsia, and with low birthweight [66]. It is unclear if some of these effects are related to the underlying maternal disease.

Azathioprine is compatible with breastfeeding due to its very minimal transfer into breastmilk [27,67]. In a small study of mothers with inflammatory bowel diseases who used azathioprine throughout pregnancy and lactation, offspring showed normal development and had similar rates of infections and hospitalizations as children born to mothers did not use immunosuppression [68]. Relatively little is known about the safety profile of tacrolimus and cyclosporine during lactation. Maximum estimated absorption of tacrolimus from breastmilk was reported in one study to be 0.23% of the maternal dose, but the clinical significance of tacrolimus at that plasma level is unclear [69].

HIGH-RISK DRUGS IN PREGNANCY AND LACTATION

The following section reviews DMARDs and other drugs routinely used in rheumatology that contraindicated during pregnancy and breast-feeding. The recently published guidelines are summarized for pregnancy (Table 1) and lactation (Table 2).

Methotrexate

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase; its actions against folate, which is essential for neural tube development of the fetus, contribute to its teratogenicity. Exposure during pregnancy is associated with an incidence of birth defects between 6 and 10% and incidence of pregnancy loss of 40% [3▪▪,5▪▪,70]. Birth defects include the aminopterin syndrome, which classically manifests as growth restriction, facial, skull, and limb dysmorphisms and defects, and neural tube defects [71]. Unintended exposure to methotrexate during pregnancy is not uncommon. In our survey of young women with inflammatory arthritis, we found that 32% of methotrexate users who experienced pregnancy had conceived while using this drug [72]. Given the widespread usage of methotrexate in rheumatic disorders, it is critical that providers and patients understand the risks of prescribing this medication among reproductive-age women who do not use contraception.

Table 1. Comparison of consensus opinions and guidelines about medication safety during pregnancy

	American College of Rheumatology (2019)	EULAR (2016)	ACOG (2019)	British Society of Rheumatology (2016)
Prednisone	Compatible[a]	Low risk	Low risk	Low risk
Hydroxychloroquine	Compatible[a]	Low risk	Low risk	Low risk
Sulfasalazine	Compatible[a]	Low risk	Low risk	Low risk
NSAIDs (classic)	Compatible[b]	Low risk	–	–
TNF-α inhibitor Strongly recommend as compatible Conditionally recommend as compatible Infliximab, adalimumab, etanercept, golimumab: conditionally recommend as compatible due to concern for transfer in third trimester Certolizumab strongly recommend as compatible through pregnancy	Compatible[c]	Low risk	Low-to-moderate risk	Low risk Infliximab: stop at 16 weeks' gestation Etanercept: stop at third trimester Adalimumab: stop at third trimester Golimumab: inadequate data
Azathioprine	Compatible[b]	Low risk	Low risk	Low risk
Tacrolimus	Compatible[a]	Low risk	–	Low risk
Cyclosporine	Compatible[a]	Low risk	Low risk	Low risk
Methotrexate *Incidence of birth defects: 6–10%* *Incidence of pregnancy loss: 40%*	Not compatible	High risk	High risk	High risk
Leflunomide	Not compatible	High risk	High risk	High risk
Mycophenolate *Incidence of birth defects: ~25%* *Incidence of pregnancy loss: 40–45%*	Not compatible	High risk	High risk	High risk
Cyclophosphamide	Not compatible	High risk, may be justified if life-threatening conditions in second and third trimesters	High risk	High risk
Anakinra	Discontinue at conception	Use if there are other options	–	High risk
Abatacept	Discontinue at conception	Inadequate information	–	High risk
Rituximab	Discontinue at conception, but can use for severe disease	Inadequate information	Unknown	High risk
Belimumab	Discontinue at conception	Inadequate information	Unknown	High risk
Secukinumab	Discontinue at conception	–	–	–
Tocilizumab	Discontinue at conception	Inadequate information	–	High risk
Usekinumab	Discontinue at conception	Inadequate information	–	–
JAK inhibitors	Unable to determine	Inadequate information	–	–
Apremilast	Unable to determine	Inadequate information	–	–
Baracitinib	Unable to determine	–	–	–

American College of Rheumatology guidelines: [a]Strongly recommend as compatible. [b]Conditionally recommend as compatible. [c]Certolizumab strongly recommend as compatible through pregnancy; infliximab, adalimumab, etanercept, golimumab: conditionally recommend as compatible due to concern for transfer in third trimester.

Table 2. Comparison of consensus opinions and guidelines about medication safety during lactation

	American College of Rheumatology (2019)	EULAR (2016)	ACOG (2019)	British Society of Rheumatology (2016)
Corticosteroids	Compatible[a]	Low risk	Low risk	Low risk
Hydroxychloroquine	Compatible[b]	Low risk	Low risk	Low risk
Sulfasalazine	Compatible[b]	Low risk	Low risk	Low risk
NSAIDs (classic)	Compatible[a]	Low risk	–	–
TNF-α inhibitor	Compatible[b]	Low risk	Low risk	Golimumab: inadequate data Otherwise low risk
Azathioprine	Compatible[a]	Low risk	Low risk	Low risk
Tacrolimus	Compatible[a]	Low risk	–	Low risk
Cyclosporine	Compatible[a]	Low risk	Low risk	Low risk
Methotrexate	Not compatible[c]	Inadequate information	High risk	High risk
Leflunomide	Not compatible[d]	Inadequate information	Inadequate information	Inadequate information
Mycophenolate	Not compatible[d]	Inadequate information	Inadequate information	High risk
Cyclophosphamide	Not compatible[d]	Inadequate information	Compatible	High risk
Anakinra	Compatible[a]	Inadequate information	–	Inadequate information
Abatacept	Compatible[a]	Inadequate information	–	Inadequate information
Rituximab	Compatible[b]	Inadequate information	Inadequate information	Inadequate information
Belimumab	Compatible[a]	Inadequate information	Inadequate information	Inadequate information
Secukinumab	Compatible[a]	–	–	–
Tocilizumab	Compatible[a]	Inadequate information	–	Inadequate information
Usekinumab	Compatible[a]	Inadequate information	–	–
JAK inhibitors	Unable to determine	Inadequate information	–	–
Apremilast	Unable to determine	Inadequate information	–	–
Baracitanib	Unable to determine	–	–	–

American College of Rheumatology guidelines: [a]Conditionally recommend as compatible (compatible). [b]Strongly recommend as compatible (compatible). [c]Conditionally recommend against use (not compatible). [d]Strongly recommend against use (not compatible).

Leflunomide

Leflunomide is a pyrimidine synthesis inhibitor that also should be avoided in pregnancy, although human data suggest that it is likely not teratogenic. Animal data overwhelming suggest that leflunomide is teratogenic; however, rodents may have an enzyme that is more sensitive to leflunomide exposure than humans. Among women, leflunomide, when discontinued prior to or early in pregnancy and washed out with cholestyramine, is not associated with increased risk of birth defects or any specific pattern of developmental abnormalities [73,74]. As the drug may be sequestered in the bile circulation for up to 2 years, a cholestyramine washout can reduce levels of the drug before pregnancy [73]. After stopping the medication, cholestyramine at a dose of 8 g should be given three times daily over 11 days, which are not required to be consecutive. If plasma levels remain higher than 0.2 mg/l, additional cholestyramine treatment could be considered [75].

Mycophenolate

Mycophenolic acids (e.g., mycophenolate mofetil and sodium) are antimetabolites and established teratogens that are associated with a particular pattern of developmental anomalies, including oral clefts, severe malformations of the ear, and cardiopulmonary abnormalities; they also are associated with spontaneous abortion. Two studies have demonstrated that an estimated 40–45% of pregnancies are lost after first trimester mycophenolate mofetil exposure and 25% of live births have a major birth defect [76,77]. Mycophenolate should be discontinued prior to conception. We recommend replacing it with pregnancy-compatible medications, including azathioprine, and then observing for RMD flare for several months prior to conception [78].

Cyclophosphamide

Cyclophosphamide, an alkylating cytotoxic drug, has been found to cause skeletal, ocular, and cleft

palate defects among first trimester-exposed fetuses. In a small study of women with breast cancer, cyclophosphamide was used in the second and third trimesters without observation of increased risk of birth defects or fetal loss [79]. It has rarely been studied in rheumatic disease pregnancies and it dosing has been coincident with pregnancy loss in some pregnancies, though it isn't known whether this was due to drug exposure or severe lupus [62]. Cyclophosphamide should be discontinued prior to conception to avoid fetal exposure and ensure that the mother is safely transitioned to an effective and pregnancy-compatible medication. Providers should consider that cyclophosphamide increases the risk of lifelong infertility, particularly among women with higher cumulative doses; ovarian failure increases with the age at the time of cyclophosphamide dosing and, among women over 40, is nearly universal [80]. Cotreatment with depot leuprolide acetate during the course of cyclophosphamide treatment has been found to protect against premature ovarian failure among young women with systemic lupus erythematosus [81].

Little safety data exist for using methotrexate, leflunomide, mycophenolate, and cyclophosphamide during breastfeeding [5▪▪], and we recommend that patients who use these medications forgo breastfeeding or are transitioned to different medications.

DRUGS WITH UNCLEAR RISK IN PREGNANCY AND LACTATION

The following section reviews DMARDs and other drugs routinely used in rheumatology with unclear or understudied risk with respect to pregnancy and lactation.

Rituximab

Rituximab is a mAb to CD-20 that, like TNF-α inhibitors, is thought to be too large to cross the placenta by simple diffusion and is not actively transported across the placenta until after fetal organogenesis has occurred. Specific harm was not identified in a registry of 153 pregnancies in mothers exposed to rituximab for cancer or autoimmune disease therapy, though late-pregnancy exposure comes with a significant risk for the infant being born without B cells [82]. Although rituximab is not recommended for routine use by any of the published guidelines, the American College of Rheumatology conditionally recommends that it could be considered for treatment of life-threatening or organ-threatening RMD in pregnancy [6▪▪].

Rituximab is considered to be compatible with breastfeeding, and drug levels appear to be very low in breastmilk – likely due to its large molecular size that inhibits transfer across the mammary tissues [83].

Small molecules: Janus kinase 2 inhibitors and apremilast

Janus kinase 2 inhibitors (e.g., tofacitinib, baricitinib) and apremilast, a phosphodiesterase-4 inhibitor, have not been adequately studied in pregnancy [54▪▪]. These small molecules are likely to cross the placenta and also to pass into breastmilk. Thus, these medications should be avoided among pregnant and breastfeeding women pending additional safety data.

Other biologics

Newer therapies, including B-cell activating factor inhibitors (i.e., belimumab), CTLA-4 inhibitors (e.g., abatacept), IL-6 blockers (e.g., tocilizumab), IL-17 blockers (e.g., secukinumab), IL-12/IL-23 (e.g., ustekinumab), and IL-1 blockers (e.g., anakinra) have not been adequately studied to provide strong recommendations toward or against their safety during pregnancy [54▪▪]. The large molecular size of these medications suggests that transmission into breast milk is low and is likely safe.

CONCLUSION

Studies suggest that 31–62% of women with rheumatic diseases stop refilling their medication prescriptions during pregnancy, including medications with low fetal risk [84–86]. Because patients are required to receive regular laboratory testing, ocular exams, and other 'toxicity monitoring' measurements to ensure that their drugs are not harming them – it is therefore unsurprising that some women with RMDs are distrustful of the potential effects of these medications on their children's health and development.

We encourage honest and accurate conversations between rheumatologists and women with RMD to ensure appropriate pregnancy planning and management. Many women withhold pregnancy plans due to fear of disapproval or being told not to conceive. Therefore, rheumatologists should inquire about pregnancy intentions in a nonjudgmental and open-ended way to encourage the woman to be truthful and to facilitate a discussion that results in the woman making decisions that are in her best interest. For many women with RMD, this means continuing pregnancy-compatible medications through pregnancy. For others, it means delaying pregnancy until RMD is well controlled off

teratogenic medications. We have created resources to assist rheumatologists and women with lupus through these challenging discussions at www.LupusPregnancy.org.

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REVIEW

Lyme disease: diagnosis and treatment

Robert T. Schoen

Purpose of review
Lyme disease is an important, vector-borne infection found throughout the temperate Northern hemisphere. The disease causes rash, acute systemic illness, and in some untreated patients, inflammatory arthritis. This review examines the emergence, clinical features and management of early Lyme disease and Lyme arthritis.

Recent findings
There has been continuing progress in characterizing the clinical manifestations, diagnostic testing and treatment of Lyme disease. Almost all patients with early Lyme disease can be cured with antibiotic treatment. In most cases, Lyme arthritis also responds to antibiotics, but some patients require additional treatment approaches.

Summary
The diagnosis of Lyme disease is based on clinical manifestations and adjunctive laboratory testing. For the rheumatologist, Lyme arthritis should be recognized by a pattern of attacks of asymmetric, oligo-arthritis, recognizable by clinical manifestations in the same way that other rheumatic diseases, such as gout or rheumatoid arthritis, are diagnosed.

Keywords
Lyme arthritis, Lyme disease, Lyme disease treatment

INTRODUCTION

Since it was recognized in 1976 [1], Lyme disease (Lyme borreliosis) has become the most common vector-borne infection in North America with 30 000 cases reported annually in the United States [2]. The actual number of cases may be 10-fold higher [2,3]. In North America, Lyme disease is caused by *Borrelia burgdorferi* and transmitted by *Ixodes scapularis* ticks in the northeast and Midwest and *Ixodes pacificus* in the West [4,5]. Lyme disease is also found in Europe, Asia, and throughout the world-wide distribution of Ixodes ticks (Fig. 1) [6]. In Europe and Asia, Lyme disease is caused by *B. burgdorferi*, but also by other borrelial genospecies, *Borrelia afzelii* and *Borrelia garini*, that cause somewhat different clinical syndromes. As a generalization, *B. burgdorferi* is the most arthritogenic genospecies, *B. afzelii* causes a distinctive skin infection, acrodermatitis chroncia atrophicans [7▪], and *B. garini* causes most frequent neurological manifestations [3]

The clinical features of Lyme disease are well characterized. It is useful to describe the illness in stages [8]. Most patients develop early stage disease, with erythema migrans, a characteristic infectious rash that develops at the site of the tick bite. Early stage disease may be localized to the skin or the organism may disseminate hematogenously, causing early disseminated disease, with constitutional symptoms and involvement of the skin, nervous system, heart, or joints [8]. Within weeks or months, some untreated patients progress to late stage disease, which consists primarily of Lyme arthritis [8].

Almost all patients with early Lyme disease can be cured with a short course of oral antibiotic therapy. But early stage disease is not always recognized or clinically apparent. In late stage disease, most patients can also be successfully treated with antibiotic therapy, but a minority have antibiotic refractory Lyme arthritis, requiring other management strategies [9,10].

In spite of advances in understanding the clinical features, diagnosis, and treatment, Lyme disease has caused misunderstanding and anxiety [11]. This misperception may result from the rapid emergence of this vector-borne infection, its multisystem features, and the potential for nervous system

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KEY POINTS

- Over the past 30 years, Lyme disease, caused by *Borrelia burgdorferi* and related borrelia, has emerged as a common vector-borne infection in North America, Europe and Asia.
- Early Lyme disease is characterized by a characteristic rash, erythema migrans, and in some patients, systemic symptoms resulting from hematagenous dissemination of the organism.
- Most cases of early Lyme disease respond promptly to recommended oral antibiotic therapy.
- Lyme arthritis occurs in a characteristic pattern of attacks of oligoarthritis.
- The majority of Lyme arthritis patients respond to oral antibiotic therapy but some require additional treatment strategies.

involvement, dormant infection, and inflammatory arthritis. Lyme disease has frequently been sensationalized [11]. At the same time, the disease has been under-reported to health authorities, adding to public concern that the disease is underappreciated by the medical community [12–14]. These factors have led some to the misbelief that chronic Lyme disease is a poorly recognized, intractable sequelae that often follows *B. burgdorferi* infection [11].

In this article, I review the emergence, clinical features and diagnosis of Lyme disease. Successful diagnosis is critical to successful treatment. Lyme disease is an infection and most patients can be cured with short courses of antibiotic therapy. In a minority of Lyme arthritis patients, other management strategies are necessary. It is also important to recognize that many patients who present to physicians with concerns about Lyme disease do not have this illness [11]. Understanding why this happens allows better education and treatment of these individuals.

LYME DISEASE EPIDEMIOLOGY

The antiquity of a parasitic relationship between spirochetes and ticks is suggested by the finding of organisms resembling modern *Borrelia* in 15 million-year-old amber-fossilized tick specimens [15]. In the modern era, the re-emergence of Lyme disease in the Northern Hemisphere results from habitat modification, including re-forestation of farmland that has allowed exponential increase in host deer populations [16].

In the United States, Lyme disease has been reported in all 50 states, but 90% of cases occur in two regions of high incidence, the northeastern and mid-Atlantic states and the upper mid-West [2,17]. In North America, Lyme disease is found in the Pacific Northwest and Canada [2,18]. (Fig. 2) [19]. Lyme disease occurs throughout Europe, particularly central Europe and Scandinavia, Russia, and Asia [6]. The disease is expanding geographically from high incidence to neighboring low incidence areas [20].

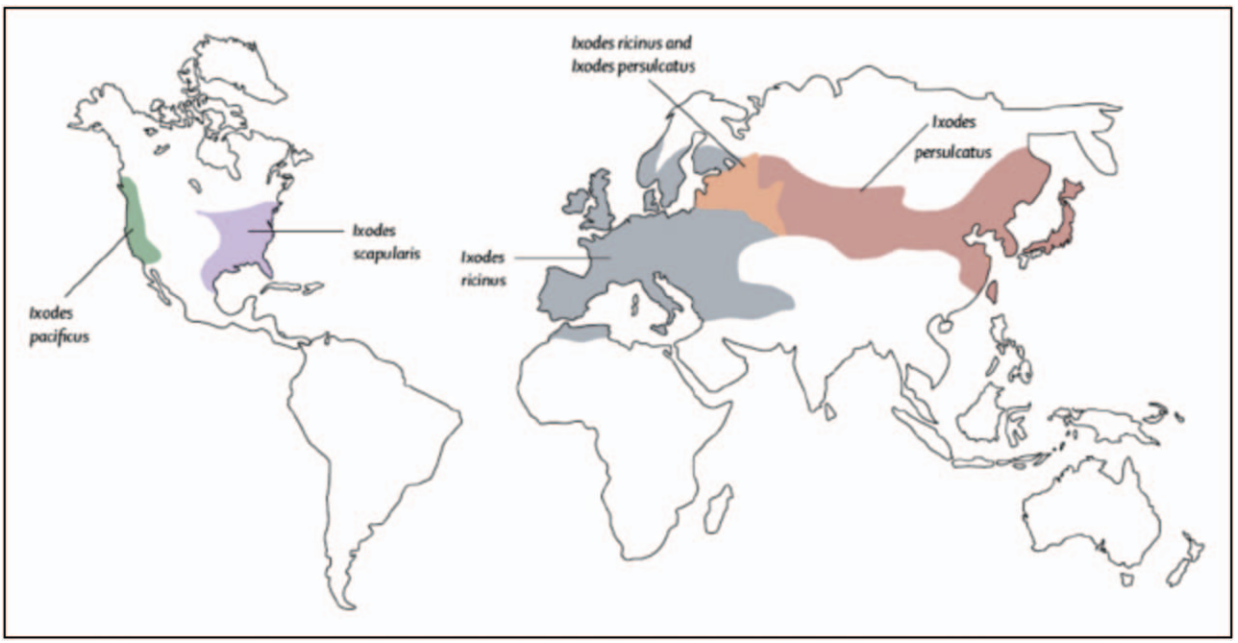

FIGURE 1. Global distribution of the Ixodes species that are the primary vectors for Lyme borreliosis in humans. Data from ref. [5].

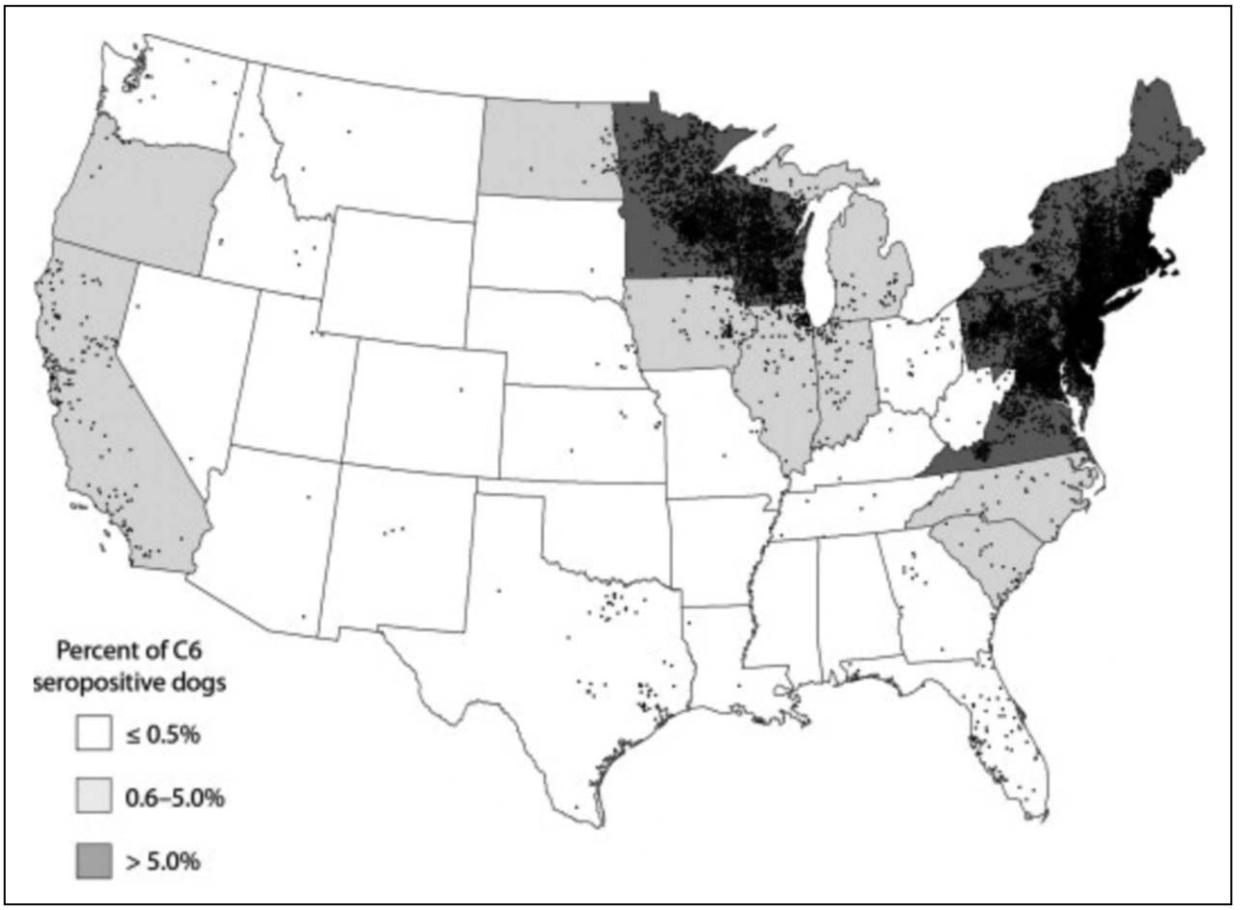

FIGURE 2. Seroprevalence of C6 anti-Borrelia burgdorferi antibody among dogs, 2001-2007, and reported human disease cases, 2010. United States. Data from [14,19].

Within endemic regions, smaller geographic areas of very high incidence have been detected [20]. The age-related risk of Lyme disease is determined by time spent at risk for tick exposure, creating a bimodal distribution of children aged 5–15 years and adults 45–55 years [2]. Risk is also increased by outdoor activities, such as forestry work and hiking [2].

Lyme disease is transmitted primarily by nymphal Ixodes ticks, which feed in the late spring and early summer. Rodents, including white-footed mice and chipmunks, are the preferred host and maintain the life-cycle of infection. White tailed deer are the primary host for adult *Ixodes* tick mating. Humans and domestic animals are dead end hosts [3].

CLINICAL FEATURES OF LYME DISEASE

Early Lyme disease

Early localized infection

The most distinctive feature of early Lyme disease is erythema migrans [21]. Patients are often unaware of a tick bite, which is usually not painful, but recognize the rash, which develops within several days (rarely more than 2 weeks) after the tick bite [22]. In the absence of antibiotic treatment, erythema migrans typically expands to more than 5 cm and has a well demarcated outer border. Usually, by the time the rash is detected, the tick is gone, but a bite punctum at the center of the rash is observable. In the majority of patients, the rash is homogeneously erythematous, slightly raised, itchy, but not painful. When the rash occurs in the axilla and groin, there is often accompanying lymphadenopathy. Central clearing of the rash ('bulls-eye' pattern) takes time to develop. As most patients diagnosed with erythema migrans are now promptly treated, this rash morphology is seen less frequently than in the past. Erythema migrans may have an atypical presentation. There may be necrosis or vesicle formation. When the rash occurs on an appendage (e.g. the ear or the foot), there may only be erythematous swelling, mimicking cellulitis. Even in the absence of antibiotic therapy, erythema migrans resolves in less than 30 days. In some patients, the rash resolves much more rapidly. In addition to the characteristics of the rash itself, the

diagnosis of early Lyme disease is based on multiple factors: *Ixodes* tick exposure, geographic risk, seasonality, and extra-cutaneous disease [23].

In patients with early localized infection, erythema migrans results from cutaneous transmission of *B. burgdorferi* from an infected tick, but not hematogenous dissemination of the organism to extra-cutaneous sites [24]. These patients may have mild constitutional symptoms, such as headache, arthralgia or low-grade fever or they may be asymptomatic other than the erythema migrans rash [3].

Early disseminated infection

Following *B. burgdorferi* infection, the organism may not remain confined to the skin but may disseminate to other skin sites, the nervous system, the heart, and the liver. In the skin, there may be secondary lesions, often smaller and more evanescent than the primary erythema migrans rash. In early disseminated infection, 15% of patients have splenomegaly or transaminitis (aspartate transaminase <400 IU/l). Patients may also develop transient myocarditis with characteristic A-V nodal conduction system abnormalities. Early-stage neurological disease includes meningitis and cranial and peripheral neuropathies. In addition to signs and symptoms related to specific organ involvement, patients with early disseminated Lyme disease often have constitutional symptoms related to bacteremia, including fever, headache, arthralgias, and malaise [8]. Without antibiotic treatment, these features may persist for weeks.

Lyme carditis

Lyme disease can affect the heart in two ways, myocarditis and A-V nodal conduction abnormalities [25]. These manifestations occur in early Lyme disease and resolve within weeks in almost all patients. Patients with A-V nodal disease have a characteristic pattern of fluctuating heart block, from first degree to Wenckebach to complete heart block [25]. Lyme disease is not believed to cause either chronic cardiomyopathy or permanent conduction system disease [26].

Neurological disease

The neurological manifestations of early Lyme disease include meningitis, and cranial and peripheral neuropathy [27–29]. Meningitis patients have fever, headache, and stiff neck. Rarely, and primarily outside of North America, meningoencephalitis is present and causes cognitive impairment and emotional lability. Cerebrospinal fluid analysis (CSF) demonstrates lymphocytic pleocytosis, elevated CSF protein and an increased CSF antibody index (ratio of CSF to serum *B. burgdorferi* antibody titer >1) [30].

The facial nerve is the most commonly affected cranial nerve, but Lyme disease can affect the eighth cranial nerve, causing hearing loss and cranial nerves involved in eye movement, causing diplopia. When peripheral nervous system involvement is present, there is often an asymmetrical, mononeuritis multiplex pattern [30].

Late stage Lyme disease

Late neurological disease

In North America, late stage neurological disease, with central nervous system involvement, is rare. Affected patients may have encephalitis with cognitive dysfunction, memory loss, and fatigue. Diagnosis is based on antecedent clinical features of early Lyme disease and confirmatory serologic and cerebrospinal fluid testing [30]. In a recent study, Lyme disease was not linked to amyotrophic lateral sclerosis [31].

Lyme arthritis

Sixty percent of patients with untreated early Lyme disease will develop Lyme arthritis [32]. As early Lyme disease treatment is usually curative, Lyme arthritis now frequently presents in patients unaware of previous early Lyme disease, including erythema migrans. Lyme arthritis may present as arthralgia only, arthralgia followed by frank arthritis, or the abrupt onset of a swollen joint [33▪▪]. Most patients have mono-arthritis, usually of the knee, or asymmetric oligo-arthritis, affecting fewer than five joints [32]. Large, relatively nonpainful joint effusions are typical. Because of an oligoarticular pattern, Lyme arthritis was originally diagnosed in children thought to have juvenile arthritis and may also mimic spondyloarthropathy [1]. Lyme arthritis often affects the knee and occurs in active individuals spending time outdoors, so it is sometimes misdiagnosed as an internal derangement. Lyme arthritis should not be confused with rheumatoid arthritis, which as it affects fewer joints, does not usually affect small joints of the hands and feet, and causes less joint pain [32].

In the absence of antibiotic treatment, Lyme arthritis occurs in a pattern of attacks and remissions, lasting for days, weeks, or months [34]. In some patients, the arthritis becomes chronic, lasting more than 1 year. Most patients are antibiotic responsive (successful response to antibiotic treatment <3 months), but another group is antibiotic refractory (treatment requires >3 months) [9,35]. Differences in *B. burgdorferi* genospecies and in host immunogenetic susceptibility may to some extent

explain the differences in antibiotic susceptibility observed for these two groups [10].

Diagnostic testing

In early Lyme disease, it is possible, using special media, to culture *B. burgdorferi* from the advancing edge of erythema migrans lesions and from blood in patients with early disseminated Lyme disease [3]. There are only rare reports of successful culture in synovial fluid, but *B. burgdorferi* DNA can be detected by PCR in synovial fluid, and less reliably, in CSF [3]. As PCR testing is not well standardized, it is not recommended for routine clinical practice. In the future, direct methods of culture, detection of *Borrelial* antigens, nucleic acid amplification, and genomic sequencing may become available [36–38].

At present, detection of *B. burgdorferi* antibody response is the only validated test for establishing the diagnosis of Lyme disease [39,40]. A two-step algorithm that relies on an initial ELISA against whole cell sonicate preparations, followed by western blot testing for both IgM and IgG antibodies, was developed to maximize sensitivity and specificity for all stages of Lyme disease [41]. Recently, the Food and Drug Administration (FDA)-approved EIA tests targeting the immune response against cell surface variable-major-protein-like sequenced expressed (VlsE) and its sixth invariable region, the C6 peptide. These simpler, more easily standardized assays may replace western blot testing [42]. A continuing problem, however, is serological over-testing, test misinterpretation, and over-diagnosis [43–45].

Lyme disease treatment

Lyme disease prevention and treatment of tick bites

Multiple strategies, including education, personal protection, domestic strategies (landscape modification and chemical pest control), deer reduction, and Lyme disease vaccines, including vaccine that target tick immunity, have been evaluated without a consensus regarding optimal intervention [46,47▪]. In a study in Westchester County, New York, the risk of acquiring Lyme disease (erythema migrans) following a documented, engorged *I. scapularis* bite was 3.2%. In the same cohort, administration of doxycycline 200 mg orally within 72 h after exposure reduced the infection rate to 0.4% [48].

Early disease

Erythema migrans ultimately resolves, even without antibiotic treatment, but therapy shortens disease duration and prevents the development of late stage disease [8]. Most patients with early disease are cured with oral antibiotic therapy [3]. For erythema migrans, doxycycline, 100 mg orally twice daily for 10–21 days or amoxicillin, 250–500 mg orally three time daily for 10–21 days are recommended for adults (except pregnant women). Doxycycline is not superior in preventing neurological disease [49▪▪]. For patients who cannot be treated with doxycycline or amoxicillin, cefuroxime axetil is an alternative. Doxycycline 1–2 mg/kg twice daily or amoxicillin 25–50 mg/kg three times daily are recommended for children with permanent dentition. Amoxicillin is effective for children less than 8 years old [3,50]. A recent systematic review found better fetal outcomes in woman treated, compared with those not treated, for gestational Lyme disease [51▪]. Two other reports suggest that patients on antitumor necrosis alpha or rituximab therapy who develop early Lyme disease may be somewhat refractory to antibiotic therapy, although they ultimately have good outcomes [52,53].

Both doxycycline and amoxicillin demonstrate excellent in-vitro activity against all North American and European Lyme borrelial genospecies [54]. There is no evidence of emergence of drug resistance [3]. Doxycycline may have better CNS penetration than amoxicillin, but doxycycline is not superior in treating early neurologic LD [49▪▪]. Doxycycline is effective against *Anaplasma phagocytophilum,* the causative organism of human granulocytic anaplasmosis, a possible co-infection [55]. Variability exists in susceptibility to macrolide antibiotics, including erythromycin [56]. Azithromycin, although active *in vitro*, is less effective than amoxicillin [57]. First generation cephalosporins, quinolone antibiotics, and sulfa drugs are ineffective [8].

Neurological disease

Limited comparative evidence defines best antibiotic treatment for Lyme neuroborreliosis [58,59]. A prospective, double-blind, European study demonstrated that doxycycline 200 mg once daily was as effective as intravenous ceftriaxone 2 g daily in early neurological Lyme disease, with no treatment failures in either group [60]. Most experts treat mild neurological manifestations, such as isolated facial nerve palsy, with oral doxycycline, or amoxicillin or cefuroxime acetil, similar to other early Lyme disease [3]. However, patients with Lyme meningitis are often hospitalized and treated with intravenous ceftriaxone 2 g for 14 days, with oral doxycycline substituted at the time of hospital discharge to complete 14 days of antibiotic treatment [3]. Rare patients develop Lyme encephalomyelitis and are typically treated with a full course of intravenous ceftriaxone given for 14 to 28 days [55].

Lyme carditis

Lyme carditis causes varying degrees of atrioventricular block that is generally well tolerated, but deaths have been reported and Lyme carditis patients are usually hospitalized for cardiac monitoring, as progression to complete heart block occurs frequently [3,25,61]. Whether antibiotic therapy alters the natural history of conduction system abnormalities is uncertain, but treatment is recommended. Typically, patients with first-degree heart block and PR interval less than 0.3 s are treated orally like other individuals with early Lyme disease. For higher degrees of AV block and PR interval greater than 0.3 s, intravenous ceftriaxone and cardiac monitoring are recommended. As the conduction system abnormality in Lyme carditis is transient, even in patients with complete heart block, permanent pacemaker insertion should be avoided [3,55].

Lyme arthritis

Most Lyme arthritis patients can be treated with doxycycline 100 mg orally twice daily for 28 days or amoxicillin 500 mg orally three times daily for 28 days [62]. Even in successfully treated patients, however, there may be persistent, inflammatory joint findings beyond 28 days of treatment. In most of these patients, arthritis will resolve over several months. These patients may benefit from nonsteroidal anti-inflammatory medication and physical therapy. In patients who fail to respond, it is important to assess patients for possible confounding factors in treatment failure. For example, although Lyme arthritis usually resolves without causing permanent joint damage, patients may have persistent joint pain from premorbid osteoarthritis rather than Lyme disease. Other patients may have pain or functional limitation from joint deconditioning. These patients will not benefit from further antibiotic therapy. In those patients who have persistent synovial inflammation, a second 28-day course of oral antibiotic therapy can be considered [10]. There is no evidence that switching from one oral agent to another (for example, giving amoxicillin after doxycycline) during a second course of antibiotic therapy improves outcome.

The benefit and timing of intra-articular corticosteroid injection in antibiotic refractory Lyme arthritis patients needs to be better defined. Most experts would recommend avoiding intra-articular corticosteroid injection during initial antibiotic treatment, because delayed arthritis resolution has been observed following such injections [63,64]. Oral corticosteroid therapy may also delay resolution in Lyme disease facial palsy patients [65,66]. In spite of these findings, recent observational, pediatric studies suggest intra-articular corticosteroid injection may resolve lingering joint inflammation, eliminating the need for further intervention [67,68▪].

In patients with persistent synovial inflammation following 28 days of oral antibiotic therapy, given twice, I consider intravenous ceftriaxone 2 g for 14–28 days [55,63]. Patients often improve after such treatment, but it is uncertain to what extent this is the result of additional antibiotic treatment or the natural history of Lyme arthritis, which is typically characterized by arthritis resolution over time [32].

About 10% of Lyme arthritis patients will fail to respond to oral and parenteral antibiotic therapy. How should these antibiotic refractory patients be managed? In many, arthritis will gradually resolve, even in the absence of further intervention [32]. In some, particularly children, intra-articular corticosteroid injection is a relatively noninvasive option. Several lines of evidence suggest that antibiotic refractory Lyme arthritis is a postinfectious, inflammatory process [69]. For this reason, some of these patients have been treated with disease-modifying antirheumatic drugs, including methotrexate, similar to treatment of rheumatoid arthritis [10,33▪▪]. In patients given methotrexate, treatment is discontinued 6–12 months after response [10,33▪▪]. After failure of antibiotics and other disease-modifying drugs, I have had limited, successful experience with short-term administration of antitumor necrosis factor biologic agents, such as etanercept, in antibiotic refractory Lyme arthritis patients who have exhausted other therapeutic options. Another strategy that has been successful in antibiotic refractory Lyme arthritis of the knee is arthroscopic synovectomy. In one 20-patient study, 75% of antibiotic refractory patients responded to surgery and remained well in 2-year follow-up [42,70].

Chronic Lyme disease and posttreatment Lyme disease

Most studies report excellent outcomes after antibiotic treatment of early Lyme disease [71–73], but some patients with well characterized early Lyme disease are believed to develop ‘post-Lyme disease treatment syndrome’ [74–76]. These patients continue to experience common subjective symptoms, such as fatigue, widespread pain and anxiety, similar to fibromyalgia patients. Other patients are diagnosed as having ‘chronic Lyme disease’, often in the absence of supporting clinical manifestations of Lyme disease or laboratory evidence of exposure [77]. Sometimes these patients are given long-term antibiotic or other unconventional therapies, even though such treatment has been repeatedly found to

lack benefit and to cause adverse events [78–82]. It is important to recognize this phenomenon of misdiagnosis and treatment of Lyme disease. Wherever possible, identification of the underlying reasons for symptoms can protect these patients from unnecessary treatment and improve outcomes.

CONCLUSION

Lyme disease is probably an ancient disease but has re-emerged in the past half century as a result of habitat modification and tick vector adaptation. The illness has engendered intense public interest. It is extremely common in endemic areas, but under-reported. It causes systemic multisystem illness and can cause neurological disease and inflammatory arthritis. Early cases have a characteristic sentinel rash, erythema migrans, but atypical cases require a high index of suspicion, especially since early disease treatment is usually curative. Lyme arthritis has characteristic clinical features and confirmatory serologic testing, which is sensitive and specific. Most Lyme arthritis patients can be successfully treated with antibiotic therapy, but a minority of require other treatment strategies.

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There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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Management issues in rheumatoid arthritis-associated interstitial lung disease

Bryant R. England[a,b] *and Daniel Hershberger*[c]

Purpose of review
Summarize recent evidence on the identification and management of rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Recent findings
Clinical and subclinical interstitial lung disease (ILD) are frequent extra-articular manifestations of rheumatoid arthritis (RA). Better means of identifying and treating RA-ILD are needed to improve the prognosis, with a median survival of only 3–7 years after diagnosis. Several serum biomarkers are currently being evaluated for their ability to detect RA-ILD. Thorough evaluation and multidisciplinary discussion remains the gold standard for establishing the diagnosis of RA-ILD. Management is challenging with most RA disease-modifying antirheumatic drugs (DMARDs) linked to pneumonitis. Methotrexate is typically avoided in clinically significant ILD, although alternative therapies including leflunomide and biologic DMARDs also carry risks in RA-ILD. Antifibrotics appear to slow the progression of ILD, and a large phase II trial exclusively in RA-ILD is underway. In addition, smoking cessation, pulmonary rehabilitation, oxygen therapy, managing comorbidities, and lung transplantation evaluation are vital to improving patient outcomes in RA-ILD.

Summary
With little high-quality evidence to guide the management of RA-ILD, multidisciplinary teams with expertise in RA-ILD are highly valuable for diagnosing and treating RA-ILD. Clinical and translational research in RA-ILD is needed to fill the many evidence gaps.

Keywords
interstitial lung disease, pulmonary fibrosis, rheumatoid arthritis

INTRODUCTION

Interstitial lung disease (ILD) is an extra-articular manifestation of rheumatoid arthritis (RA) first reported by Ellman and Ball in 1948 [1]. In this review, we summarize recent evidence on the identification and management of RA-associated interstitial lung disease (RA-ILD).

EPIDEMIOLOGY AND OUTCOMES OF RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

Between 5 and 10% of patients with RA will develop clinically significant ILD [2,3], and another 20–30% may have subclinical involvement [4]. Risk factors for RA-ILD include male sex, older age, tobacco use, higher RA disease activity, extra-articular disease features (e.g., subcutaneous nodules), and seropositivity for RA autoantibodies [rheumatoid factor and anticitrullinated protein antibodies (ACPAs)] [2,3,5,6▪,7▪].

While the median survival has been reported to be less than 3 years [2], two recent observational studies found the median survival to be 7 years after diagnosis [8▪,9▪]. In addition to its impact on survival, RA-ILD places a tremendous burden on healthcare systems with mean total 5-year healthcare costs exceeding $170 000 per patient [8▪].

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KEY POINTS

- ILD is an extra-articular manifestation of RA that leads to poor patient outcomes and substantial healthcare costs.
- Multidisciplinary discussion of the clinical findings, blood tests, high-resolution computed tomography images, and pulmonary function tests is considered the best approach to diagnose RA-ILD.
- Optimal DMARDs and other immunomodulatory therapies in RA-ILD are not known and most have been associated with cases of pneumonitis.
- Antifibrotics may have an adjunct role in managing progressive RA-ILD.
- Quality evidence is lacking for most diagnostic and management considerations in RA-ILD, illustrating the need for clinical and translational research in RA-ILD.

Two of the most important prognostic factors in RA-ILD are the pattern of ILD and ILD severity. The most common patterns of RA-ILD are usual interstitial pneumonia (UIP), characterized radiographically by honeycombing and traction bronchiectasis, and nonspecific interstitial pneumonia (NSIP), characterized radiographically by diffuse ground glass opacities and the absence of honeycombing [2,10,11]. A meta-analysis of 10 cohort studies including 1256 patients with RA-ILD estimated a 1.6-fold higher risk of death for those with a UIP pattern compared with other patterns [12▪]. Although radiographic appearance is clearly important, several studies have found that pulmonary physiology [e.g., forced vital capacity (FVC)] is more prognostic than ILD pattern. Severity of ILD by pulmonary physiology and high-resolution computed tomography (HRCT) is strongly associated with progression (physiologic and radiographic) and mortality in RA-ILD [13–15].

IDENTIFYING RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

Because the initial manifestation may be inflammatory arthritis (85–90% of cases) or ILD in patients who develop RA-ILD [3,5], both rheumatologists and pulmonologists have roles in its detection and evaluation (Fig. 1).

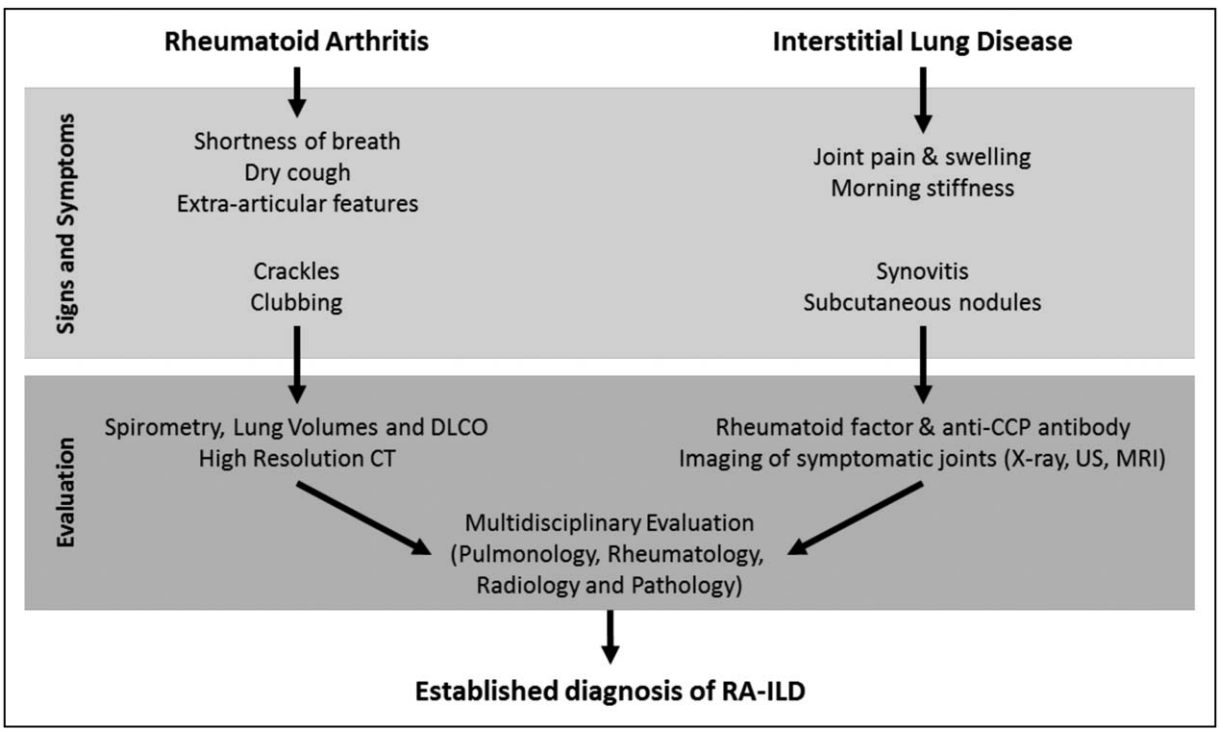

FIGURE 1. Approach to the identification of rheumatoid arthritis-associated interstitial lung disease. The initial presentation of rheumatoid arthritis or interstitial lung disease should prompt evaluation for other signs and symptoms attributable to rheumatoid arthritis-associated interstitial lung disease. Testing for pulmonary and articular manifestations followed by multidisciplinary discussion can establish the diagnosis of rheumatoid arthritis-associated interstitial lung disease. CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; US, ultrasound.

Identifying interstitial lung disease in rheumatoid arthritis

The high prevalence of subclinical ILD on HRCT in patients with RA demonstrates that screening approaches relying on clinical signs and symptoms will be poorly sensitive for detecting ILD [4,16]. To improve on the sensitivity of clinical findings, an algorithm to detect Velcro rales in recorded breath sounds from an electronic stethoscope was developed. In 137 RA patients who underwent HRCT, electronic breath sounds had a sensitivity of 93.2% and specificity of 76.9% for detecting ILD and outperformed clinical symptoms, exam findings, chest radiograph, and pulmonary function tests (PFTs) [17]. Validation in regular clinical settings is needed.

There is substantial interest in identifying serum biomarkers for RA-ILD since early identification may aid in preventing irreversible damage resulting from delays in diagnosis. In a large, international, case–control study, a *MUC5B* promoter variant (rs35705950) was associated with three-fold higher odds of RA-ILD compared with RA alone [18▪▪]. Our group performed a multicenter cross-sectional study that found the presence of anti-malondialdehyde-acetaldehyde antibodies to be associated with two-fold higher odds of ILD in RA [19▪]. Other biomarkers that have been previously examined include matrix metalloproteinase (MMP)-7, surfactant protein D, pulmonary and activation-regulated chemokine, INF-γ-inducible protein 10, anticitrullinated heat shock protein 90, antibodies to cross-reactive peptidyl-arginine 3/4, and anticitrullinated alpha enolase antibodies [20–24]. To date, there has not been validation of most of these biomarkers or integration into clinical care.

Identifying rheumatoid arthritis in interstitial lung disease

When ILD is the initial manifestation, providers must differentiate RA as the underlying cause from other connective tissue diseases (CTD) and idiopathic interstitial lung diseases. In addition to history and exam focused on articular symptoms, testing for RA autoantibodies (rheumatoid factor and ACPAs) should be completed. Although ACPAs are highly specific (>95%) for RA in most settings [25], they may also occur in the setting of chronic lung diseases even in the absence of RA [26]. Individuals with ACPAs but without inflammatory arthritis appear to be at high-risk for developing RA later [27]. Many of the biomarkers which show promise for identifying ILD in RA may not be useful for differentiating RA-ILD from other ILD. A recent study of two independent RA-ILD cohorts demonstrated overlap in serum proinflammatory cytokines and MMPs in RA-ILD and idiopathic pulmonary fibrosis (IPF) [28▪].

ESTABLISHING THE DIAGNOSIS AND TREATMENT TEAM IN RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

The gold standard for diagnosing RA-ILD is a multidisciplinary discussion of history, clinical exam, blood testing, HRCT, PFTs, and when performed, lung biopsy. Although most multidisciplinary discussion of newly diagnosed ILD includes pulmonologists, radiologists, and pathologists, the inclusion of rheumatologists improves the detection of CTD-ILD [29]. Given the correlation between HRCT and lung tissue findings as well as the morbidity accompanying surgical lung biopsy, biopsy is not typically pursued unless there is uncertainty in the diagnosis. Transbronchial cryobiopsies are a novel, less invasive method to acquire tissue to establish the diagnosis of ILD, though standardization of the procedure and delineation of its role in the diagnostic evaluation are still being determined [30]. After establishing the diagnosis of RA-ILD, a multidisciplinary team including support staff (e.g., nurses, pharmacists, and respiratory therapists) is crucial for ongoing management, and referral to specialized centers with CTD-ILD programs should be considered, when available.

OVERVIEW OF THE MANAGEMENT OF RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

The authors approach to managing RA-ILD is shown in Fig. 2. We begin by assessing disease severity, risk factors, and patient preferences. Supportive interventions are implemented for all patients. In patients with clinically significant or progressive ILD (based on clinical symptoms, PFTs, HRCT), we modify use of RA disease-modifying antirheumatic drugs (DMARDs). If RA-ILD progresses, we consider alternative immunomodulatory therapy and antifibrotics.

NONPHARMACOLOGIC THERAPIES

Smoking tobacco is the strongest environmental risk factor for both RA and ILD, and counseling on smoking cessation is of paramount importance. Ambulatory oxygen therapy is routinely prescribed for patients with a PaO_2 of 55 mmHg or less or SpO_2 of 88% or less. Despite widespread use, oxygen therapy has questionable benefit in regards to dyspnea, exercise tolerance, and mortality [31–33].

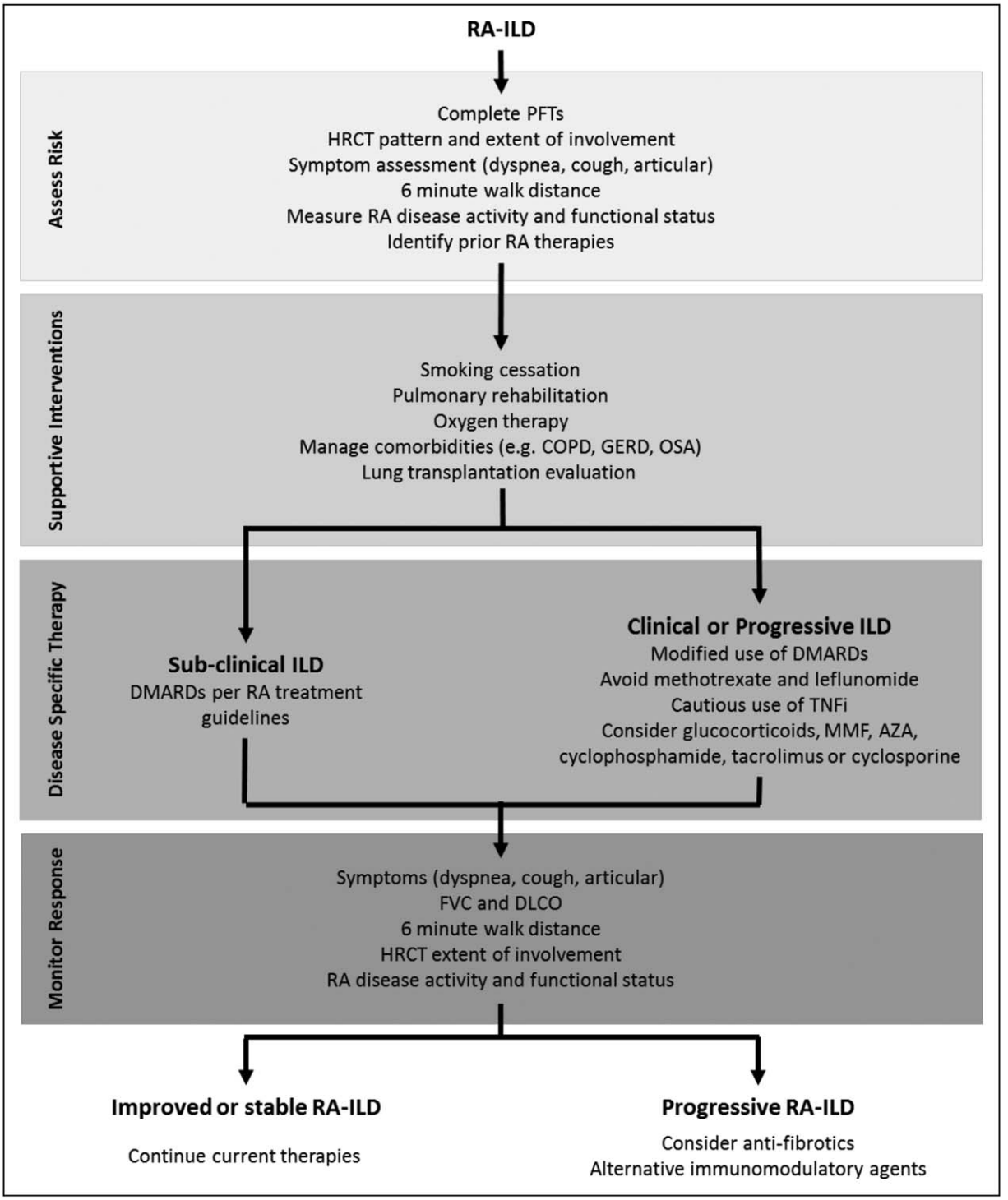

FIGURE 2. Approach to the management of rheumatoid arthritis-associated interstitial lung disease. Management of rheumatoid arthritis-associated interstitial lung disease begins by assessing severity and risk for progression. All patients should receive nonpharmacologic therapies. Those with clinically significant rheumatoid arthritis-associated interstitial lung disease may have their rheumatoid arthritis disease-modifying therapies adjusted and consideration given to other immunomodulatory therapies and glucocorticoids. If progression occurs despite these therapies, antifibrotics and alternative immunomodulatory therapies should be considered. AZA, azathioprine; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; DMARD, disease-modifying antirheumatic drug; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; MMF, mycophenolate mofetil; OSA, obstructive sleep apnea; PFT, pulmonary function tests; TNFi, tumor necrosis factor inhibitor.

Even though patients with CTD-ILD appear to benefit less than patients with other forms of ILD [34], pulmonary rehabilitation meaningfully improves exercise capacity, reduces dyspnea, and improves quality of life [35]. Lung transplantation evaluation should be considered in all patients with progressive ILD. Patients with RA-ILD that undergo lung transplantation have a similar risk of rejection and mortality as patients with other ILD [36,37].

SELECTING PHARMACOLOGIC THERAPIES

The outcomes in RA have dramatically improved with aggressive treatment strategies and an expanding armamentarium of DMARDs. Complicating the choice of DMARDs in RA-ILD is that most DMARDs have been linked to drug-induced pneumonitis [38]. We review the evidence for pharmacologic therapies in RA-ILD (all off-label), focusing on ILD outcomes given the existence of guidelines for the management of articular disease in RA [39,40].

Glucocorticoids

Glucocorticoids are typically part of the initial treatment regimen for clinically significant RA-ILD, based on experience in CTD-ILD rather than data demonstrating efficacy in RA-ILD [41]. NSIP and organizing pneumonia ILD patterns are more responsive to glucocorticoids than UIP [41,42], though data specifically in RA-ILD are lacking. Glucocorticoids have several dose and duration dependent long-term side effects including infection and osteoporosis [43,44]. Therefore, they are best suited for the initial management or treating acute exacerbations although transitioning to other therapies with more favorable long-term safety profiles.

Methotrexate

Pneumonitis occurs in only 0.3–0.4% of patients with RA treated with methotrexate [45,46], and methotrexate is not a risk factor for RA-ILD. In fact, results from prospective early RA inception cohorts showed trends towards lower odds of developing ILD in patients with RA treated with methotrexate [odds ratio 0.54, 95% confidence interval (CI) 0.28–1.06] [7▪]. Because preexisting lung disease is a risk factor for methotrexate pneumonitis [47], the difficulty in distinguishing methotrexate pneumonitis from exacerbations or progression of ILD, and that a lack of pulmonary reserve may predispose to increased mortality if pneumonitis were to occur, many providers discontinue or avoid methotrexate in RA-ILD. Although prone to confounding and selection bias, the limited studies evaluating methotrexate use in RA-ILD have not observed worse outcomes with its use [48,49]. We typically avoid the use of methotrexate in clinically significant and/or progressive RA-ILD and engage patients in shared decision making prior to use of methotrexate in RA-ILD. The safety of methotrexate in RA-ILD is a critically important question.

Other conventional synthetic disease-modifying antirheumatic drugs

Avoidance of methotrexate in those with or at risk for RA-ILD is partially responsible for a higher rate of ILD observed with leflunomide treatment [50]. However, pneumonitis is well known to also occur with leflunomide use. Preexisting ILD and prior methotrexate pneumonitis are risk factors for death in leflunomide pneumonitis [51], suggesting it should not be the standard alternative to methotrexate in these situations. Pneumonitis has also been reported with sulfasalazine [52]. There is a paucity of data on the safety of hydroxychloroquine in RA-ILD.

Tumor necrosis factor inhibitors

Although several cases of new-onset ILD or exacerbations of ILD have been reported after tumor necrosis factor inhibitors (TNFi) use [53,54], comparative studies are conflicting. In retrospective cohort studies in the British Society for Rheumatology Biologics Register, TNFi were not associated with a higher risk of death compared with conventional synthetic disease-modifying antirheumatic drugs in RA-ILD [55], but there were trends towards better survival with rituximab (hazard ratio 0.53, 95% CI 0.26–1.10) compared with TNFi [56]. Analyses of large US administrative claims databases have not found significant differences in respiratory events between patients with RA-ILD using TNFi compared with tocilizumab, rituximab, and abatacept [49,57]. However, there were numerically fewer respiratory events among initiators of abatacept compared with TNFi [57]. In addition to confounding and selection bias, misclassification of RA-ILD is problematic in these observational studies as demonstrated by extensive testing of the accuracy of administrative algorithms for RA-ILD [58].

Other biologic disease-modifying antirheumatic drugs and Janus kinase inhibitor

Beyond the aforementioned studies comparing with TNFi [49,56,57], there is only limited, uncontrolled data on these agents in RA-ILD. Small, uncontrolled

studies generally have shown the majority of patients with RA-ILD treated with rituximab, tocilizumab, or abatacept to remain stable or improved by PFTs [59–62]. A small case series did not find exacerbations of ILD with tofacitinib treatment [63], and in the SKG mouse model, tofacitinib effectively treats ILD [64]. Biologic DMARDs appear to have a role in other CTD-ILD [65,66], and several studies are ongoing in CTD-ILD. A double-blind randomized controlled trial (RCT) comparing rituximab to cyclophosphamide in CTD-ILD (RA-ILD excluded) is ongoing [67]. Phase II RCTs of abatacept in RA-ILD (NCT03084419) and myositis-ILD (NCT03215927) are recruiting.

Other immunomodulatory therapies

The role of other immunomodulatory therapies such as mycophenolate mofetil (MMF), cyclophosphamide, azathioprine, cyclosporine, and tacrolimus in RA-ILD remains unclear. In a retrospective analysis of 125 CTD-ILD treated with MMF ($n = 18$ RA-ILD), MMF was associated with improvement in lung function in those with a NSIP pattern and stability in those with a UIP pattern [68]. Both cyclophosphamide and MMF have demonstrated efficacy in systemic sclerosis (SSc)-ILD in double-blind RCTs [69,70]. Azathioprine is often used as an alternative to methotrexate in RA-ILD. A single center retrospective cohort study of CTD-ILD ($n = 97$, 24% RA-ILD) found that patients treated with azathioprine had similar clinical events and longitudinal PFTs compared with MMF [71]. There are case reports/series of RA-ILD improving with cyclosporine and tacrolimus [72–75]. Although these other immunomodulatory therapies (e.g., MMF, azathioprine) may be effective for ILD, providers must consider their potential for greater toxicities and more modest effects on articular disease [76–78].

Antifibrotics

Currently two antifibrotics are U.S. Food and Drug Administration (FDA) approved for the management of IPF, nintedanib and pirfenidone. They both are actively being studied in CTD-ILD. The INBUILD study was an international, double-blind RCT comparing nintedanib to placebo in patients with progressive, fibrotic lung disease (13% RA-ILD) [79▪▪]. In this study, patients treated with nintedanib had a slower rate of FVC decline over 52 weeks, but there were no significant differences in subjective symptoms or clinical events. Diarrhea was the major side effect of nintedanib, occurring in 67% of treated patients compared with 24% on placebo. A RA-ILD specific double-blind phase II RCT comparing pirfenidone to placebo is currently enrolling (TRAIL1, NCT02808871) and will illustrate the effects of antifibrotics on articular disease in addition to ILD [80]. In a mouse model of RA-ILD, nintedanib was effective for both lung and articular manifestations [81]. However, in the SENSCIS trial, a large, double-blind RCT comparing nintedanib to placebo in SSc-ILD, less decline in FVC was seen with nintedanib (resulting in FDA approval for SSc-ILD), but it was not effective for the non-ILD manifestation of skin fibrosis [82].

MANAGING COMORBIDITIES IN RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

Chronic obstructive pulmonary disease

Even among nonsmokers, chronic obstructive pulmonary disease (COPD) frequently accompanies RA-ILD. In a multicenter retrospective study, 27% of nonsmokers with RA-ILD had emphysema on CT [83]. In these individuals, emphysema was independently associated with a UIP pattern and poorer survival. The high prevalence and poor outcomes of concomitant COPD in RA-ILD warrants diligent adherence to the global initiative for chronic obstructive lung disease recommendations for COPD management [84].

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is common in RA-ILD, with approximately 50% of patients with RA-ILD having a diagnosis of GERD [8▪]. The relationship between GERD and ILD is debated. A recent meta-analysis of 18 case–control studies of GERD and IPF found the existing association to be confounded by smoking [85]. Pharmacologic (e.g., proton pump inhibitors, H2 blockers) and nonpharmacologic (weight loss, dietary modification, elevating head of bed) treatments are frequently prescribed in ILD and conditionally recommended in IPF management guidelines [42]. Equally as contentious is whether proton pump inhibitors increase the risk of pneumonia [86]. Therefore, providers must balance ill-defined risks and benefits of antacid use in RA-ILD.

MONITORING TREATMENT RESPONSE

Monitoring treatment response in RA-ILD includes both assessment of articular and respiratory disease activity and severity. The American College of Rheumatology recently convened a working group to provide recommendations on preferred RA disease activity and functional status measures [87▪,88▪].

The five preferred RA disease activity measures were the Disease Activity Score in 28-joints, Clinical Disease Activity Index, Simplified Disease Activity Index, Routine Assessment of Patient Index Data 3, and Patient Activity Scale-II [87▪]. The three preferred functional status measures were the PROMIS physical function 10-item short form, Health Assessment Questionnaire-II, and Multidimensional Health Assessment Questionnaire [88▪].

The Outcomes Measures in Rheumatology CTD-ILD working group performed a large Delphi process to identify important domains and outcomes measures for multicenter RCTs in CTD-ILD. The identified core domains and measures (in parentheses) were dyspnea (Medical Research Council dyspnea scale and Dyspnea-12), cough (Leicester cough questionnaire), health-related quality of life (Short Form 36 and patient global assessment), lung imaging (overall extent of ILD on HRCT), lung physiology (FVC and diffusing capacity for carbon monoxide), and survival [89]. These were selected based on relevance to multicenter RCTs, so these should serve as a guide, rather than a mandate, on measures to follow in routine care.

CONCLUSION

ILD frequently complicates RA, dramatically impacts patients' lives, and places a great financial burden on patients and healthcare systems. Multidisciplinary diagnosis and management is critical to optimizing patient outcomes, especially given the paucity of data to guide treatment decisions. Nonpharmacologic therapies should be universally implemented. The optimal DMARDs and other immunodulatory therapies as well as the role for antifibrotics are not well established. International working groups and multicenter RCTs are needed and in place to begin to address the many evidence gaps in RA-ILD management [90▪▪].

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Conflicts of interest

There are no conflicts of interest.

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The American College of Rheumatology and the Association of Physicians of Great Britain and Ireland convened a summit on CTD-ILD with a multidisciplinary panel of experts to identify unmet needs and future research directions.

Future use of musculoskeletal ultrasonography and magnetic resonance imaging in rheumatoid arthritis

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Purpose of review
Musculoskeletal ultrasonography (MSUS) and MRI play important roles in diagnosis, monitoring, and prognostication of rheumatoid arthritis. This review highlights recent literature in this field and aims to provide insight into the future use in clinical practice.

Recent findings
Recent studies concerning the use of MSUS and MRI in clinical practice show how MSUS and MRI can improve diagnosis and monitoring of rheumatoid arthritis and how they can predict both radiographic progression and clinical outcome (e.g., successful tapering of medical treatment). Moreover, novel technical developments of the two imaging modalities, such as 3D ultrasonography, ultrasound image reading with convolutional neural network, image fusion (MSUS and MRI) and whole-body MRI show promising results. Further validation of these novel techniques is required prior to implementation.

Summary
MSUS and MRI will be important parts of the future management of rheumatoid arthritis patients, mostly because of their ability to detect rheumatoid arthritis changes at a very early stage and to predict the course of disease. However, the exact role in routine clinical practice is still to be defined.

Keywords
imaging, magnetic resonance imaging, musculoskeletal ultrasonography, rheumatoid arthritis

INTRODUCTION

Initiation of early aggressive treatment of rheumatoid arthritis has been recognized as essential to gain rapid disease control and suppress inflammation [1] and thus to prevent pain, joint destruction, and impaired physical function. There is an increasing attention to how imaging in daily clinical practice can improve time of diagnosis and monitoring of treatment to optimize patient outcome. Moreover, the possibility of using imaging technology to indicate the prognosis for early rheumatoid arthritis patients is a highly discussed topic in the recent literature [2▪▪,3–6▪].

Musculoskeletal ultrasonography (MSUS) and MRI have the capability to sensitively detect rheumatoid arthritis manifestations such as early bone erosions, bone marrow edema (MRI only), synovitis, the degree of vascularization (Doppler activity/post-contrast enhancement), tendinopathy and tenosynovitis [7,8]. They are therefore increasingly applied in clinical practice and in research settings regarding diagnosis, monitoring, and prognostication of rheumatoid arthritis patient outcomes. The primary advantage of MSUS is the extension of the clinical examination in real-time, whereas the primary advantage of MRI is the possibility to visualize intraosseous abnormality. More advantages and disadvantages are listed in Table 1.

This review aims to summarize and discuss the most recent literature, covering the use of MSUS and MRI in clinical practice focusing on publications during the last two years. Furthermore, we aim to provide insight into future use of these imaging

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KEY POINTS

- MSUS and MRI are sensitive imaging modalities, which both have proven utility in diagnosis and monitoring of rheumatoid arthritis patients.
- MSUS and MRI can predict radiographic progression and tapering failure.
- MSUS and MRI can be used to document whether inflammation is present in patient-reported flares.
- MSUS and MRI driven T2T strategies have not proved to be superior to clinical T2T strategies.

technologies in the management of rheumatoid arthritis.

DIAGNOSIS

A standard clinical examination of a patient suspected for rheumatoid arthritis includes assessment of joint swelling and tenderness. According to the The American College of Rheumatology/The European League Against Rheumatism (ACR/EULAR) 2010 criteria [9–11], the presence of MSUS and MRI detected synovitis may be used to determine the extent of joint involvement. However, the modalities are rarely implemented as a routine part of the standard diagnostic set-up for rheumatoid arthritis patients in the clinic even though both MSUS and MRI have been shown to be more sensitive than clinical joint assessment [12–16].

MSUS and MRI were both included in the EULAR 2013 recommendations [17] regarding the use of imaging in the clinical management of rheumatoid arthritis. In the 2016 update of the EULAR recommendations for the management of early arthritis, MSUS is still recommended for detecting arthritis, whereas the use of MRI is only recommended in difficult patient cases, because of the relatively long scanning time, limited access and the possible lack of specificity suggested by the prevalence of MRI findings in 'normal' populations [1]. However, such 'normal' populations will include patients with other conditions (e.g., osteoarthritis), and neither synovitis nor bone marrow edema (BME) is pathognomonic for rheumatoid arthritis. Consequently, these findings should be interpreted in the clinical context just as in axial spondyloarthritis [18]. Thus, the topic of MRI findings in the 'normal' population and optimal thresholds for MRI findings is still debated [19–21].

The same issues are discussed regarding MSUS findings in the 'normal' population, where some studies have documented the presence of grade 1

Table 1. Comparison of MSUS and MRI: advantages and disadvantages

	MSUS	MRI
Advantages	No ionizing radiation	No ionizing radiation
	Guide to invasive procedures	Visualization of bone marrow edema, which has strong prognostic value
	Evaluation of several joint areas in one session	Central storage and reading of images, facilitating comparison of sequential MRIs
	No contrast agent is required	Multiplanar tomographic imaging of the body in any plane
	Accessible	Simultaneous assessment of all joints and entheses (WB-MRI*)
	Patient friendly	
	Relative inexpensive	
	No contra indications	
	Can be used in pregnancy	
	Visualizes structures in real-time	
Disadvantages	Cannot penetrate bone	Long examination time
	Operator dependent	Relatively higher cost
	Machine dependent	Lower availability
	Operator training required	Only one anatomic area per examination (except WB-MRI*)
		Exclusion of patients with claustrophobia**
		Exclusion of patients with certain metallic implants
		Potential adverse events when administration of contrast agent

MSUS, musculoskeletal ultrasonography.
*Whole-body magnetic resonance imaging (WB-MRI).
**Some MRI units are open, allowing scanning of patients with claustrophobia.

synovial hypertrophy and erosive-like changes in healthy controls, indicating the need of a 'cut off' for disease in daily clinical practice regarding both imaging modalities [22,23].

The possibility of using MSUS in a screening strategy for preclinical rheumatoid arthritis was recently examined in a prospective cohort study of 273 patients with risk of developing rheumatoid arthritis (first-degree relatives) [24] and concluded that MSUS abnormalities have no prognostic value for the development of rheumatoid arthritis. Moreover, the role of MSUS defined tenosynovitis in predicting rheumatoid arthritis development [25] was recently explored in a prospective study, in which 107 patients with clinical synovitis had MSUS assessment of joints and tendon compartments. After 18 months, the diagnostic outcome was determined using the 2010 ACR/EULAR classification criteria and showed that MSUS-defined tenosynovitis provided independent predictive value for rheumatoid arthritis development. Based on these results, it was recommended that future research in image-based predictive algorithms should include the tendon compartment as a variable. The comparison of MSUS, radiography and clinical investigations in detection of early rheumatoid arthritis development was recently examined in a multicenter cross-sectional study including 189 patients with nonspecific musculoskeletal symptoms [26]. They examined fingers and wrist joints and found MSUS to be the most specific for detecting early rheumatoid arthritis.

A recent comprehensive review [27] including randomized controlled trials and systematic reviews highlights that even though MSUS have a high sensitivity and specificity and is widely available and well accepted by clinicians and patients, the exact role of MSUS in the routine diagnostic set-up of suspected rheumatoid arthritis still needs to be further examined and the cost-effectiveness clarified.

To the best of our knowledge, no studies have been published during the last two years regarding the use of MRI in diagnosis of rheumatoid arthritis. However, earlier studies have presented independent predictive value of MRI for the development from undifferentiated arthritis to actual rheumatoid arthritis disease [28,29].

MONITORING AND TREAT-TO-TARGET STRATEGY

The key factors in routine monitoring of rheumatoid arthritis disease activity are a combination of patient-reported outcomes, blood samples (c-reactive protein/erythrocyte sedimentation rate) and clinical examination focusing on joint swelling and tenderness [30], all included in the composite scores such as Disease Activity Score (DAS, 28 joints) or the simplified disease activity index (28 joints) [31,32]. However, patient-reported symptoms do not always correlate with the findings during a clinical examination [33] and the use of imaging tools such as MSUS and MRI can give important information by assessing the inflammatory activity, potentially helping the physician to avoid unnecessary initiation of treatment or premature tapering [4▪]. Moreover, MSUS and MRI may be useful in choosing treatment strategy when the clinical disease activity score are elevated but there is a concern about false elevation. If no synovitis is found by MSUS or MRI treatment escalation may be unnecessary [34,35]. It is well known that tender joints have a major impact in the disease activity score and these joints seldom represent inflammation [36]. However, to our knowledge no studies have examined this topic yet.

To assess imaging changes during treatment, specific scoring systems are necessary. During the last decade, validated standardized scoring systems for quantifying inflammatory and/or joint damage in rheumatoid arthritis have been developed: Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) for MRI and the European League Against Rheumatisms-Outcome Measures in Rheumatology (EULAR-OMERACT) score for MSUS [7,37▪▪,38–40]. The EULAR-OMERACT MSUS scoring system assesses changes in lesions but does not suggest which joints to assess. A recent study developed and validated a new inflammatory scoring system for rheumatoid arthritis patients, including not only MSUS but also adding other relevant disease activity measures such as C-reactive protein (CRP) and the number of swollen joints, called the UltraSound Activity Score [41▪]. This scoring system may allow better assessment of disease activity than clinical only or MSUS only scoring systems; however, the comparison with existing scoring systems is needed. Another proposed scoring system is an individualized-ultrasound scoring system [42▪], where the most clinically inflamed joints are chosen for evaluation. This individualized approach showed superior results by detecting more joints with erosions than a predetermined joint set. Whether a personalized approach versus the predetermined joint sets approach could also detect more synovitis has yet to be determined.

Studies have also examined if a reduced joint set could detect treatment response, thereby reducing examination time and still maintaining sufficient information about the rheumatoid arthritis

inflammation load. The overall tendency in the literature is that limited joint sets perform similarly as the extended sets, but there is still no final agreement [43–47]. Moreover, there has been an interest in whether a unilateral scoring system could reduce examination time without significant loss of information.

A recent study [48] found that the hand with clinically more swollen joints is always more inflammatory active than its counterpart and that the dominant hand is never more active than the non-dominant hand. This information should be taken into account if choosing unilateral scoring systems and may have an impact on which hand that should be chosen for MRI examinations.

The sensitivity of MSUS and MRI to detect changes in joint inflammation during treatment is well known and has further been underlined in a recent study that compares synovial biopsies with MSUS and MRI findings [37▪▪]. Decreases in both MSUS and MRI synovitis were associated with reductions in histological synovitis. MSUS changes during treatment are typically evaluated by Doppler activity; however, recent studies have demonstrated that synovial hypertrophy independently of the presence of Doppler activity improves during treatment, even grade 1. Moreover, the ability of grade 1 synovial hypertrophy to change during treatment is similar in hands and feet [49▪,50].

The roles of MSUS and MRI in routine monitoring using standardized scoring systems have yet to be determined, including the impact on clinical outcomes. In a randomized study including 111 patients with newly diagnosed rheumatoid arthritis, a DAS-28 driven treat-to-target strategy (T2T) and a MSUS-driven T2T strategy were compared and no statistical difference in clinical outcome was found [51]. Similar findings were seen in the ARCTIC (Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasound in a Clinical TIght Control regimen) trial where 230 patients were randomized to receive either aggressive tight clinical control strategy or an MSUS tight control strategy. The systematic use of MSUS in the follow-up of all patients with early rheumatoid arthritis was not found to improve clinical outcome compared with the aggressive clinical tight control strategy [52].

When it comes to MRI-guided T2T strategies, a recent study (IMAGINE-RA) demonstrated no effect on achievement of remission of clinical disease activity (DAS-28-CRP <2.6) and no reduction in radiographic progression [53▪], when compared with a clinical T2T strategy. However, it is important to notice that several of the secondary and explorative outcomes examining physical function and other measures of disease activity favored the MRI T2T strategy [53▪]. Common to all these studies is that they only investigate the short-term benefit of imaging-based T2T strategy and therefore it is still unknown whether using MSUS or MRI findings in T2T strategies would show improved long-term results. The IMAGINE-RA trial has planned an observational 10 years follow-up which hopefully will clarify this. Nevertheless, there is a need for further randomized studies with a longer follow-up to assess the utility of both MSUS and MRI in monitoring of rheumatoid arthritis patients [54] but also studies assessing the added value in routine clinical practice where very tight clinical control is not applied are needed.

PREDICTING DISEASE OUTCOME

There is strong evidence in the literature that both MSUS and MRI can predict radiographic progression in rheumatoid arthritis [5▪,55]. The predictive value of BME examined by MRI is already well known and a strong independent predictor of radiographic progression [56–59] documented in both short and long-term follow-up studies (2–11 years) [5▪,60,61]. A recent randomized controlled trial [62▪], enrolling seropositive, methotrexate (MTX)-naive patients with early rheumatoid arthritis found that the presence of a high degree of inflammation (osteitis, synovitis, or in combination) in the clinically most active hand by MRI indicated poor prognosis. Further, different thresholds for MRI activity were defined dividing patients in low to high risk for progression. However, translating the thresholds into a readily usable score for routine clinical use is still needed. A novel study [3▪] found that MRI changes seen already one month after rheumatoid arthritis treatment initiation have the potential to predict long-term radiographic progression, thus allowing rapid assessment of the effectiveness of treatment.

A recent study evaluates the ability of MRI to predict disease development in patients who are in clinical remission. A cohort of routine care rheumatoid arthritis patients in sustained remission on biological disease-modifying antirheumatic drugs (bDMARDs) was tapered according to predefined guidelines. Low MRI combined inflammation score (synovitis, tenosynovitis, and BME) and/or combined damage score (erosion and joint space narrowing) before tapering were independent predictors for successful tapering, as were 1 or less previous bDMARD and male gender [6▪].

Studies examining the predictive value of MSUS have shown that Doppler MSUS also has the potential of predicting rheumatoid arthritis radiographic

progression [2▪▪,63]. A large cohort study examining the predictive value of single joint MSUS for the risk assessment of radiographic joint damage on a subsequent median three-year period found that both Doppler activity and gray scale synovitis, separately or in combination, were associated with the development of radiographic erosions [2▪▪]. Moreover, it has been reported that Doppler activity may predict tapering failure [64]. The presence of Doppler activity can also predict flares in rheumatoid arthritis patients [65–67,68▪,69], which is important information, as the number of flares are associated with worse clinical and functional outcomes. This suggests that the decision on treatment adjustments can be made on a safer basis if imaging is used. Further, patient-reported flares have been shown to be associated with inflammation by MSUS and MRI [68▪,69], thus indicating that patient-reported joint assessment could aid in capturing flares between routine clinical visits.

FUTURE USE OF MUSCULOSKELETAL ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING

During the last 20 years, there has been a dramatic technical improvement within both MSUS and MRI. New techniques have emerged such as three-dimensional (3D) ultrasound, contrast-enhanced ultrasound, MSUS image reading with convolutional neural network, image fusion and whole-body MRI (WB-MRI).

3D MSUS technology has been reported in some studies to be more sensitive than conventional 2D [70–72] (Fig. 1), but the role of contrast-enhanced ultrasound is still debated [73–75]. Thus, the use and place in clinical practice are not yet established, and how these techniques can improve the management of rheumatoid arthritis patients is still unknown.

The use of convolutional neural network (CNN) to score ultrasound images in a standardized way is currently under examination and the first study shows promising results [76▪▪]. The neural network was used to divide the patients in healthy/diseased and to score the images according to the OMERACT-EULAR Synovitis Score from 0 to 3 (where 0–1 = healthy and 2–3 = diseased). The agreement between the CNN and the rheumatologist was high (measured by using Cohen's κ statistic; weighted κ 0.84), indicating that the new neural network technology may in the future be used to score synovitis activity and may be one way to solve the issue of operator dependency in MSUS.

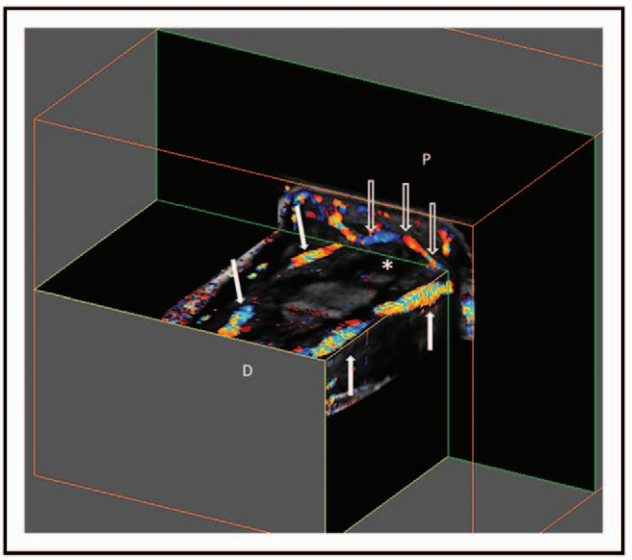

FIGURE 1. Three-dimensional musculoskeletal ultrasonography (3D MSUS). 13D MSUS examination of the palmar interphalangeal part of the right hand's second finger, which demonstrates two digital arteries (white arrows) and a transverse feeding vessel (open arrows). *Flexor tendon and sheet. Distal (D), proximal (P).

Image fusion enables fusion of MSUS and MRI images, which gives each MSUS probe position an exact projection of the corresponding anatomical area on a previously obtained MRI image (Fig. 2). During the live MSUS assessment, it is then possible to compare the disease by both modalities. A pilot study found MSUS and MRI to have a high agreement using this method when assessing tenosynovitis [77]. Image fusion may also have a role for diagnostic interventions, but more research is necessary to clarify the clinical benefits.

Whole-body MRI (WB-MRI) is a relatively new method that allows imaging of the entire body in one scanning session, that is, axial and peripheral joints and entheses (Fig. 3). Rheumatoid arthritis patients often have involvement of multiple joints; therefore, WB-MRI has a large potential for examining the total inflammation load [78,79]. A consensus-based WB-MRI scoring system has been developed and validated [80]. Only few studies regarding the use of WB-MRI in rheumatoid arthritis patients exist [78,79,81], but if subsequent studies can demonstrate its feasibility, discriminatory ability, and interscan reliability, WB-MRI may become a powerful imaging tool in the future.

All the above-mentioned techniques may gain more importance in the future both as outcome measures in clinical trials and potentially also for objective assessment in routine clinical practice.

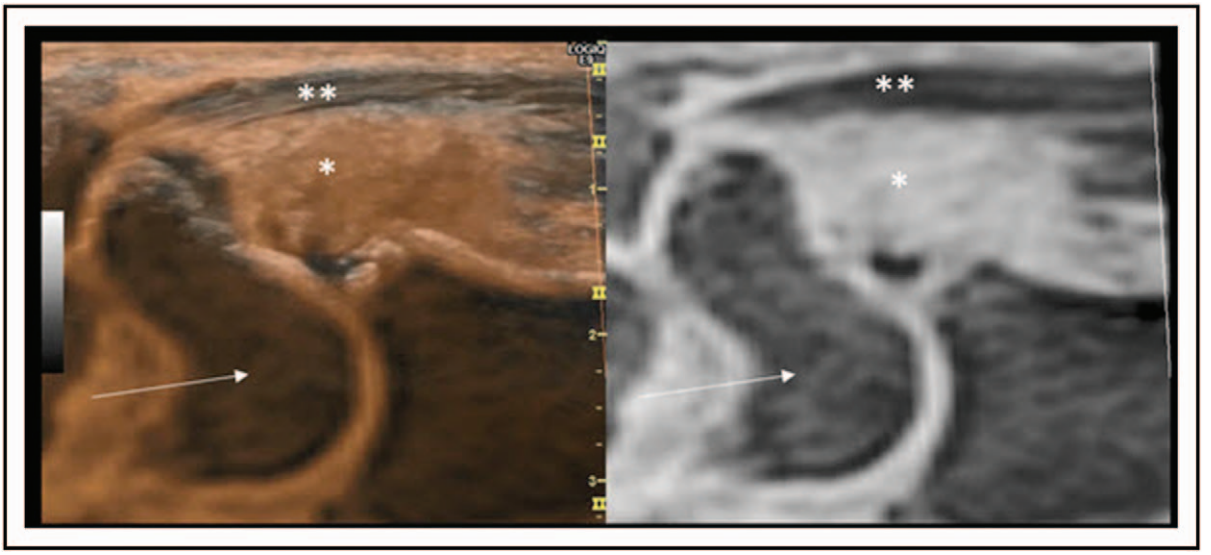

FIGURE 2. Image fusion of musculoskeletal ultrasonography (MSUS) and MRI. MSUS-MRI overlay (left) and MRI (right) image in sagittal plane of the wrist of a rheumatoid arthritis patient. **The flexor carpi radialis tendon with tenosynovit. *Synovitis in the palmar radial part of the wrist. The scaphoid was used as bony landmark for the image fusion (white arrows).

CONCLUSION

MSUS and MRI are sensitive imaging modalities, which both have proven utility in diagnosis, monitoring, and prognostication of rheumatoid arthritis patients. Continuous technical improvements occur and new techniques show promising results. MSUS and MRI will most likely become important parts of a more personalized treatment strategy of rheumatoid arthritis patients, however, exactly how and when these modalities should be used for

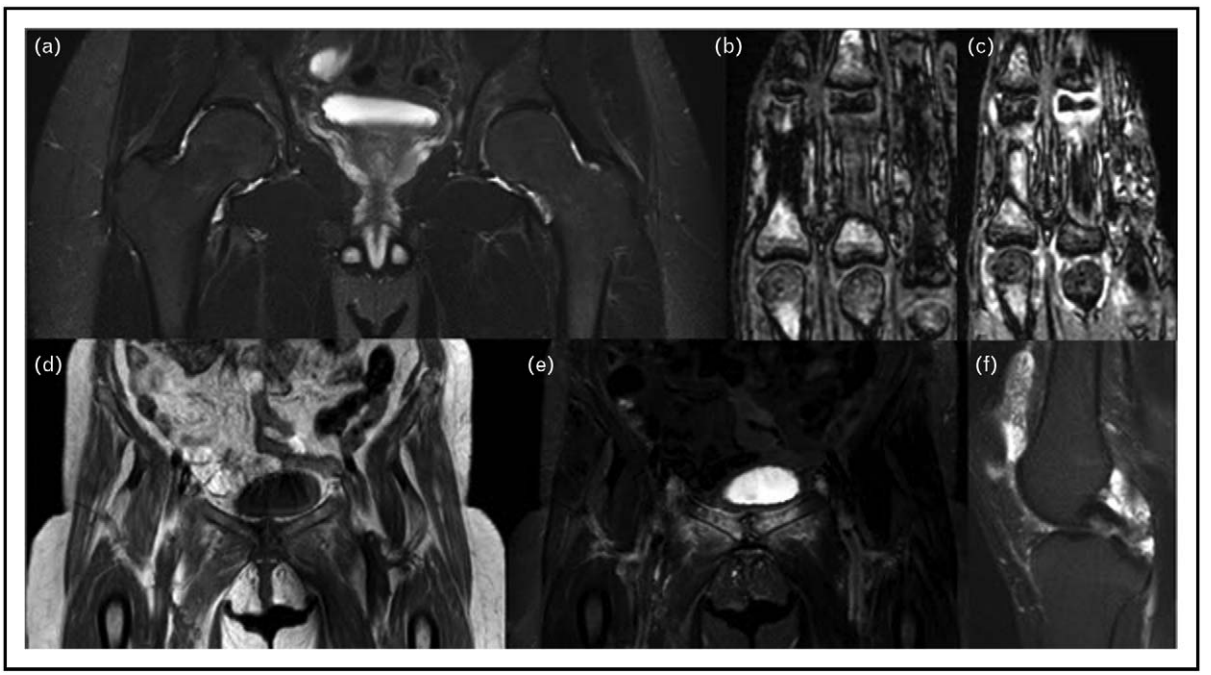

FIGURE 3. Whole-body magnetic resonance imaging (WB-MRI). Whole-body MRI images: (a) mild bilateral hip joint synovitis (coronal short tau inversion recovery (STIR) image); (b–c) synovitis in metacarpophalangeal and proximal interphalangeal joints (Coronal T1-weighted pre and postcontrast images); (d–e) bilateral severe soft tissue inflammation and bone marrow edema at the symphysis (coronal T1-weighted and STIR images); and (f) severe knee joint synovitis and effusion (STIR image).

optimal management of rheumatoid arthritis patients remains to be clarified.

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Conflicts of interest

There are no conflicts of interest.

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This large cohort study found a predictive value of both Grey scale ultrasound, Power Doppler ultrasound, and Combination ultrasound regarding the development of erosions in rheumatoid arthritis patients during the subsequent three years.

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New galaxies in the universe of shared decision-making and rheumatoid arthritis

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Purpose of review
Implementing shared decision-making (SDM) is a top international priority to improve care for persons living with rheumatoid arthritis. Using SDM tools, such as decision aids improve patients' knowledge and support communication with their clinicians on treatment benefits and risks. Despite calls for SDM in treat-to-target, studies demonstrating effective SDM strategies in rheumatology clinical practice are scarce. Our objective was to identify recent and relevant literature on SDM in rheumatoid arthritis.

Recent findings
We found a burgeoning literature on SDM in rheumatoid arthritis that tackles issues of implementation. Studies have evaluated the SDM process within clinical consultations and found that uptake is suboptimal. Trials of newly developed patient decision aids follow high methodological standards, but large-scale implementation is lacking. Innovative SDM strategies, such as shared goals and preference phenotypes may improve implementation of treat-to-target approach. Research and patient engagement are standardizing measures of SDM for clinical uses.

Summary
Uptake of SDM in rheumatoid arthritis holds promise in wider clinicians' and patients' awareness, availability of decision aids, and broader treat-to-target implementation strategies, such as the learning collaborative. Focused attention is needed on facilitating SDM among diverse populations and those at risk of poorer outcomes and barriers to communication.

Keywords
outcome measure, patient decision aid, rheumatoid arthritis, shared decision-making, treat-to-target

INTRODUCTION

Implementing shared decision-making (SDM) is a priority outlined in international guidelines to improve quality of care for persons living with rheumatoid arthritis [1,2]. SDM is a process by which rheumatologists collaborate with patients to provide high-quality care based on best available evidence and eliciting patient's values and preferences [3–5]. SDM is important in all aspects of care, from appropriately informing patients of the rheumatoid arthritis diagnosis to generating a personalized treatment target and management plan [3].

One of the key current challenges to managing rheumatoid arthritis is fully implementing the treat-to-target approach [6▪,7▪]. Early, intensive and rapid control of the disease prevents accelerated joint damage, loss of function and cardiovascular morbidity [6▪,7▪,8]. The treat-to-target approach involves choosing a shared goal for treatment, assessing progress and making decisions to escalate treatments to reach a target [6▪,9]. SDM is an overarching principle to help navigate the treat-to-target approach [6▪].

Many barriers have been identified to using SDM in rheumatoid arthritis care. Clinicians perceived patients' preferences and knowledge concerning medication to act as limiting factor to the treat-to-target approach [8–10]. Patients also often disagree with key treat-to-target recommendations, such as short-term treatment adjustments or targeting of low disease activity and remission, instead favor quality of life and pain as targets [11]. Of particular concern, deliberation and SDM about

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KEY POINTS

- Shared decision-making is not yet embedded in clinical consultations for rheumatoid arthritis.
- New trials of decision aids improved patient knowledge and reduced decisional conflict concerning treatment options, but large-scale trials are lacking.
- Innovative strategies including shared goals and preference phenotypes support implementation of SDM in a treat-to-target approach.
- Core outcome domains are being identified to measure the impact of incorporating shared decision-making in clinical practice, which may spur research on training or easy-to-use tools.

the best treatment choices to reach patient goals was sidetracked by third-party insurance providers that can approve or deny authorized medication [8]. This situation reflects the obstacles posed by a broken funding model in the United States healthcare system to fully realize SDM when caring for patients.

Despite the emphasis on SDM to guide treatment choices, studies in rheumatoid arthritis were underrepresented in a 2017 Cochrane review of 105 studies of decision aids with only one published trial and two ongoing studies [12]. Another Cochrane review on strategies to increase use of SDM by health professionals identified only one trial on a decision aid for rheumatoid arthritis that enhanced knowledge and reduced decisional conflict [13,14]. A recent systematic review of interventions to support SDM in treatment decisions in long-term conditions included 23 studies, none of rheumatoid arthritis [15].

An evidence gap is evident between the proposed principles by large organizations in rheumatology and what occurs in real-world practice. Patients' experience of SDM is suboptimal, particularly for persons with communication barriers, such as limited health literacy [14,16]. We explore the universe of SDM and reflect upon the most significant recent advances for persons living with rheumatoid arthritis.

IS SHARED DECISION-MAKING HAPPENING IN CLINICAL CONSULTATIONS?

Designing strategies to foster SDM in clinical practice requires an understanding of whether and how decision-making processes happen in clinical consultations [17,18]. This is the starting point of both the *Ottawa Decision Support Framework* and the Mayo Clinic's method of direct observation of consultations during the design of decision aids [17,18]. This evidence is limited for many decision-making processes happening in clinical consultations for rheumatoid arthritis.

Mathijssen *et al.* [19▪▪] recorded 168 clinical consultations with rheumatoid arthritis patients in two centers in the Netherlands to investigate if and how SDM occurred in clinical practice. The authors audio-recorded consultations and assessed them using the 'observing patient involvement in decision making' (OPTION) scale, a five-item tool that measures SDM from an observer perspective. OPTION was scored between 0 and 100, with a higher score representing higher level of SDM. The authors found a mean OPTION score of 28.3, and a range from 0 to 75, which they interpreted as representative of substantial variability and low-to-moderate levels of SDM when deciding on rheumatoid arthritis treatments. The authors found that a longer consultation time of 10 min was associated with slightly higher SDM score, and that decisions to make changes to a patient's treatment (e.g. stopping medication) required more SDM.

We consider this article highly relevant to the field. Data collection happened between 2015 and 2017, coinciding with the publication of international guidelines calling for SDM in rheumatoid arthritis. This study provides a clear picture of usual clinical practice because participants were not aware that they would be assessed for SDM during data collection. The suboptimal level of SDM underscores the need to develop tools and strategies to foster SDM in clinical consultations. Future studies should assess if and how SDM occurs in order to map the diversity of decisions that happen in rheumatoid arthritis care and allow for carefully designed interventions to facilitate uptake.

Key messages: SDM is not yet embedded in clinical consultations for rheumatoid arthritis. There is a need to develop and test effective strategies and tools to foster SDM in clinical practice.

DESIGNING INNOVATIVE STRATEGIES TO FOSTER SHARED DECISION-MAKING

Recent literature highlights teams who are designing innovative strategies to foster SDM in clinical practice. In this section, we delineate SDM innovations as decision aids, goal sharing strategies and identification of preference phenotypes.

Advances in decision aids

Decisions aids are one of the best known and effective strategies to foster SDM in clinical practice but

are rarely used in rheumatoid arthritis [12,20]. Li *et al.* [7▪] conducted a mixed-methods study to assess the impact of an interactive online patient decision aid (ANSWER-2) on patients' decisional conflict, medication-related knowledge and self-management capacity. In 50 patients with a median disease duration of 5 years, using the decision aid significantly improved the proportion of patients with a decisional conflict score lower than 25 (20% before and 52% after the intervention, $P < 0.001$), which is associated with a higher likelihood of following through on a decision.

Li *et al.* [7▪] followed high-quality standards for the design of decision aids including working with knowledge users (e.g. rheumatologists and patients). The decision aid targeted the decision to begin or switch to a new biologic or small-molecule agent. SDM in rheumatoid arthritis involves specifying the context for the decision with SDM being most relevant after patients have had an inadequate response to methotrexate monotherapy. ANSWER-2 uses a web-based format and multilevel adaptative design that progressively provides relevant information to patients. This is an important step forward for rheumatoid arthritis care where many options with complex benefits and risks occur.

However, this study showed that some patients expressed mixed reactions to the usefulness of the decision aid [7▪]. Some found it helpful in improving knowledge whereas others stated it was 'the rheumatologist's job' to describe medication attributes: '[. . .] I really think it's a waste of time. [. . .] It's the rheumatologist's job, if he's going to do his job properly, to relay this information to the patient'. This contrast highlights a key point in SDM: tools cannot replace the conversation and collaboration between patient/family and clinician. Tools can support and facilitate SDM. This patient's response underscores the importance of eliciting patient preferences for involvement, and tailor knowledge transfer and decision-making processes to each individual patient/clinical context who faces their own unique situation [21].

In another trial, Pablos *et al.* [22▪] developed and tested a decision aid to support treatment decisions among patients in Spain with moderate-to-severe rheumatoid arthritis who did not achieve therapeutic goals with their current treatment. In their beta testing with 54 patients and 6 rheumatologists, the authors showed that using the decision aid reduced decisional conflict score by 8.6 points.

In contrast to many decision aids developed in the United States, for use mainly in a private healthcare system, this trial focused on a European population. Implementing SDM in other healthcare systems and cultures will likely require developing new or adapting decision aids in contexts where options and costs may differ significantly. Also, there may be variation across cultures regarding expectations of healthcare, the patient–clinician dynamic, and thus, require interventions to help raise awareness and train clinicians to implement SDM.

We observe that decision aids for rheumatoid arthritis focus solely on medication treatment choices. Newer decision aids should consider incorporating other treatment options. Sepucha *et al.* published the DECIDE-OA trial comparing two decision aids for helping patients with osteoarthritis decide about surgical options. This choice is relevant for a subset of patients with rheumatoid arthritis [23,24]. Our patients also benefit from rehabilitation interventions early during their disease and it will be fundamental to discuss these options in future SDM conversations.

Most decision aids for rheumatoid arthritis are at the pilot trial stage. We have yet to see a large-scale randomized trial that assesses longer term outcomes, such as adherence to treatment sequences, healthcare utilization and improvement in health outcomes [25]. The SUNDAE reporting guidelines for trials of decision aids will likely guide researchers in their implementation and trial initiatives [26,27].

Shared goals to foster shared decision-making

Many current SDM frameworks skate over the goal-setting phase of the decision-making process [28]. Setting goals is a key aspect of rheumatoid arthritis care, including the start of the treat-to-target approach when choosing targets [6▪,9,11]. A recent systematic review identified over 400 patient goals and expectations in rheumatoid arthritis [29]. Patients expressed a diversity of goals, such as improving pain, lowering stress, increasing well being, having better peer support and education about the disease, access to services and tools to communicate with healthcare providers [29]. The goal setting phase of rheumatoid arthritis care is vital to patients' lives and goes beyond composite measures of disease activity targets.

Shared goals between patients and clinicians are far from being achieved: a recent survey found that half of patients with rheumatoid arthritis are uncomfortable raising concerns or fears with their physicians, whereas the latter wished patients would discuss more their goals [30]. Barton *et al.* [31▪] examined goal conceptualization in a qualitative study with 19 rheumatoid arthritis patients and 18 rheumatology clinicians. The authors identified two overarching domains of shared goals: knowledge and

stress [31▪]. Knowledge was important for making informed decisions for patients, and ensured adherence and medication safety was key for clinicians. Stress impacted patients' experience with healthcare and their treatment choices. The authors found a misalignment between patients' and clinicians' view on shared goals in rheumatoid arthritis.

This study is highly relevant to implementing SDM in a treat-to-target approach to reach concordance in goal setting. Direct quotes from patients and clinicians show that we are not addressing clear mechanisms of the SDM process in rheumatoid arthritis care, including knowledge and alignment with value and preferences. Thus, if a clinician and a patient cannot agree on shared goals, the SDM process can neither occur nor can they effectively follow a treat-to-target approach. The authors are designing a tool to improve goal elicitation and alignment of shared goals in rheumatoid arthritis management.

Integration of patient-reported outcomes into clinical encounters may also facilitate communication about goals and expectations [32]. In one study, patients completed Patient-Reported Outcomes Measurement Information System (PROMIS) measures before consultation with a rheumatologist [33]. Using PROMIS improved communication and facilitated SDM about treatment options by better understanding the patient's symptoms, behaviours, lifestyle and preferences for treatment. Teams aim to implement patient outcome measures in real time using an electronic dashboard, which will make it easier to integrate in rheumatology clinics [34].

Identifying preference phenotypes

Eliciting patients' values and preferences is a central aspect of SDM, yet a complex endeavour in rheumatoid arthritis because of the uncertainty of the disease trajectory. Fraenkel *et al.* [35] assessed preference phenotypes to facilitate the SDM process. Among 1273 participants with rheumatoid arthritis who failed methotrexate monotherapy, the authors identified five preference phenotypes that would likely have the strongest impact on their subsequent treatment decisions. Most patients' decisions would be impacted by the cost of medication, followed by the risk of bothersome side effects, risk of rare side effects, mode of administration of medication, onset of action and risk of serious infections [35]. Simplifying preference phenotypes before clinic visits is an innovation in SDM that has the potential to make it easier for clinicians to acknowledge, elicit and address patients' preferences.

Guided by the preference phenotypes, Hsiao *et al.* [36▪▪] designed a value clarification tool to support SDM for treatment escalation decisions. The tool differs from traditional decision aids: it anchors the process on preference phenotypes likely to impact subsequent treatment decisions based on their values and goals. Ninety-six clinician–patient dyads used the tool, which resulted in more medication choices offered to patients and a higher number of visits in which medication characteristics and costs were discussed. More patients expressed their values and preferences concerning treatment escalation decisions and these decisions were more likely to be concordant with what mattered most to patients [36▪▪].

Key messages: new trials of decision support tools showed effectiveness to improve SDM process concerning treatment options in rheumatoid arthritis. Innovative SDM strategies including setting shared goals and phenotyping patients' preferences are being leveraged to guide treatment decisions and support the treat-to-target approach. Large-scale trials that implement SDM tools and strategies in clinical practice are needed along with rigorous standardization of SDM measures of impact.

OMERACT CORE OUTCOME DOMAINS TO MEASURE SHARED DECISION-MAKING IN RHEUMATOLOGY

A barrier to implementing SDM in clinical practice is deciding whether SDM occurred and how to measure its impact. In 2015, OMERACT (Outcome Measures in Rheumatology) created a working group on SDM to identify core outcome domains to be used in trials of SDM interventions in rheumatology [37,38]. The group published a white paper outlining a six-step process for SDM and five core outcome domains [39▪▪]. The proposed five core outcome domains to measure the impact of SDM include:

(1) Knowledge: does the patient know more about treatment options and benefits and risks after being exposed to a SDM intervention?
(2) Alignment with values and preferences: does the SDM tool help the patient choose the treatment that has the characteristics that matter most to them?
(3) Confidence: does the patient feel that they made the best decision?
(4) Satisfaction: is the patient satisfied about the decision-making process?
(5) Adherence: did the patient follow through with the chosen option?

The working group will publish concise whiteboard videos early in 2020 to describe their process and outline the proposed domains. After establishing

Table 1. Proposed research priorities and research questions to improve our understanding of shared decision-making in rheumatoid arthritis

Research components	Research priorities	Research questions
Shared decision-making process at the level of clinical consultation	Assess if and how shared decision -making happens in diverse clinical consultations for rheumatoid arthritis	What are the different decisions facing patients with rheumatoid arthritis at the different steps of their care process?
Strategies to foster shared decision-making in rheumatoid arthritis.	Pursue development of new decision aids using adaptative and computer-assisted designs Pursue large-scale pragmatic randomized trials of decision aids and/or clinician training to determine their effectiveness Expand innovative SDM strategies, such as shared goals and preference phenotypes	Are there more effective implementation strategies beyond the learning collaborative to support uptake of SDM in clinical practice? Is there a differential effect of SDM tools among persons with limited health literacy?
Measuring SDM and its impact in clinical practice	Following consensus on Core Outcome Domains for SDM, identify valid, reliable and easy-to-use tools to measure the impact of SDM in clinical practice	Does SDM improve rheumatoid arthritis outcomes (e.g. disease activity, quality of life)? Can SDM reduce disparities in health outcomes in rheumatoid arthritis?

SDM, shared decision-making.

consensus on core domains, the group will then identify of a core set of measurement tools for SDM in clinical practice. Several tools already exist to measure SDM, but mainly for research purposes [40]. A recent article focused on the comparison of three short SDM measures (SDM Process_4, CollaboRATE and SURE) and found these measures to have valid psychometric properties [41]; however broad use of the measures in rheumatology is lacking. These measures are easy to use and could be implemented in clinical care for rheumatoid arthritis.

Key messages: collaborative efforts to identify and standardize core domains to assess the impact of SDM interventions on patients with rheumatoid arthritis are actively underway. The next phase will be to identify best current and practical tools for measuring SDM in clinical practice and develop new ones if required.

CONCLUSION

Our understanding of SDM in rheumatoid arthritis is in its infancy but expanding rapidly. Current evidence addresses barriers to the implementation of SDM that may serve other fields of medicine. The rheumatology community must define the best ways to foster meaningful SDM in clinical consultations, unravel innovative SDM interventions and measure SDM in clinical practice. We need to design multifaceted implementation strategies that combine clinician training and SDM tools to fully realize SDM in practice. We propose a set of research priorities and unanswered questions that will improve our understanding of SDM (Table 1). Ongoing exploration of this expanding universe must continue.

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Conflicts of interest

There are no conflicts of interest.

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This study assessed the impact of a decision aid targeting treatment escalation decisions. It differs from traditional SDM approaches by anchoring the process on preference phenotypes likely to impact subsequent treatment decisions. This study demonstrates that using SDM strategies in the context of treat-to-target decisions is feasible and likely to have positive impact on the process of care.

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Inhalants other than personal cigarette smoking and risk for developing rheumatoid arthritis

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Purpose of review
The current review summarizes the current evidence on inhalants other than personal cigarette smoking and risk for developing rheumatoid arthritis (RA).

Recent findings
Personal cigarette smoking has been implicated as an environmental risk factor for seropositive RA, perhaps by inducing autoimmunity at pulmonary mucosa. Since many patients with RA are nonsmokers, other inhalants are being investigated as potential RA risk factors. Recent case–control and cohort studies have investigated passive cigarette smoking, air pollution, inhalant-related occupations, silica, pesticides, household environment, and allergic inhalants as inhalant exposures for RA risk. Inhalant-related occupations and silica inhalants have the most consistent evidence for associations with increased RA risk. However, most studies relied on retrospective designs and had limited ability to adjust for personal cigarette smoking or investigate associations among nonsmokers.

Summary
Several inhalants other than personal cigarette smoking may be associated with increased risk for developing RA. These results support the hypothesis that inhalants, pulmonary mucosal inflammation, and RA pathogenesis may be linked. Future studies are needed to firmly establish the independence of these findings from personal cigarette smoking and to determine the specific inhalants and biologic mechanisms related to RA pathogenesis.

Keywords
inhalants, passive smoking, pollution, rheumatoid arthritis, silica

INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic autoimmune disorder characterized by a painful and disabling polyarthritis [1]. Personal cigarette smoking has the strongest evidence as an environmental RA risk factor [2–4]. Personal cigarette smoking is specifically associated with seropositive [rheumatoid factor or anticitrullinated protein antibody (ACPA) positivity] RA, responsible for up to 35% of the risk for seropositive RA [5,6]. Smoking cessation has also been associated with reduced risk for developing seropositive RA [7▪▪]. The mucosal paradigm for seropositive RA pathogenesis hypothesizes that RA may develop at inflamed pulmonary mucosa in individuals with genetic predisposition where autoantibodies may be produced years prior to clinical RA onset [8–14].

Other environmental exposures are also likely to be related to RA since many nonsmokers develop RA. While smoking rates have steadily declined over the last few decades in the United States, the incidence of RA has remained stable arguing that other environmental risk factors are important in RA pathogenesis [15]. Similar to personal cigarette smoking, other inhalants are hypothesized to induce local pulmonary mucosal and systemic inflammation [16]. In addition, specific inhalants may induce protein citrullination that could result in loss of immune tolerate to generate ACPA locally in pulmonary tissue prior to systemic production and articular inflammation. Thus, inhalants other than personal cigarette smoking may be important in RA

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KEY POINTS

- Studies have investigated passive cigarette smoking, air pollution, inhalant-related occupations, silica, pesticides, household environment, and allergic inhalants as inhalant exposures possibly related to RA risk.
- Inhalant-related occupations (such as construction and coal mining) and silica inhalants have the most consistent evidence for associations with increased RA risk.
- Some studies suggest that passive smoking may be related to RA risk, but many had limited ability to account for personal smoking.
- Overall, the available literature supports the paradigm that inhalants, pulmonary mucosal inflammation, and seropositive RA pathogenesis may be linked.

pathogenesis. However, studies investigating inhalants for RA risk need to carefully account for cigarette smoking in analyses. For example, some inhalant-related occupations may be highly correlated with personal cigarette smoking making it difficult to identify independent associations. Smoking status (never/past/current) may be insufficient to capture granularity on intensity and duration of smoking. Investigating associations among never smokers may overcome some of these challenges.

The purpose of this narrative review is to provide an overview of recent studies that are investigating inhalants other than personal cigarette smoking for RA risk. We described the following inhalants that have the most literature for an association with RA: passive cigarette smoking, air pollution, inhalant-related occupations, silica, pesticides, household environment, and allergic inhalants. We did not include personal cigarette smoking since this has been detailed in previous reviews [4,17–20].

PASSIVE CIGARETTE SMOKING

Several studies have investigated passive cigarette smoking and RA risk, reporting conflicting results (Table 1) [21▪–23▪,24,25]. The nuances of passive smoking, including age at exposure, intensity, duration, and location (home/work) of exposure, are challenging to measure and self-report may be prone to error or recall bias. Careful measurement and study design for analysis of personal cigarette smoking is important since passive and personal smoking are highly correlated and personal smoking likely imparts higher doses of harmful inhalants than passive smoking. Stratifying by personal smoking status or restricting the analysis to never smokers provides the highest evidence for the effect of passive smoking on RA risk since the never smoker subgroup is unlikely to be confounded by personal smoking. If smokers are analyzed, adjustment for personal smoking behavior is essential, with continuous pack-years preferred over never/past/current (or never/ever) status, since smokers may have very different duration/intensity of smoking and this could introduce confounding. Failure to account for personal smoking when investigating the association between passive smoking and RA risk may weaken the validity of the results. Even investigating childhood smoking may be mediated/confounded by later personal smoking (highly correlated with parental smoking), so these studies should ideally still account for personal smoking. Table 1 provides details about the methods of accounting for personal smoking in each study.

Fetal exposure to cigarette smoking has been shown to increase RA risk [24]. Evidence from two studies suggested that smoke exposure during childhood may be associated with an increased RA risk [23▪,24]. Neither study adjusted for personal smoking as the populations of interest were children, but those who were exposed to high levels of passive smoking may have been more likely to become smokers themselves [23▪,24]. One of the studies stratified by adult personal smoking status (never/ever) [23▪]. RA onset was earlier in smokers exposed to passive smoke during childhood than those without childhood exposure, although not statistically significant [23▪]. Passive smoke exposure during adulthood has not consistently been linked with increased RA risk [21▪–23▪,25]. Three studies found no association between various measures of adult passive smoking and RA risk, after considering personal smoking [21▪,22▪,25]. Two of these studies were performed among only never smokers [21▪,25] while the other adjusted for adult personal smoking status (never/past/current) [22▪]. The absence of a relationship between passive smoking and RA risk may be explained by a minimum threshold below which there is no effect of passive smoke exposure on RA risk [21▪], although most studies use a binary passive smoke exposure of exposed/not exposed. One study using a higher passive smoking pack-year cut-point suggested a possible dose effect on RA risk [22▪]. Further research is needed to investigate passive smoking and RA risk independent of personal cigarette smoking.

AIR POLLUTION

Ambient pollutants are composed of a mixture of gases [carbon monoxide (CO), nitrogen dioxide

Table 1. Selected studies associating passive cigarette smoking with risk of rheumatoid arthritis

Reference	Study design	Population Sample (*n*) RA outcomes (*n*)	Passive smoking exposure methods	RA outcome methods	Personal cigarette smoking and other adjustment variables	Effect size (95% confidence interval) for passive smoking and RA risk	Comments
Jaakkola and Gissler [24]	Prospective cohort	Finland, national registries, singleton births, <7 years of age *n* = 58 841 *n* = 44 incident RA	Finnish Medical Birth Registry, categorical (no smoking, <10 cigarettes/day, >10 cigarettes/day)	Hospitalization and/or billing code	No personal smoking adjustment (but population was <7 years old) Sex, maternal parity, maternal age, marital status, maternal occupation, birth weight, gestational age	RA and other polyarthritis in first 7 years of life: **OR 2.10 (1.30–3.40)**	Effect of maternal smoking on RA risk limited to girls Higher exposure to smoke increased the risk of RA and other polyarthritis in girls All cases were juvenile-onset; may not be generalizable to adult RA
Costenbader *et al.* [25]	Prospective cohort	United Status, Nurses' Health Study, female nurses *n* = 103 818 *n* = 453 incident RA	Self-report, categorical (per 10 years lived with smoker)	1987 ACR criteria	Stratified by ever/never smokers and ever smoker analysis adjusted for personal smoking (continuous, pack-years) BMI, alcohol use, paternal occupation, age at menarche, parity, duration of breastfeeding, postmenopausal hormone use	All RA among ever smokers, >30 years lived with smoker (reference: 0 years): RR 1.59 (0.92–2.74) All RA among never smokers, >30 years lived with smoker (reference: 0 years): RR 1.46 (0.92–2.32)	Living with smoker for >30 years associated with increased RA risk, although not statistically significant No dose effect Measured smoke exposure at home and work
Hedström *et al.* [21▪]	Case–control	Sweden, never-smokers aged 18–70 years (EIRA) *n* = 2353 *n* = 589 incident RA	Self-report, categorical (per 10 years passive smoke exposure)	1987 ACR criteria	All never smokers Age, sex, residential area, ancestry	ACPA-positive RA: OR 1.0 (0.8–1.2) ACPA-negative RA: OR 0.9 (0.7–1.2)	No trend between duration of passive smoking and RA risk No significant age-related or sex-related differences
Seror *et al.* [23▪]	Prospective cohort	France, females (E3N Cohort) *n* = 71 248 *n* = 371 incident RA	Self-reported (≤a few hours a week vs >a few hours a day of childhood smoke exposure, <1 h/day vs ≥1 h/day of adult smoke exposure)	Self-report and billing code	No personal smoking adjustment (stratified analysis as never/ever smoking) Age	Childhood passive smoking and all RA: HR 1.43 (0.97–2.11) Adult passive smoking and all RA: HR 0.96 (0.69–1.34)	RA onset earlier in smokers also exposed to smoke in childhood
Kronzer *et al.* [22▪]	Case–control	Minnesota and Florida, Mayo Clinic Biobank participants *n* = 4084 *n* = 1023 prevalent/incident RA	Self-report, categorical (per 10 pack-years smoke exposure, exposure in home vs workplace)	Self-report, billing code, and/or 2010 ACR criteria	Personal smoking status (never/past/current) Age, sex, BMI, race, education, year, residential area	Home exposure and all RA: OR 1.06 (0.91–1.23) Workplace exposure and all RA: OR 1.01 (0.86–1.17) Combined home and workplace and all RA per 10 pack-years: OR **1.04 (1.00–1.09)**	Also investigated age at first exposure, duration, and packs/day Potential dose effect observed No difference in effect of passive smoking on nonsmokers vs smokers Also investigated asthma and allergies for RA risk

Statistically significant results are bolded. ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EIRA, Epidemiological Investigations of Rheumatoid Arthritis; HR, hazard ratio; OR, odds ratio; RA, rheumatoid arthritis.

(NO_2), ozone (O_3), and sulfur dioxide (SO_2)] and fine particulate matter ($PM_{2.5}$: $\leq$2.5 μm in diameter; PM_{10}: $\leq$10 μm in diameter). Several studies reported an association between high levels of air pollution and increased RA risk, although there is less evidence linking specific air pollutants and RA [26–32]. The mechanisms linking air pollution and RA may be explained by the association between air pollutants, including wood-smoke, O_3, and particulate matter and the production of RA-specific autoantibodies [31–36]. Industrial emissions have been linked to elevated ACPA [35]. Conversely, there was no association between PM and RA-related autoantibodies [37]. These conflicting results may be explained by differences in methods of measuring air pollution exposures.

Industrial air emissions have also been linked to increased RA risk [26]. A study investigating the 1952 London Great Smog in London found an association between this early-life exposure to air pollution and subsequent RA risk [26]. Intense dust cloud exposure from the 9/11/01 World Trade Center terrorist attack in the United States was associated with an almost two-fold increased risk of systemic autoimmune diseases, most commonly RA [32]. However, a prospective cohort study found no association between the risk of RA and adult exposure to gaseous pollutants (NO_2 and SO_2) or PM [38]. Two other studies corroborated these null findings [30,39]. The importance of time windows of exposure to air pollution and source of pollutants in relation to RA risk should be a focus for future research.

Several other studies have used proximity to traffic as a marker of air pollution [30,31,39]. Traffic proximity was associated with an increased risk of RA [30,39] and serum C-reactive protein (CRP) level [31]. Socioeconomic status (SES) was found to be an important confounder, with a negative correlation between RA risk and SES [29,33]. Many studies investigating the association between air pollution and RA risk considered markers of SES as confounding factors, including area-level income, education, and ZIP code, but there is likely still unmeasured confounding [26–34,40▪].

INHALANT-RELATED OCCUPATIONS

Several studies have investigated inhalant-related occupations as RA risk factors. Among these studies, some investigated RA risk for occupations as a group compared with a control group not in that occupation [39,41,42,43▪▪,44], while others investigated different exposures within a given type of occupation for RA risk [40▪,45–48]. These occupations fall primarily under the category of manual labor work that are more common for men (Table 2) [45,49]. Individuals in manual labor occupations that involve high levels of repetitive physical strain may induce joint damage that results in higher levels of osteoarthritis and healthcare utilization, both of which may impact the likelihood of receiving a clinical diagnosis of RA [45,46]. These occupations often involve many potential inhalant exposures, making it difficult to identify which factor may be responsible for associations [50].

Farming has been associated with increased RA risk [41,42,46,49–51]. Pesticide use is the most commonly studied exposure among farmers, with recent studies now addressing other tasks and exposures in the farming industry [43▪▪]. Table 2 shows the associations found among regular application of chemical fertilizer, nongasoline solvents, and other cleaning solvents [43▪▪]. Fertilizer use was found to be associated with increased RA risk [44,50], and a statistically significant association for substantial organic solvent use [42]. In contrast, exposure to farm animals was found to be inversely associated with RA risk, though not statistically significant [50], while another study found farm animal dust to be significantly associated with increased RA risk [40▪,47]. Working with Grain and crops also showed an association with increased RA risk, though not statistically significant [44,50]. Age and timing of these inhalant exposures along with accounting for the use of protective gear is warranted for future studies [43▪▪]. Solvents are less studied for RA risk, yet are present in other occupations such as engineering, painting, and simple tasks like cleaning hands [43▪▪].

Another commonly studied inhalant-related occupation for RA risk includes construction workers [49]. Asbestos is a common exposure for construction workers, and some studies suggest an association with RA risk [42,44,48,50]. However, two studies showed no significant association [9,10]. Tasks within construction work such as bricklaying, or material handling operators are significantly associated with increased risk of RA due to exposure to various noxious airborne particles [52]. Among military workers, smoke from burn pits has been associated with RA [53]. One found no association of metal working with RA risk [49], while others suggested increased RA risk but were not statistically significant [42,43▪▪,44]. A significant association was found for scrap recyclers and RA risk [54]. Other dusts such as mineral dust and noxious particles from the coal mining industry/quarry workers have shown to be associated with RA risk [49,55▪▪].

Since women are more likely than men to develop RA, female-predominant occupations have also been studied for RA risk. Within the textile

Table 2. Selected studies associating inhalant-related occupations with risk of rheumatoid arthritis

Reference	Study design	Selected occupations investigated	Effect size (95% confidence interval) for occupation and all RA risk	Postulated occupational inhalants	Comments
Lundberg *et al.* [46]	Retrospective cohort	Farmers Spray painters and lacquer workers Concrete and construction workers	Male: **RR 1.3 (1.0–1.6)** Male: **RR 2.4 (1.1–5.4)** Male: **RR 1.4 (1.1–2.0)**	Organic solvents and other various noxious airborne particles	Analyzed workers exposed to same occupation for 10+ years Also investigated other manual labor jobs Did not adjust for smoking
Olsson *et al.* [48]	Case–control	Farmers Asphalters Textile workers	Male: **OR 1.8 (1.0–3.5)** Male: **OR 14.0 (1.2–16.2)** Male: OR 2.0 (0.3–16.2)	Various noxious airborne particles	Required 20 years from time of work exposure to date of RA diagnosis Adjusted for age and smoking status Also investigated other manual labor occupations
De Roos *et al.* [39]	Nested case–control	Farmers Welders	OR 1.8 (0.6–5.0) OR 1.8 (0.6–5.6)	Pesticides Welding fumes	Adjusted for age and state but not for smoking Investigated types of pesticides used and frequency
Noonan *et al.* [51]	Nested case–control	Military Shipyard worker/ship construction Construction	**OR 2.11 (1.04–4.30)** OR 1.80 (0.72–4.46) OR 1.32 (0.66–2.65)	Asbestos	Evaluated number of exposure pathways Adjusted for smoking history Measures based on self-report
Li *et al.* [40▪]	Retrospective cohort	Farmers Textile workers Miners and quarry workers	Male: **SIR 1.2 (1.1–1.2)**; Female: SIR 1.0 (0.9–1.2) Male: SIR 0.8 (0.6–1.1); Female SIR 0.8 (0.7–1.1) Male: **SIR 1.4 (1.0–1.9)**	Various noxious airborne particles	Analyses were stratified by predominant male and female occupations Adjusted for age, years, region, and education
Jones *et al.* [53]	Prospective cohort	Military	OR 1.17 (0.83–1.64) OR 1.07 (0.77–1.50)	Smoke from open-air burn pits	Adjusted for smoking status, sex, age, and race Investigated several other working-class occupations
Cappelletti *et al.* [54]	Retrospective cohort	Scrap Recyclers	**RR 6.7 (2.00–19.02)**	Particulate matter	Did not adjust for smoking
Ilar A *et al.* [52]	Case–control	Bricklayers/ concrete workers Material handling operators Electrical and electronic workers	**OR 2.9 (1.4–5.7)** **OR 2.4 (1.3–4.4)** **OR 2.1 (1.1–3.8)**	Various noxious airborne particles	Adjusted for smoking pack-years, alcohol, BMI, and education Also investigated other occupations
Parks *et al.* [47]	Prospective cohort	Farming (high chemical fertilizer use) Farming (high nongasoline solvent use) Farming (high other cleaning solvent use)	**HR 1.5 (1.11–2.02)** **HR 1.4 (1.09–1.80)** **HR 1.40 (1.09–1.80)**	Chemical fertilizer Nongasoline solvents Other cleaning solvents	Adjusted for smoking pack-years, state, education, and pesticides Also investigated several other tasks and exposures related to farming
Schmajuk *et al.* [55▪▪]	Case–control	Coal miners	**OR 3.6 (2.1–6.2)**	Coal	Analyzed men from Appalachia (coal mining region) Adjusted for smoking status, ergonomic factors, and race/ethnicity

Statistically significant results are bolded. ACR, American College of Rheumatology; HR, hazard ratio; OR, odds ratio; RA, rheumatoid arthritis; RR, relative risk; SIR, standardized incidence ratio.

industry, women exposed to textile dust were suggested to be at higher risk for developing RA [56], and other studies have reported higher rates of RA in the textile industry overall [44,50].

SILICA

Several studies support the association between silica exposure and increased RA risk (Table 3) [40▪,57–63]. Three large studies found an association between silica exposure and both seropositive and seronegative RA [40▪,57,64▪▪]. The link between silica and seropositive RA was corroborated by two other studies, although they did not find a significant association with seronegative RA [59,60]. Conversely, one study showed a protective effect of silica exposure on risk of RA [65]. However, the study population was small and limited to pottery, sandstone, and refractory materials workers and may have been prone to depletion of susceptibility bias since many of these workers had kept their occupations for decades when assessed for RA risk [65].

Several studies have observed a dose-response effect between silica exposure and increased RA risk [40▪,58,60,61,63]. The risk of developing seropositive RA was particularly high among highly exposed individuals, such as those working in rock drilling [60,61] or stone crushing [58,61,63]. Furthermore, the duration of silica exposure was associated with increased seropositive RA risk [40▪]. This dose–response relationship may explain why the risk of RA was attenuated among women, as women had lower duration and intensity of silica exposure than men [40▪]. Conversely, older men had a particularly increased risk of RA, as they had a higher duration of silica exposure [61].

Several studies have investigated silica-smoking interactions, suggesting higher risk among individuals exposed to both silica and personal cigarette smoking than either exposure alone or neither inhalant exposure [57,59,60,63,64▪▪]. Three studies observed a significant silica-smoking interaction for seropositive RA [59,60,64▪▪].

Several studies have investigated the association between silica exposure and the production of RA-specific autoantibodies, such as rheumatoid factor [66,67]. One study observed a positive relationship between duration of silica exposure and elevation of rheumatoid factor [67]. However, rheumatoid factor was only present in RA patients with silicosis [67]. Another study found no association between silica exposure and rheumatoid factor [66]. However, silica exposure and smoking are highly correlated so it may be difficult to disentangle possible associations with RA.

PESTICIDES

Two studies observed a modest, nonsignificant association of pesticide use and RA [42,51]. Another study found no relation of pesticides with RA in both males and females [50]. Childhood residential exposure to pesticides was associated with RA [68]. The association among different age groups supports the need for further research is needed across the lifespan regarding pesticide exposure and risk for RA [69▪].

Female spouses of pesticide applicators exposed to specific agricultural pesticides were found to have a greater risk for RA [68], and maneb/mancozeb pesticide was newly associated with increased overall risk for RA [68]. The most commonly used pesticide, glyphosate, was only found to be moderately associated with RA [68]. In contrast, another study of female spouses did not find an association between specific classes of pesticides and RA [39]. Among postmenopausal women, a dose response trend for personal application was found [70]. Measured serum levels of dioxin- and nondioxin- like polychlorinated biphenyls were found to be associated with RA among women [41].

A study of male pesticide sprayers and RA risk measured four levels of exposure among several different pesticide classes [71]. They found fonofos, carbaryl, and chlorimuron ethyl to be associated with RA; trends were identified with the use of atrazine and toxaphene [71]. A study of male pesticide sprayers found statistically significant associations with RA perhaps related to pesticide, insecticide, fungicide, organophosphate, guanidine, and quinoe exposures [72]. Several limitations are observed when studying this exposure such as exposure misclassification, timing and frequency of pesticides [68], as well as other unidentified specific exposures [69▪]. Furthermore, quantification of pesticide exposure varied across studies. Some studies classified occupations as exposed or nonexposed [43▪▪,46], while more rigorous exposure assessments also accounted for method of application, duration, quantity, and frequency of pesticide exposure [69▪,70–73].

HOUSEHOLD ENVIRONMENT

Moisture damage to buildings and homes may cause mold and other microbial growth with negative health outcomes [73,74]. Two studies investigated the link between indoor mold and microbial inhalants and RA risk [73,74]. These studies followed for clusters of systemic inflammatory rheumatic diseases in moisture-damaged offices [73,74]. The populations of both studies were mostly women and there were only a few RA outcomes [73,74]. Another

Table 3. Selected studies associating silica inhalants with risk of rheumatoid arthritis

Reference	Study design	Population Sample (*n*) RA outcomes (*n*)	Silica exposure methods	RA outcome methods	Cigarette smoking and other adjustment variables	Effect size (95% confidence interval) for silica and RA risk	Comments
Klockars *et al.* [62]	Retrospective cohort	Central and south western Finland, male granite workers aged 15 to 72 years *n* = 1026 *n* = 35 RA	Dust concentration measured in workplace	1987 ACR criteria	No smoking adjustment Age, residential area	Incidence of disability pensions for RA: **RR 5.08 (3.31–7.79)**	Prevalence of RA and prevalence of patients receiving free medications for RA were significantly higher among granite workers than the general population
Turner *et al.* [65]	Case–control	United Kingdom, pottery, sandstone, and refractory material (aluminosilicate or silica) workers *n* = 290 *n* = 58 RA	Duration of physician-performed occupational history	Physician-diagnosed RA	Smoking status (ever or never) Age, sex, date, occupation, parity, pneumoconiosis	Per 10 years silica exposure and all RA: **OR 0.31 (0.16–0.61)**	Only study suggesting a protective effect of silica for RA risk Also investigated other cumulative silica exposures
Stolt *et al.* [61]	Case–control	Sweden, men aged 18 to 70 years (EIRA Study) *n* = 552 *n* = 276 incident RA	Self-reported exposure to stone dust, rock drilling, or stone crushing	1987 ACR criteria	Smoking status (ever or never) Age, residential area	All RA: **OR 2.2 (1.2–3.9)** RF-positive RA: OR 1.9 (0.9–4.0) RF-negative RA: OR 2.1 (0.8–5.1)	Older men were at particularly increased risk of all RA
Stolt *et al.* [60]	Case–control	Sweden, men aged 18–70 years (EIRA Study) *n* = 1236 *n* = 577 incident RA	Self-reported exposure to stone dust, rock drilling, or stone crushing	1987 ACR criteria	No smoking adjustment Age, residential area	All RA: OR 1.39 (0.98–1.96) ACPA-positive RA: **OR 1.67 (1.13–2.48)** ACPA-negative RA: OR 0.98 (0.57–1.66)	Rock drilling exposure showed particularly high risk of ACPA-positive RA Analyses were also stratified by smoking and shared epitope status Detected statistically significant silica-smoking interaction for ACPA-positive RA
Yahya *et al.* [59]	Case–control	Malaysia, males aged 18–70 years (MyEIRA Study) *n* = 362 *n* = 129 incident RA	Self-reported exposure to stone dust, rock drilling, or stone crushing	1987 ACR criteria	No smoking adjustment Age, sex, residential area	All RA: OR 2.0 (0.9–4.6) ACPA-positive RA: **OR 2.4 (1.0–5.6)** ACPA-negative RA: OR 0.9 (0.2–4.5)	Also stratified by smoking status and investigated silica-smoking interaction All subjects exposed to silica were also smokers
Blanc *et al.* [57]	Retrospective cohort	Sweden, male construction workers aged 30 to 84 years *n* = 240 983 *n* = 713 incident RA	Job-exposure matrices	Billing code	Smoking status (ever or never) Age	**All RA: RR 1.33 (1.11–1.60)** Seropositive RA: **RR 1.28 (1.02–1.61)** Seronegative RA: **RR 1.46 (1.03–2.07)**	Also investigated other organic dusts and risk of autoimmune diseases
Vihlborg *et al.* [58]	Retrospective cohort	Sweden, male iron foundry workers and general Swedish population *n* = 2187 *n* = 18 seropositive RA	Silica dust measurements for job categories (mg/m^3)	Billing code	No smoking adjustment Age, sex, year	Seropositive RA: **SIR 1.70 (1.01–2.69)**	Also investigated sarcoidosis
Ilar *et al.* [50]	Case–control	Sweden, EIRA Study and national registers *n* = 126 534 *n* = 11 285 RA	Job-exposure matrices	2+ visits for RA and DMARD receipt	Smoking pack-years (continuous) Age, sex, county, year, alcohol use	All RA: **OR 1.3 (1.2–1.5)** Seropositive RA: **OR 1.4 (1.2–1.5)** Seronegative RA: **OR 1.2 (1.0–1.4)**	OR for seropositive RA higher with number of years exposed to silica Results attenuated among women

Statistically significant results are bolded. ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; DMARD, disease modifying antirheumatic drug; EIRA, Epidemiological Investigations of Rheumatoid Arthritis; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk; SIR, standardized incidence ratio.

cluster of patients that developed systemic inflammatory rheumatic diseases was studied among a group of 11 workers in a moisture-damaged office, some of which developed seropositive RA [74]. The cases of rheumatic diseases tended to accumulate among participants working closest to the wall with the worst microbial damage [74]. More rigorously designed studies are needed to determine whether household environment inhalants may be related to RA.

ALLERGIC INHALANTS

Allergies and autoimmune disorders like RA may result from hypersensitivity to antigens [75]. Since *HLA* loci are the strongest genetic risk factors for both allergies and RA, some individuals may have common genetics that predispose to both conditions. Some studies found that the presence of allergies and occurrence of autoimmune disorders act as antagonists due to being mediated by either Th1 and Th2 immune responses. However, the literature has conflicting results related to allergies and RA risk. For example, individuals with hay fever may have lower RA risk [76,77]. In contrast, allergies were found to be associated with increased risk of RA [22▪]. Individuals with atopic dermatitis had increased RA risk [78], while a Taiwanese study found significant associations between allergic conditions such as atopic dermatitis or allergic rhinitis and increased RA risk [79]. A Danish prospective cohort study found no statistically significant associations between atopic dermatitis and RA [75]. Another study also found no evidence of an inverse relationship is present between atopic dermatitis and autoimmune disorders [80].

OTHER INHALANTS

While relatively prevalent in the general population, to our knowledge other forms of inhaling tobacco or nicotine using devices like vapes, hookah, and cigars have not been studied in relation to RA risk. Vaping (or e-cigarette use) is a relatively new inhalant method that has also not been studied for RA risk. Prescription and recreational drug inhalants have also not been also studied in relation to RA risk. Investigating the relationship between these inhalant behaviors and risk for developing RA or RA-related autoantibodies would be a promising future research direction.

CONCLUSION

The identification of cigarette smoking as a strong environmental risk factor for RA has helped to elucidate a paradigm for RA pathogenesis related to inhalants and pulmonary mucosal inflammation. This has also led to investigations around other inhalants since many nonsmokers develop RA. Many inhalants have been investigated for RA risk. Inhalant-related occupations and silica inhalants have the most consistent literature suggesting associations with increased RA risk. However, the data supporting these associations rely on mostly retrospective designs with limited ability to account for personal smoking. For example, many miners are also cigarette smokers so it is difficult to establish an independent relationship with RA. Adjusting for smoking status may not sufficiently capture the nuances of smoking intensity and duration that may vary significantly between groups of past or current smokers. Many of the inhalant-related occupations are predominantly male so may not be generalizable to the female majority of RA patients. The literature is relatively conflicted or sparse for other inhalants such as passive cigarette smoking, air pollution, pesticides, household environment, and allergic inhalants for RA risk. Many of these inhalant exposures are relatively difficult to measure and rely either on self-report or geographic location which may introduce error or be difficult to replicate in other studies. Lack of data on personal cigarette smoking in some of these studies may be limiting since smoking likely provides a higher dose of noxious inhalants than the exposures being investigated. The timing of exposure throughout the life course is also challenging to analyze since many of the studies only had a relatively small time window of measurement of these chronic exposures or rely on recall. While inhalants are hypothesized to be specific to seropositive RA, many studies were unable to phenotype RA by serologic status.

Despite these limitations, there have substantial advances in identifying potential inhalants related to RA risk over the past few years. Overall, these results provide further support the hypothesis that inhalants, pulmonary mucosal inflammation, and RA pathogenesis may be linked. Future prospective studies are needed to firmly establish the independence of these findings from personal cigarette smoking and to determine the specific inhalants and biologic mechanisms related to seropositive RA pathogenesis.

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Conflicts of interest

There are no conflicts of interest.

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Preclinical rheumatoid arthritis and rheumatoid arthritis prevention

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Purpose of review
This review is to provide an update on the current understanding of rheumatoid arthritis (RA) development related to disease development prior to the onset clinically apparent synovitis (i.e. Pre-RA), and opportunities for disease prevention.

Recent findings
A growing number of studies have demonstrated that serum elevations of autoantibodies rheumatoid factor, antibodies to citrullinated protein/peptide antigens (ACPAs) and antibodies to other posttranslationally modified proteins (e.g. carbamylated proteins) are highly predictive of future development of inflammatory arthritis/RA during a period that can be termed Pre-RA. Other factors including genetic, environmental, symptoms and imaging findings can also enhance prediction. Moreover, several novel biomarkers and changes in autoantibodies (e.g. glycosylation of variable domains) have been identified in Pre-RA. There has also been growing evidence that initiation and propagation of RA-related autoimmunity during the Pre-RA phase may be related to mucosal processes. The discovery of Pre-RA has also underpinned the development of several clinical prevention trials in RA; specifically, the PRAIRI study demonstrated that a single dose of rituximab can delay the onset of clinically apparent IA in at-risk individuals. Additional studies are evaluating the ability of drugs including abatacept, hydroxychloroquine and methotrexate to prevent or delay future RA.

Summary
The results from ongoing natural history and prevention trials in RA should further inform several critical issues in RA prevention including identification and enrolment of individuals at high-risk of imminent RA, the efficacy, safety and cost-effectiveness of prevention, and potentially the identification of new targets for prevention.

Keywords
antibodies to citrullinated protein antigens, autoantibodies, preclinical, rheumatoid arthritis, rheumatoid arthritis prevention, rheumatoid factor

INTRODUCTION

Advances in therapies, early treatment and treat-to-target strategies have improved outcomes for many individuals with rheumatoid arthritis (RA). However, despite these advances, once the first onset of clinically apparent inflammatory arthritis occurs in RA, even with therapy, most individuals do not return to a predisease state of symptoms [1,2▪]. Additional barriers in care of individuals with RA include delays in diagnosis, difficulties in access to rheumatology specialists and rising costs of drugs [3,4,5▪]. As such, RA is disease that could be benefitted from preventive interventions.

Supporting the possibility of prevention, multiple studies demonstrate a period of development of RA that is characterized by abnormalities of autoantibodies and other biomarkers in absence of and prior to the appearance of clinically identifiable inflammatory arthritis that characterizes RA. This period can be termed 'Pre-RA' [6], and its inclusion in an overall model of RA development is presented in Fig. 1. Importantly, the discovery of Pre-RA has led to the development of several

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KEY POINTS

- Rheumatoid arthritis (RA) develops in stages, with a Pre-RA period that can be identified by circulating biomarkers and other factors in absence of clinically apparent inflammatory arthritis.
- Clinical trials have been completed or are underway designed to identify methods to prevent or delay the future onset of clinically apparent inflammatory arthritis in high-risk individuals.
- A deeper understanding of the natural history of RA development, especially in the Pre-RA stages, may lead to improved prediction models for future RA as well as identification of new targets and approaches for prevention of RA.
- Participation from multiple stakeholders is needed to change the management of RA to a paradigm wherein prevention becomes a routine part of clinical care.

prevention trials in RA that may soon result in a paradigm shift in RA wherein preventive interventions are included in the management of this disease.

Herein, we will review several of these key recent findings in Pre-RA and describe a potential research agenda related to prevention.

OVERVIEW AND ADVANCES IN UNDERSTANDING OF PRE-RHEUMATOID ARTHRITIS

The major autoantibody systems described in Pre-RA have been rheumatoid factor and antibodies to citrullinated protein antigens (ACPAs) [7,8], the most common available version of which is the anti-cyclic citrullinated peptide (CCP) assay [9]. Furthermore, the emerging technologies such as multiplex arrays have identified that there are reactivities to multiple citrullinated antigens prior to the first citrullinated peptides and epitope spreading over time [10,11]. Other autoantibody systems are also abnormal in Pre-RA including antibodies to carbamylated proteins as well as other posttranslationally modified proteins such as acetylated proteins [12,13]. Of note, other autoantibodies such as antibodies to malondialdehyde-acetaldehyde adducts (anti-MAA) have been described in RA [14], but not yet in the Pre-RA period. Furthermore, although alterations during Pre-RA in the glycosylation of the Fc portion of antibodies have been known [15], newer studies have identified glycosylation changes in the variable portions of autoantibodies [16]. Additional biomarkers and processes have also been identified in Pre-RA, including elevations of survivin [17], increases in 14-3-3 eta [18] and alterations of B and T cell subsets [19,20]. Furthermore low levels of omega-3 fatty acids have also been associated with an increased risk of progression to inflammatory arthritis in ACPA-positive individuals [21].

Although Pre-RA can be characterized by initiation and then expansion of autoimmunity inflammation prior to the onset of clinically apparent inflammatory arthritis, to date, the specific initiating and propagating factors in disease development are unknown. However, of particular interest to understanding the initiation and propagation of RA-related autoimmunity in the Pre-RA stage, a transition to clinically apparent inflammatory arthritis, as well as potentially to identify novel targets for treatment and prevention, is understanding the anatomic site of initiation of RA-related autoimmunity in Pre-RA. Importantly, although RA-related autoantibodies may be generated in the joints in individuals with established disease [22], several imaging studies, and one biopsy study, suggest that in most individuals who exhibit circulating RA-related autoantibodies, the joints do not have detectable synovitis [23–25]. If the joints are indeed without inflammation in Pre-RA, two questions can be raised: where are the RA-related autoantibodies being generated and what factors drive propagation and transition to clinically apparent IA?

To address those questions, emerging data suggest that mucosal sites within the lung, oral cavity and gut may contribute to the evolution of RA from Pre-RA to clinically apparent inflammatory arthritis

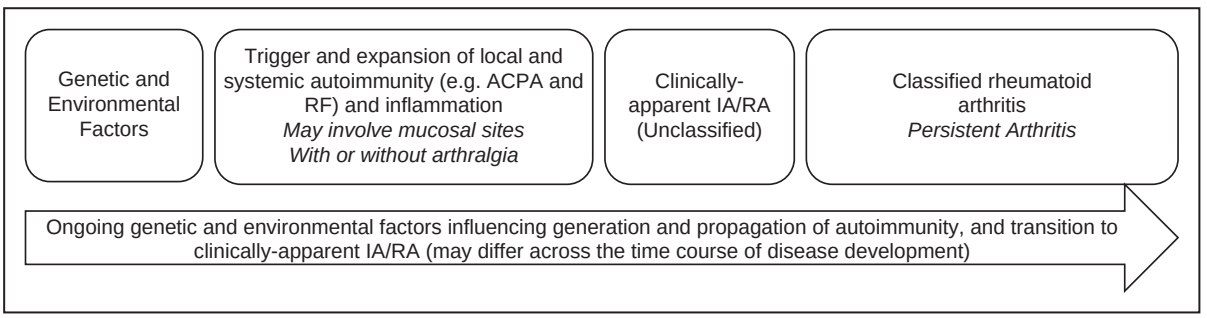

FIGURE 1. Model of rheumatoid arthritis development.

(reviewed in [26▪▪]). Supporting this, there have been findings that ACPA generation in the lung in individuals at-risk for future RA is related to mucosal inflammation and neutrophil extracellular trap formation [27]. Other data suggest that the periodontal region and oral mucosa may play an important role with periodontal inflammation and local citrullination in the initiation of RA autoimmune response [28–30]. ACPA generation with peptidylarginine deiminase types-2 and 4 detection has been shown in the gingival tissue associated with inflammation in individuals without RA [31]. In particular, although data are somewhat conflicting, the periodontal pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been suggested to be associated with the ACPA in patients with RA or in animal models [32,33]. Furthermore, an increased prevalence and severity of periodontal inflammation has been associated with serum ACPA elevations in first-degree relatives of patients with RA [34,35]. In addition, a recent study demonstrated increased prevalence of periodontitis and *P. gingivalis* in ACPA-positive individuals without inflammatory arthritis [36].

Gut mucosa plays an important role on development and maintenance of an individual's immune system as much as the lung and oral cavity. Although the gut mucosa could have a role in disease pathogenesis of RA, the data supporting an association between the gut and autoimmunity in Pre-RA pathogenesis are limited [37]. However, some studies have suggested that gut microbiota may play some role in the early evolution of RA including findings that gut microbiome was altered in RA with early patients compared with controls [37–39]. In particular, *Prevotella copri* was reported to be enriched in untreated early RA patients and an at-risk group [37,40].

Importantly, several recent studies raise the point that mucosal processes may play a role in the transition from Pre-RA to clinically apparent RA. Specifically, Kelmenson *et al.* [41] demonstrated that IgG ACPA was elevated the earliest in Pre-RA, while IgA ACPA increased around the time of transition to clinically apparent RA. Furthermore, Arleevskaya *et al.* [42] identified that the incidence of upper respiratory tract infections was higher in those who developed RA than controls. Finally, Jubair *et al.* [43] noted in a collage-induced murine model of collagen-induced arthritis that antibiotics given after initial triggering of immunity with collagen injection abrogated future arthritis to a greater extent than when antibiotics were given before collagen injection.

In aggregate, these latter studies suggest that mucosal processes may act as cofactors or propagating factors in the development of RA perhaps once systemic autoimmunity has already developed. However, more studies are needed in order understand the exact role that these processes play in RA development, and how ultimately these processes could be identified and targeted for prevention.

PREDICTION OF FUTURE RHEUMATOID ARTHRITIS

There have been multiple retrospective case–control as well as prospective longitudinal studies in which biomarker markers and other factors have been evaluated for their ability to predict the likelihood and timing of future clinically apparent inflammatory arthritis/RA [7,8,44,45] and reviewed in [46▪].

In general, in case–control studies, seropositivity for ACPA and/or rheumatoid factor strongly predicts future development of clinical RA, with positive predictive values (PPVs) typically more than 80%. Furthermore, several prospective studies of ACPA-positive individuals, identified variously through family studies, cohorts of symptomatic outpatients and population screenings, have demonstrated PPVs for development of RA ranging from nearly 20 to more than 70% over 2–5 years of follow-up [21,44,45,47,48]. In these studies, the presence of ACPA, especially in high levels and accompanied by rheumatoid factor positivity, are the most powerful predictors of future RA. However, other features also can improve prediction. These include self-reported joint pain and tenderness on examination, ongoing smoking, obesity and genetic factors such as the shared epitope [21,44,45,46▪,47,48].

In addition, imaging may also improve prediction of the development of future RA. In particular, Rakieh *et al.* [44] found in a study of 100 ACPA-positive individuals, 50 of whom developed inflammatory arthritis/RA, that the presence of a positive power doppler ultrasound finding, even in absence of a joint thought to have synovitis based on physical examination, improved prediction of future RA. These findings raise an important issue about the role of imaging in defining inflammatory arthritis, especially in individuals who may not have clear joint inflammation based a physical examination that has long been the gold standard of diagnosis and management in RA. Indeed, a general consensus that is based on studies demonstrating that in some individuals who exhibit circulating RA-related autoantibodies, that inflammatory arthritis may not be present. However, these findings of a power doppler signal suggest that a subset of

individuals with systemic autoimmunity may indeed have inflamed joints; in addition, other studies have suggested that structures adjacent to the joints such as tendons may be inflamed in ACPA-positive individuals in the absence of clear articular synovitis [49]. But, given that there is growing understanding that imaging, including ultrasound and MRI may identify synovitis even in individuals considered healthy [50,51▪,52], and that there may be high variability in interpretation of images, there will need to be more research done before imaging alone could be used routinely to identify a form of arthritis that warrants treatment, even in absence of traditional clinically apparent inflammatory arthritis by examination.

Importantly, in a study of first-degree relatives of patients with RA from an indigenous population in Canada, Tanner *et al*. found that although some individuals with autoantibody positivity (ACPA and/or rheumatoid factor) progressed to RA, a number of individuals with elevated RA-related autoantibodies did not develop RA during follow-up, and in some cases lost positivity over time [53]. These findings highlight how factors apart from autoantibody positivity contribute to the pathogenesis and prediction of RA. However, Kelmenson *et al*. [41] have demonstrated that clinical RA may still develop in patients how lose autoantibody positivity during Pre-RA. Furthermore, Barra *et al*. [54,55] have demonstrated that approximately 10% of individuals will be seronegative at the time of initial identification of clinically apparent inflammatory arthritis, and then later develop ACPA and/or rheumatoid factor positivity. As such, further studies are needed to understand the biology and predictive value of fluctuating autoantibodies in RA development.

Importantly, history and examination findings alone can may also identify individuals at high risk of developing inflammatory arthritis/RA. Specifically, a 2016 EULAR task force defined a set of high-risk characteristics in individuals with arthralgias but without arthritis, a phenotype termed clinically suspect arthralgia (CSA) [56]. CSA can be assessed by the following: recent onset of symptoms, MCP joint symptoms, symptoms worst in the early morning, morning stiffness more than 60 min, first-degree relative with RA, and on examination, difficulty making a fist and positive MCP 'squeeze test; if three or more of these factors are present, there is nearly 90% sensitivity and 74% specificity that an individual will develop inflammatory arthritis by physical examination. CSA has been validated to some extent in additional work [57]; however, its broad use in identifying individuals at-risk for future inflammatory arthritis needs additional study.

STRONG PREDICTIVE MODELS FOR FUTURE RHEUMATOID ARTHRITIS HAVE LED TO THE DEVELOPMENT OF PREVENTION STUDIES

Building on the predictive ability of autoantibodies, and in particular ACPA, for future RA, over the past several years, multiple trials have been developed to evaluate the potential for pharmacologic intervention to prevent or delay the future onset of RA. Of these, the PRAIRI study (Prevention of clinically manifest RA by B cell directed therapy in the earliest phase of the disease) has recently been published [58▪▪]. In PRAIRI, 81 individuals who were ACPA and rheumatoid factor positive as well as had an elevated C-reactive protein were randomized to receive either a single infusion of either rituximab 1000 mg or placebo (and all individuals received intravenous corticosteroids). At a median follow-up time of 29 months, the rate of development of inflammatory arthritis/RA was not significantly different between groups (34% in treated group vs. 40% in the placebo group). However, the time to development of inflammatory arthritis/RA in 25% of individuals was delayed by nearly 12 months in the rituximab group. More overall adverse events were observed in the rituximab group, but these were deemed not to be treatment-related.

There are several other prevention trials in RA currently underway with estimated completions in the early 2020s. A U.S. placebo-controlled study entitled StopRA (Strategy for the Prevention of Onset of Clinically-Apparent RA) is enrolling individuals with anti-CCP3 positivity at a level at least two times the upper limit of normal, regardless of whether arthralgia is present [59]. The enrolment is planned for 200 individuals, and the intervention is hydroxychloroquine for 1 year. Another placebo-controlled study is entitled APIPPRA (Arthritis Prevention in the Pre-Clinical Phase of RA with Abatacept) and is being conducted in the UK and The Netherlands [60]. Individuals with arthralgia and either an ACPA level at least three times the upper limit of normal or ACPA and rheumatoid factor positivity will be randomized to receive abatacept or a placebo for one year, with follow-up for an additional year after completion of the study drug. Additional studies to prevent or delay future RA are testing statins [61] in autoantibody-positive individuals without inflammatory arthritis, and methotrexate in individuals with arthralgia and 'subclinical' inflammatory arthritis based on imaging [62].

The results from these studies should be highly informative to the field on several fronts, including the feasibility and methodology of identifying autoantibody individuals without inflammatory arthritis through clinics, population-based screening or

otherwise, identifying 'true' rates of progression to inflammatory arthritis/RA in order to refine predictive models and study inclusion criteria, and the efficacy and safety of pharmacologic interventions. In particular, the PRAIRI study noted a delay but not a complete halt to the development of RA, suggesting that longer durations of therapy are needed to adequately prevent the onset of clinically apparent inflammatory arthritis in at-risk individuals. Although a permanent 'reset' of the immune system from a limited intervention would be ideal, even starting continuous therapy earlier may have overall benefit. Such an approach could afford improved quality of life and protection against joint damage.

WHAT ARE NEXT STEPS TO IMPLEMENT PREVENTION IN RHEUMATOID ARTHRITIS?

The clinical trials mentioned above will provide highly useful data related to prediction, efficacy and safety with the agents tested (Table 1). Furthermore, because finding individuals who are in a Pre-RA phase of RA is difficult as they may not present to clinical care, these trials should also develop infrastructure to identify at-risk individuals that can be utilized in future studies. This infrastructure could be similar to networks such as 'TrialNet' that have been built and utilized to support clinical prevention trials in Type 1 Diabetes [63,64]. Proposed infrastructure would include clinics that can refer individuals with autoantibody positivity and lacking inflammatory arthritis to research centres, as well as include screening efforts in higher-risk populations such as first-degree relatives of patients with RA, or more general population screens.

Perhaps most importantly, because these trials will represent the largest cohorts of ACPA-positive individuals yet studied prospectively, it is also hoped that data from the clinical, genetic and environmental exposure assessments performed during these trials, as well mechanistic studies, will inform the next generation of prevention trials. Of particular interest will be validation of prediction models for future RA. This is important in part because current evidence suggests that not all ACPA-positive individuals, even with other high-risk features such as symptoms, will go on to develop inflammatory arthritis/RA at least within studied time periods. Therefore, there is a potential for overtreatment if every ACPA-positive individual is given a preventive intervention. However, risk–benefit calculations will need to take into account several factors including the risk of the preventive intervention. This is because a because a mild intervention such as lifestyle change or relatively benign drug may be acceptable even if risk for future RA is low. In contrast, individuals with very high risk for future RA may be willing to take more powerful agents, although it may also be that they are so far along in the evolution of RA that prevention may be very difficult to attain with only modest interventions. Furthermore, all the agents used in the above-mentioned prevention trials are known to be effective in clinically classified RA; however, it may be that there are new biologic targets for prevention that can be identified through more in-depth study of Pre-RA, and these interventions may be stage-specific. For example, an individual who is earlier in Pre-RA may need to focus on lifestyle changes, or certain biology pathways, while others who are at-risk for more imminent RA may need different biologic pathways targeted. Identifying these potentially new targets

Table 1. Key steps to implementing rheumatoid arthritis prevention

Deep understanding of existing prevention trials to enhance understanding of prediction of future disease, understand efficacy and potentially identify new targets for prevention
Identification of appropriate targets for prevention May include pharmacologic targets, dietary and lifestyle interventions Will need to take into account the genetic, environmental (including micro-organisms) that initiate and propagate RA
Broad agreement on terminology applicable to the natural history of RA
Understanding of individuals' preferences for participating in screening and prevention for RA
Develop highly accurate prediction models for future RA These models can use established and emerging biomarkers and other factors. Will need to estimate overall risk for future RA, as well as timing of future RA so that interventional studies can be designed around specific time intervals and estimates of outcomes of RA
Development of infrastructure to identify individuals at-risk for future RA who are informative in clinical trials that can be leveraged to implement prevention trials in RA (and ultimately other rheumatic diseases)
Engage rheumatology, primary care, healthcare systems (including governmental), public health agencies and industry to support prevention
Ultimately understanding the overall efficacy and cost-effectiveness of RA prevention so that RA prevention can be broadly implemented and have a positive impact on public health

will require close collaborations between academics and industry.

Another important consideration in prevention is individuals' preferences for preventive interventions, that is what will a person be willing to take, and for how long, in order to prevent RA? Several studies have explored this already, and found that much depends on an individual's personal estimation of their risk for RA, their knowledge of RA and what the clinically apparent disease could mean to them, and the safety and potential efficacy of a therapy [65–67]. To date, these studies have been conducted in largely hypothetical situations, but existing trials will hopefully provide insight into what individuals are willing to do to understand their risk for RA, and what steps they are willing to take to prevent disease.

Future trials may be able to target specific lifestyle or dietary interventions for RA prevention [68–70]. As many studies have identified that the Pre-RA presence of smoking and obesity are risks for an individual to transition to future clinically apparent RA, perhaps these factors could be targeted through smoking cessation and weight loss. Incorporating the issue of individuals' preferences for interventions, studies have found that education regarding RA risks may lead to willingness to change [71,72], although the impact of these changes on the long-term development of RA has not yet been studied. A caveat is that lifestyle modifications are difficult to influence; as such, it may be that the dominant studies for RA prevention will be pharmacological, although such studies will need to consider potential additional incorporation of lifestyle measures, especially as individuals may adopt these types of interventions on their own and that could influence trials if done in a nonsystematic fashion.

Clinical prevention trials will also provide a basis to evaluate the real-world cost-effectiveness of preventive therapies. This is a critically important part of prevention, especially in regards to gaining the support of large-scale systems (e.g. governmental and health insurance agencies) for prevention, where a goal may be that all individuals get periodic assessment for personal risk for RA, much like lipids are tested and treated in cardiovascular disease prevention.

There is also a growing understanding that a variety of conditions such as lung disease [26▪▪], heart disease [73] and mental health disorders [74] may precede a formal diagnosis of RA. This is an intriguing area and could indicate that RA-related autoimmunity has pathogenicity on other organ systems apart from the joints in Pre-RA. This area needs further exploration, as it could indicate an 'autoimmune-opathy' associated with RA-related autoantibody elevations that may ultimately warrant intervention, even if inflammatory arthritis is not present.

The rheumatology community needs to buy-in to prevention as well. There has been a tendency for rheumatologists to avoid treatment of individuals with only biomarker abnormalities, in other words 'treat the patient, not the test'. This has been to a large extent due to the lack of specificity for rheumatic disease of some tests such as rheumatoid factor and antinuclear antibodies. However, although avoiding overtreatment is important [75], strong predictive values for future RA using models that include biomarkers and other factors will help overcome barriers to prevention in RA as well as potentially other rheumatic diseases. Indeed, there is a study underway in the United States called SMILE (Study of Anti-Malarials in Incomplete Lupus) to determine if hydroxychloroquine can halt or delay the progression from incomplete lupus to classifiable disease [76]. Findings from the prevention studies in RA and SLE may help change the paradigm of these diseases as well as other rheumatic/autoimmune diseases that follow a similar mode of development.

CONCLUSION

The understanding of Pre-RA development is growing, and prediction of future RA is improving. On the basis of strong predictive power of autoantibodies, and in particular ACPA, several prevention trials have been completed or are ongoing in RA. The information from the published PRAIRI is intriguing, and additional information from the ongoing clinical trials for prevention, as well as other natural history studies may soon move the field forward to where prevention is routinely implemented in clinical care of RA.

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Conflicts of interest

K.D.D. has served as a consultant for Microdrop LLC, Bristol-Myers Squibb, Inova Diagnostics, ThermoFisher and Janssen Research and Development. There are no conflicts of interest for the remaining authors.

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Skeletal muscle disease in rheumatoid arthritis: the center of cardiometabolic comorbidities?

Brian J. Andonian and Kim M. Huffman

Purpose of review
Despite its critical roles in body movement, structure, and metabolism, skeletal muscle remains underappreciated in the context of rheumatoid arthritis. In rheumatoid arthritis, chronic inflammation, physical inactivity, and medication toxicities impair skeletal muscle. These skeletal muscle alterations contribute to continued rheumatoid arthritis disparities in physical function and cardiometabolic health.

Recent findings
In the prebiologic disease-modifying antirheumatic drug era, rheumatoid arthritis skeletal muscle atrophy was the central feature of 'rheumatoid cachexia,' a hypermetabolic state driven by chronic systemic inflammation and muscle protein degradation. In the current era, rheumatoid arthritis muscle deficits are less visible, yet persist as a key component of 'sarcopenic obesity.' In rheumatoid arthritis sarcopenic obesity, chronic inflammation, physical inactivity, and medication toxicities contribute to muscle contractile deficits, inflammation, altered metabolism, and intramuscular adiposity, a key predictor of rheumatoid arthritis disability and insulin resistance.

Summary
Rheumatoid arthritis skeletal muscle disease in the current era is defined by impaired contractile function (poor strength and endurance) and sarcopenic obesity (decreased muscle mass, increased fat mass, and intramuscular adiposity). These muscle impairments contribute to disability and cardiometabolic disease in rheumatoid arthritis. Management should focus on monitoring of rheumatoid arthritis muscle function and body composition, limiting potentially myotoxic drugs, and prescription of exercise training.

Keywords
cardiometabolic disease, disability, rheumatoid arthritis, sarcopenic obesity, skeletal muscle

INTRODUCTION

Rheumatoid arthritis is an autoimmune and inflammatory disease characterized by polyarticular synovial inflammation. Although synovial inflammation is the hallmark of disease, rheumatoid arthritis autoimmunity and disease begin many years prior to clinically detectable arthritis and impact nearly every organ system [1,2]. As a result of the insidious pathogenesis of rheumatoid arthritis, even in the current era of widespread biologic disease-modifying antirheumatic drug (bDMARD) use, persons with rheumatoid arthritis are still at high risk for disability, cardiometabolic disease, and early mortality [3▪,4–7]. These comorbidities share a central feature of rheumatoid arthritis impairments in an underappreciated and vitally important organ, skeletal muscle.

Skeletal muscle constitutes more than one-third of the body's mass, functions to maintain the body's structural integrity, and provides voluntary contractile function as the basis of movement. Skeletal muscle metabolism is critical for generating energy for movement as well as whole-body homeostasis. Skeletal muscle dysfunction can manifest in a number of ways from weakness and an inability to move to altered metabolism and insulin resistance. Additionally, impaired skeletal muscle size, structure, and cellular function are hallmarks of cardiometabolic and chronic diseases of aging [8–11]. Despite rheumatoid arthritis classification as a systemic disease [2], rheumatoid arthritis skeletal muscle alterations and subsequent consequences are often overlooked.

Rheumatoid arthritis skeletal muscle disease is marked by inflammation, adiposity, reduced strength (dynapenia), and mass (sarcopenia) as well

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KEY POINTS

- The hypermetabolic state of rheumatoid cachexia that defined pre-bDMARD era rheumatoid arthritis skeletal muscle disease has been largely replaced by a more hypometabolic state of decreased skeletal muscle mass, increased fat mass, and intramuscular adiposity (sarcopenic obesity), in close association with physical inactivity, insulin resistance, lipid abnormalities, and cardiovascular disease risk.
- Skeletal muscle weakness and dysfunction are common in rheumatoid arthritis skeletal muscle disease; however, overlap inflammatory myopathy with immune cell infiltration is rare.
- The molecular phenotype of rheumatoid arthritis skeletal muscle disease involves alterations in muscle inflammatory cytokines, oxidative metabolism, and satellite cell remodeling pathways.
- Corticosteroids directly impair rheumatoid arthritis muscle protein synthesis and function, whereas NSAID, antimalarial, statin, and TNF inhibitor medications may contribute to a lesser extent to rheumatoid arthritis skeletal muscle disease.
- Combined resistance and aerobic exercise training is the most evidence-based therapy for the management of rheumatoid arthritis skeletal muscle and associated cardiometabolic disease.

as impaired endurance/oxidative metabolism [12,13▪▪,14▪▪,15,16]. This rheumatoid arthritis skeletal muscle profile strikingly resembles an early aging phenotype [17] and persists even with the relatively recent advent of potent bDMARDs. The persistence of this phenotype along with its implication in the continued elevated rates of rheumatoid arthritis disability, cardiometabolic disease, and early mortality [3▪,4–7] suggest rheumatoid arthritis skeletal muscle deserves more attention within the current broader research agenda aiming to improve both rheumatoid arthritis cardiovascular and overall health. In this review, we describe the rheumatoid arthritis skeletal muscle phenotype defined by pre-bDMARD treatment era (prior to the year 2000) studies and then incorporate newer work (current DMARD era) to refine rheumatoid arthritis muscle disease. Pre-bDMARD era data are critical to understanding disease in the absence of most medications; unfortunately, these remain relevant for and manifest in persons with poor access, contraindications, and noncompliance to pharmacologic treatment. Investigations that are more recent highlight the complexities of rheumatoid arthritis disease, numerous medications, and widespread physical inactivity. Given the key role of muscle in cardiometabolic risk, we focus on the interrelationships between rheumatoid arthritis skeletal muscle and cardiometabolic disease. We will also discuss the impact of rheumatoid arthritis pharmacotherapies and propose management strategies, with particular focus on the benefits of exercise training, to improve rheumatoid arthritis skeletal muscle function and overall health.

SKELETAL MUSCLE DYSFUNCTION IN RHEUMATOID ARTHRITIS

Despite its relatively low prevalence, rheumatoid arthritis is one of the most common and costly causes of physical impairment and disability [18]. Rheumatoid arthritis disability is multifactorial, stemming from inflammation driving fatigue, joint swelling, and damage leading to pain, all culminating in physical inactivity and poor aerobic capacity [16,19]. One key factor driving disability is impaired skeletal muscle, resulting from combinations of systemic inflammation, inactivity, and medication toxicity. The relative contributions of each is difficult to ascertain but a direct effect of inflammation is implicated by the presence of dynapenia and skeletal muscle deficits early in disease; consequences which are independent of corticosteroid use and loss of muscle mass [20,21]. Nonetheless, at all stages of rheumatoid arthritis disease activity and duration, muscle deficits persist, with muscle strength and endurance deficits impacting performance of functional tasks, such as walking up and down stairs [22].

Although inflammation is an important driver of rheumatoid arthritis skeletal muscle disease, frank immune cell infiltrate into rheumatoid arthritis muscle is rare. The cooccurrence of an inflammatory myopathy (i.e., dermatomyositis or polymyositis) and rheumatoid arthritis has long been described; however, the so-called entity rheumatoid myositis remains to be well characterized [23,24]. The incidence of a classic inflammatory myopathy presenting in rheumatoid arthritis is very low, ranging widely from less than 0.1% to as high as 8% [25,26]. Further complicating these epidemiologic issues, 'rheumatoid myositis' is also likely susceptible to diagnostic misclassification (i.e., rheumatoid arthritis diagnosis instead of antisynthetase syndrome). The clinical presentation of this rheumatoid arthritis–myositis overlap syndrome is a progressive, symmetric proximal muscle weakness in association with elevated erythrocyte sedimentation rate and creatine kinase level [24,25]. Skeletal muscle histology in these cases shows predominately T and B-cell perivascular and endomysial infiltrates, as well as muscle fiber atrophy and degeneration [25]. A medium vessel vasculitis

is another cause of symptomatic myopathy in rheumatoid arthritis [26], though this phenomenon is rare in the current DMARD era.

Even in the absence of immune cell infiltration, inflammation still contributes to rheumatoid arthritis skeletal muscle dysfunction [27]. For example, rheumatoid arthritis patients with extraarticular manifestations, typically associated with very active disease, have increased skeletal muscle endothelial cell expression of human leukocyte antigen DQ (HLA-DQ) and interleukin-1 [28]. Rheumatoid arthritis skeletal muscle also has increased concentrations of interleukin-6 when compared with age, sex, race, and BMI-matched controls [12]. In addition, muscle interleukin-1β and interleukin-8 associate strongly with rheumatoid arthritis disease activity, whereas muscle interleukin-1β and interleukin-6 associate with physical inactivity and disability [12].

As compared with these predominant molecular abnormalities in the current DMARD era, pre-bDMARD era rheumatoid arthritis muscle histopathology shows significant muscle fiber alterations. Pre-bDMARD rheumatoid arthritis muscle fibers are smaller, especially type II (fast twitch/white/glycolytic) fibers [26,29]. As compared with osteoarthritis muscle, pre-bDMARD rheumatoid arthritis muscle also has a lower ratio of type I (slow twitch/red/oxidative) to type II fibers [30,31]. In contrast, in the current DMARD era, rheumatoid arthritis muscle fiber-type alterations are not evident, strongly implicating the untreated rheumatoid arthritis disease process and high amounts of inflammation in those pre-bDMARD era muscle fiber changes [32,33▪▪]. In current DMARD era rheumatoid arthritis, fiber-type alterations are lacking but muscle bundles show regenerative features of myonuclei and differentiated satellite cells, hypothetically, compensating for chronic systemic inflammation at lower levels than in the pre-bDMARD era [33▪▪]. Typically, satellite cell differentiation and proliferation are balanced, however, current DMARD era rheumatoid arthritis muscle programs promote satellite cell differentiation at the expense of proliferation; inflammatory pathways are upregulated in concert with profibrotic pathways; and glycolysis is favored in a setting of inefficient oxidative metabolism [12]. Further, current DMARD era rheumatoid arthritis muscle impairments extend to exercise training adaptations, in particular training-induced responses in cytokine pathways critical for muscle remodeling and growth [34▪]. Ultimately, these studies have just begun to unravel the complex molecular mechanisms underpinning muscle dysfunction in rheumatoid arthritis, and further work needs to be done.

RHEUMATOID CACHEXIA AND ALTERED BODY COMPOSITION

Rheumatoid cachexia was first described by Roubenoff *et al.* [35] in a 1994 landmark study as reduced body cell mass accompanied by a chronic systemic inflammation-driven, hypermetabolic state. The systemic inflammation includes elevated circulating concentrations of tumor necrosis factor-α (TNF) and interleukin-1β [35]. Notably, the rheumatoid cachexia hypermetabolic state coexists with reduced physical activity. Together, inflammation, hypermetabolism, and physical inactivity led to increased muscle protein breakdown, often compounded by reductions in muscle synthesis with chronic corticosteroid use, and gross muscle atrophy [36].

In the current DMARD era, low muscle mass, or sarcopenia, persists in the setting of high rheumatoid arthritis disease activity and systemic inflammation and strongly predicts physical function impairment [14▪▪,15,37]. However, more commonly in current DMARD era rheumatoid arthritis, functional impairments occur when sarcopenia coexists with excessive body fat mass and intramuscular fat accumulation [14▪▪,38]. This accumulation of fat, within muscle as well as surrounding muscle (intra and intermuscular adiposity), is correlated with disease activity and likens rheumatoid arthritis muscle to that of individuals 15 years older [39▪▪,40▪]. These recent findings suggest that the pre-bDMARD era defined hypermetabolic, generalized wasting state of classic rheumatoid cachexia has transitioned to a state of sarcopenic obesity and an early aging phenotype of rheumatoid arthritis skeletal muscle disease.

Obesity, with or without sarcopenia, is strongly linked to many chronic diseases in the general population, including cardiovascular disease (CVD) [41]. In rheumatoid arthritis, obesity is associated with disease development, increased inflammatory disease activity, and decreased response to conventional and bDMARD drug use [42–44]. Counterintuitively, epidemiologic studies have questioned if obesity is actually protective of rheumatoid arthritis CVD and all-cause mortality in what is referred to as the 'obesity paradox' [45▪▪]. The seemingly paradoxical relationship of obesity to CVD, which is also seen in multiple of other chronic disease states including cancer, is now appreciated as a semantic and measurement related phenomenon. The driving factors for this issue are multifactorial, including multiple sources of confounding, such as unintentional weight loss associated with severe chronic diseases and because BMI is a poor measure of adiposity [46]. Further, BMI is unable to account for the disproportionate reductions of muscle mass in rheumatoid arthritis described above. For example, in a

cohort of 141 persons with rheumatoid arthritis, BMI classified as obese 20% of women and 41% of men whereas, dual X-ray absorptiometry (DXA)-based obesity rates were 44% for women and 80% for men [47]. Remarkably, DXA classifies 50% of persons with rheumatoid arthritis as having sarcopenia, defined by a fat-free mass index below the 10th percentile [48]. Thus, sarcopenia, as opposed to a lack of obesity, is one explanation for why low BMI and weight loss are strong predictors of increased cardiovascular mortality in rheumatoid arthritis [45▪▪].

SKELETAL MUSCLE AND CARDIOVASCULAR DISEASE RISK IN RHEUMATOID ARTHRITIS

Though incident rheumatoid arthritis CVD and mortality appear to be gradually declining [49,50], CVD in rheumatoid arthritis remains significantly elevated when compared with the general population [51▪]. These epidemiologic findings highlight the need for an improved understanding of the mechanisms leading to rheumatoid arthritis cardiometabolic risk and management strategies to reduce this risk. In the general population, CVD risk is inversely related to skeletal muscle mass [52▪]. Similarly, in rheumatoid arthritis, CVD risk factors have bidirectional interactions with skeletal muscle (i.e., physical inactivity exacerbates rheumatoid arthritis muscle disease, whereas rheumatoid arthritis muscle disease contributes to physical inactivity), yet relatively little attention has focused on the association of rheumatoid arthritis CVD and rheumatoid arthritis skeletal muscle disease (Fig. 1).

Rheumatoid arthritis CVD risk can be subcategorized into 'traditional' and 'rheumatoid arthritis-specific' CVD risk factors. 'Traditional' CVD risk factors include physical inactivity, chronic tobacco use, excess adiposity, and type 2 diabetes mellitus/insulin resistance. Physical inactivity as well as low cardiorespiratory fitness consistently predict CVD and mortality in persons without [53,54] and with rheumatoid arthritis [55,56]. Further, exercise training concurrently improves rheumatoid arthritis cardiorespiratory fitness, skeletal muscle dysfunction, and overall CVD risk [57–60]. Another traditional CVD risk factor, chronic tobacco use [61], both worsens rheumatoid arthritis pathogenesis and exerts significant negative impacts on skeletal muscle [62,63].

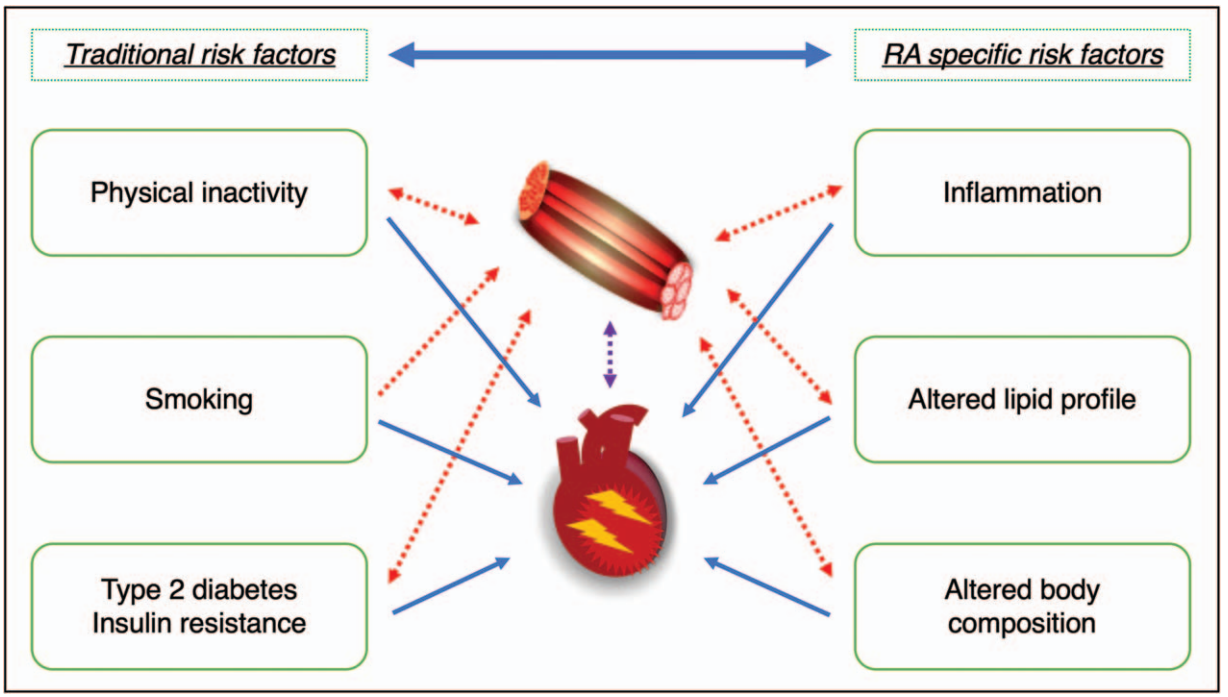

FIGURE 1. Skeletal muscle and cardiometabolic disease in rheumatoid arthritis: Risk factors for cardiovascular disease (CVD) include 'traditional' and 'rheumatoid arthritis specific' subgroups, where 'rheumatoid arthritis specific' risks are due high levels of chronic inflammation. The large two-sided arrow denotes the significant overlap and association between CVD risk factor subgroups. The smaller undashed arrows denote direct effects of risk factors contributing to rheumatoid arthritis CVD. The small dashed arrows denote multidirectional interactions between skeletal muscle disease, CVD, and CVD risk factors in rheumatoid arthritis.

Skeletal muscle is critical for understanding insulin resistance in the fed state, as muscle is the primary organ responsible for glucose uptake after a meal and impaired muscle glucose metabolism contributes to the pathogenesis of type II diabetes. The CVD risks of impaired glucose tolerance and skeletal muscle insulin resistance occur frequently in rheumatoid arthritis [64], particularly in those using chronic prednisone [65]. Rheumatoid arthritis skeletal muscle insulin resistance associates strongly with inflammatory markers [66], which disrupt pathways for insulin-stimulated glucose uptake [67]. However, intramuscular adiposity, rather than inflammation, may play a larger role in insulin resistance for established, longstanding disease [65].

'Rheumatoid arthritis-specific' CVD risk factors are largely driven by disease-associated chronic inflammation. Although systemic inflammation is increasingly appreciated as a strong risk factor for the development of CVD [68], it is unclear whether the effects of inflammation on skeletal muscle and body composition – discussed above – are a direct mediator of rheumatoid arthritis CVD risk. Indirectly, inflammation leads to use of rheumatoid arthritis medications such as corticosteroids that contribute to the sarcopenic obesity phenotype and increased CVD risk. Another unique rheumatoid arthritis-specific CVD risk is dyslipidemia where contrary to the association seen in the general population, low concentrations of total and low-density lipoprotein-cholesterol (LDL) confer greater CVD risk in rheumatoid arthritis [69,70,71▪]. This paradox results from inflammation inhibiting reverse cholesterol transport [72] and increasing macrophage lipid accumulation [73], leading to characteristic alterations in lipoprotein particle size [74]. Interestingly, independent from relationships with systemic inflammation, the rheumatoid arthritis lipid profile is associated with physical inactivity [75]. These findings suggest that management of lipid abnormalities and CVD risk in rheumatoid arthritis may require interventions to improve both inflammation and skeletal muscle function.

IMPACT OF RHEUMATOID ARTHRITIS MEDICATIONS ON SKELETAL MUSCLE AND CARDIOMETABOLIC DISEASE

Rheumatoid arthritis sarcopenia has strong associations not only with chronic inflammation but also with pharmacotherapies, especially glucocorticoids [30,76]. However, the exact pathways connecting rheumatoid arthritis medications with muscle function, body composition, and cardiometabolic risk remain unclear (Table 1). Glucocorticoids have profound effects on skeletal muscle, including promoting muscle atrophy and reducing muscle strength [77,78]. These untoward glucocorticoid effects on muscle occur early and are perpetuated with prolonged use [78,79▪]. Glucocorticoids impair the anabolic effects of insulin, preventing muscle protein synthesis via multiple mechanisms centered on inhibition of the mammalian target of rapamycin [80]. In combination with inflammatory cytokines, glucocorticoids increase proteolysis via upregulation of the ubiquitin–proteasome pathway [81]. Additionally, glucocorticoids, particularly at dose equivalents of prednisone 7.5 mg daily or greater, appear to potentiate cardiovascular disease risk [82]. Still, there remains question whether circadian rhythm-based or intermittent corticosteroid dosing, as opposed to usual continuous daily dosing, incur the same untoward effects of corticosteroids on rheumatoid arthritis skeletal muscle.

The skeletal muscle effects of other rheumatoid arthritis medications are less clear and thus deserve further study. For example, although nonsteroidal antiinflammatory drugs (NSAIDs) may improve skeletal muscle remodeling following injury with short-term use [83], the skeletal muscle effects of long-term NSAID use are mixed [84,85]. NSAIDs impair muscle satellite cell function important for muscle growth [84]; however, they also may improve muscle capillarization and mitochondrial protein activity following exercise training [85]. Importantly, there is growing evidence supporting NSAID use as a risk factor for myocardial infarction [86], and thus further critical study assessing NSAID

Table 1. Influence of medications and exercise training on rheumatoid cachexia and cardiovascular disease risk

	Corticosteroids	NSAIDs	Antimalarials	Methotrexate	TNFi	IL-6i/JAKi	Statins	Exercise
Skeletal muscle function	↓	↔	↓	↔	↔	↔	↓	↑[a]
Skeletal muscle mass	↓	↔	↔	↔	↔	↑[a]	↔	↑[a]
Fat mass	↑	↔	↔	↔	↑	↔	↔	↓[a]
CVD risk	↑	↑	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]

Up ↑ and down ↓ arrows signify positive and negative associations, respectively, based on current evidence. Horizontal ↔ arrows signify no apparent association, based on current evidence. CVD, cardiovascular disease; IL-6i, interleukin 6 inhibitors; JAKi, Janus kinase inhibitors; NSAIDs, nonsteroidal antiinflammatory drugs; TNFi, tumor necrosis factor inhibitors.
[a]Signifies an advantageous effect on skeletal muscle and CVD risk.

effects on rheumatoid arthritis muscle and CVD is warranted.

Hydroxychloroquine and other antimalarial medications are known inhibitors of autophagy, a critical cellular homeostatic process. Excessive cumulative doses of antimalarials lead to deposits within skeletal and cardiac muscle, with histopathology showing a vacuolar myopathy with curvilinear bodies [87]. The clinical presentation of antimalarial myopathy is often nonspecific, with mild muscle weakness and normal creatine kinase (CK) levels, and therefore myotoxicity from is potentially underdiagnosed [88,89]. Although there is a potential for myotoxicity, hydroxychloroquine use may still improve CVD risk in rheumatoid arthritis, though data in this regard are limited [90]. The effect of hydroxychloroquine on managing sarcopenic obesity is unknown. Methotrexate may also improve CVD risk in rheumatoid arthritis [91]; however, there doesn't seem to be any methotrexate benefit for rheumatoid arthritis skeletal muscle disease [92].

Similarly, observational studies suggest that TNF inhibitors (TNFi) improve rheumatoid arthritis CVD risk, though there remain questions regarding the cardiometabolic effects of TNFi [93]. For example, TNFi in rheumatoid arthritis is associated with an increase in android fat mass and potentially a decrease in lean muscle mass following their initiation [94]. Additionally, in a small rheumatoid arthritis cohort completing 10 weeks of high-intensity interval training, no patient taking TNFi achieved body composition improvements following the intervention [34▪]. In comparison, rheumatoid arthritis management with interleukin-6/Janus kinase/signal transducer activator of transcription (JAK-STAT) inhibition has beneficial effects on improving rheumatoid arthritis lean mass [95] and lipid profiles [96]. Interleukin-6/JAK-STAT inhibition is also reported to improve CVD risk in rheumatoid arthritis [97,98]. Interestingly, improvements in visceral adiposity following exercise training are interleukin-6 dependent in nonrheumatoid arthritis participants [99▪], and thus the influence of interleukin-6 inhibition on rheumatoid arthritis fat metabolism necessitates ongoing study.

Interleukin-1β inhibition is also worth briefly noting, even though modulation of this pathway has limited efficacy for rheumatoid arthritis management, as the antiinterleukin-1β monoclonal antibody canukinumab decreases recurrent CVD events in nonrheumatoid arthritis populations [100]. This finding highlights the potential for novel anticytokine therapies to improve skeletal muscle and cardiometabolic disease in rheumatoid arthritis through mechanisms unrelated to rheumatoid arthritis disease control.

Statins also deserve specific mention here given their antiinflammatory properties and widespread use in reducing CVD risk [101]. In rheumatoid arthritis, statins likely improve CVD risk similar to the general population, but this benefit has yet to be conclusively shown [102▪]. Statin-induced myopathy is a relatively common adverse effect, whereas statin-related muscle functional deficits occur *in vitro* and may be underrecognized clinically [88,103▪]. The specific impact of statins on rheumatoid arthritis muscle is unclear [104].

IMPROVING SKELETAL MUSCLE HEALTH IN RHEUMATOID ARTHRITIS

Management of skeletal muscle health in rheumatoid arthritis requires initial assessment and monitoring, and both pharmacologic and lifestyle interventions. In Fig. 2, we outline a proposed management flowchart for improving rheumatoid arthritis muscle health, and, consequently disability and CVD risks. Although rheumatoid arthritis skeletal muscle impacts on outcomes and costs need better definition, ideally, new rheumatoid arthritis patients should undergo baseline assessments of body composition [105] and muscle function [106] with periodic reassessment. Fortunately, the general rheumatoid arthritis treatment strategy of targeting treatment to remission promotes muscle health by minimizing harmful effects of inflammation on skeletal muscle. Another focus of medication management should be to limit potentially myotoxic drugs and minimize physical inactivity. Thereafter, perhaps the most effective and well-tolerated therapy, even in the setting of active inflammatory disease and previous joint damage, for rheumatoid arthritis muscle disease is exercise training. Strength or resistance training increases rheumatoid arthritis muscle strength and mass, and reduces fat mass, disability, and disease activity without worsening joint damage [58,59,107–109]. Endurance or aerobic training, combined with or without strength training, further improves body composition, muscle endurance, disease activity, and CVD risk profiles in rheumatoid arthritis [57,60,110,111▪]. Of note, the beneficial effects of exercise training on rheumatoid arthritis muscle function and fat mass reduction persist for several years; however, increases in lean mass wane with resumption of prior inactivity [112,113]. Thus, lifelong physical activity is critical for rheumatoid arthritis skeletal muscle and overall health, as advocated by the recent The European League Against Rheumatism (EULAR) recommendations, and more in-depth study on the mode, intensity, frequency, and duration of exercise training for rheumatoid arthritis is needed [114▪].

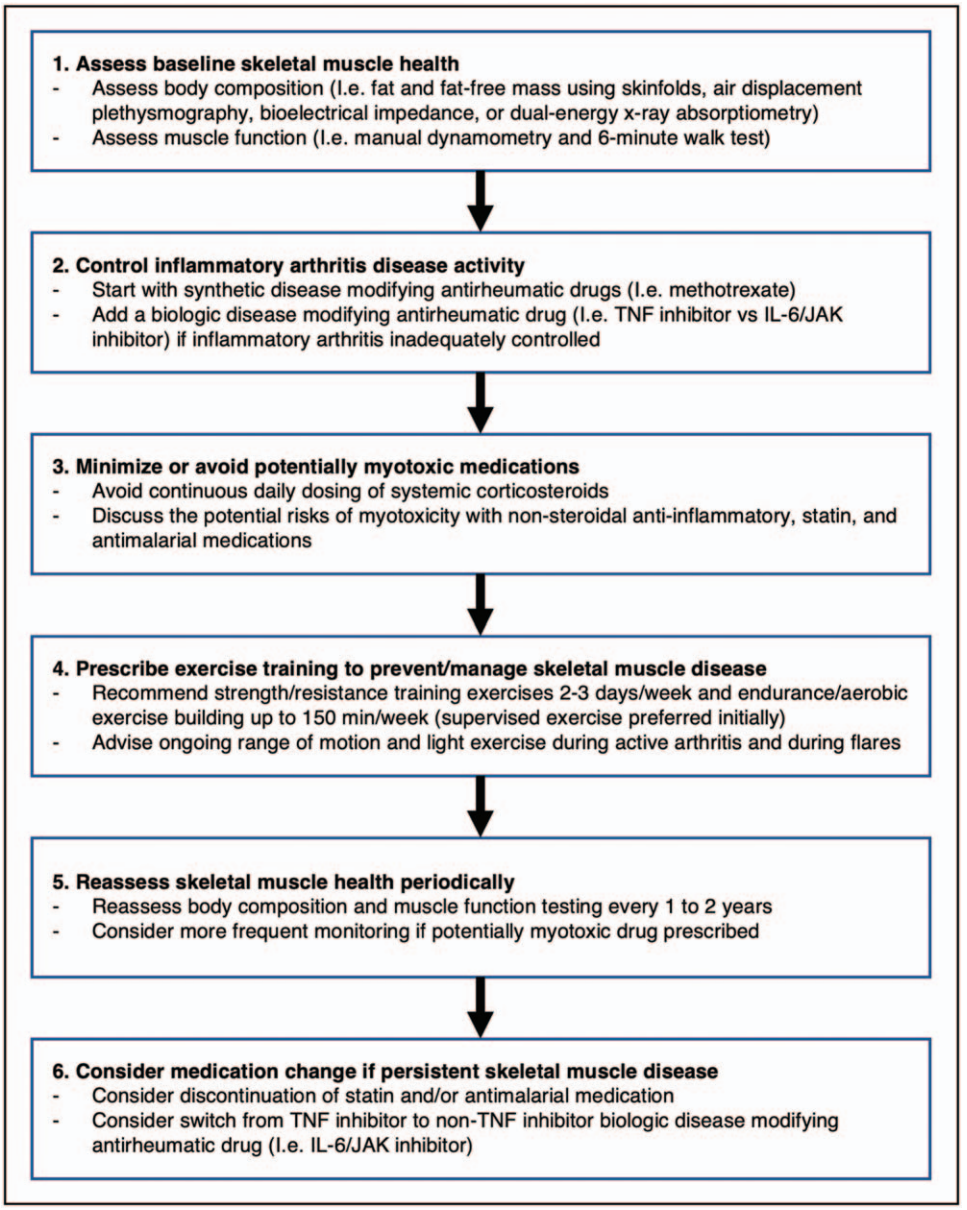

FIGURE 2. Flowchart for the management of skeletal muscle disease in rheumatoid arthritis. *Source*: Original.

CONCLUSION

Rheumatoid arthritis skeletal muscle disease constitutes impairments in both muscle function and mass in close relationship with inflammation, adiposity, insulin resistance, lipid abnormalities, and cardiovascular disease. Rheumatoid arthritis medications may alternatively worsen or improve rheumatoid arthritis skeletal muscle disease; however, our current understanding of the complex molecular interplay of antiinflammatory pharmacotherapy, muscle health, and systemic metabolism is limited. Although we expect knowledge of rheumatoid arthritis skeletal muscle disease to evolve, we encourage rheumatologists and allied practitioners to not ignore rheumatoid arthritis skeletal muscle given its close ties to CVD risk and overall health. We recommend that future studies prioritize longitudinal evaluation of rheumatoid arthritis muscle health, rheumatoid arthritis pharmacotherapy effects on skeletal muscle, and the use of lifestyle interventions to combat rheumatoid arthritis skeletal muscle disease and its coexisting cardiometabolic comorbidities.

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Conflicts of interest

There are no conflicts of interest.

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

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Benefits and promotion of physical activity in rheumatoid arthritis

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Purpose of review
The aim of this article is to describe the benefits of physical activity and exercise on rheumatoid arthritis disease activity, functioning, and symptoms; and offer recommendations for promotion of physical activity and exercise among people with rheumatoid arthritis.

Recent findings
In addition to well-known benefits of exercise such as improving cardiovascular health and metabolic syndrome and reducing obesity, exercise has consistently shown rheumatoid arthritis-specific benefits. Exercise and increases in physical activity improve clinically measured disease activity, reduce symptoms such as fatigue and pain, and improve function and mental health. In spite of these benefits, most people with rheumatoid arthritis are inactive. Patient barriers to engaging in physical activity may include fears of joint damage, rheumatoid arthritis symptoms, and lack of understanding that physical activity improves the symptoms that may be barriers. However, the greatest barrier to healthy levels of physical activity among individuals with rheumatoid arthritis appears to be the lack of direction from healthcare providers.

Summary
Exercise is safe and highly beneficial for people with rheumatoid arthritis. Because receiving recommendations from healthcare providers may be the factor most strongly associated with engaging in physical activity or exercise, providers are encouraged to give patients positive messages about the benefits of physical activity and the extremely low risks of harm.

Keywords
exercise, physical activity, rheumatoid arthritis, sedentary

INTRODUCTION

Although exercise was once thought to exacerbate inflammation and disease activity, it is now recognized as safe and is recommended for people with rheumatoid arthritis [1,2▪▪]. Exercise and physical activity have well-documented effects on improving rheumatoid arthritis aerobic capacity, obesity, metabolic syndrome, cancer risk, and cardiovascular disease morbidity and mortality [3▪▪,4,5▪,6▪]; we will not cover those effects. Instead, this chapter outlines the benefits of physical activity and exercise on rheumatoid arthritis disease activity, functioning, and symptoms and offers recommendations for promotion of physical activity and exercise among people with rheumatoid arthritis. Figure 1 provides an overview of the harms of physical inactivity and sedentary behavior contrasted with the profound benefits of physical activity and exercise in rheumatoid arthritis.

TERMINOLOGY: EXERCISE, PHYSICAL ACTIVITY, PHYSICAL INACTIVITY, AND SEDENTARY TIME

Most physical activity interventions in rheumatology have used structured *exercise* programs. These programs have varied in content (e.g., aerobic conditioning, resistance exercise, stretching), level of supervision (e.g., group setting or unsupervised), location (e.g., community center, gym, home-based), intensity (low, moderate, or vigorous activity),

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KEY POINTS

- Exercise is safe for persons with rheumatoid arthritis.
- Exercise and physical activity have rheumatoid arthritis-specific benefits such as improvements in disease activity, reductions in fatigue and pain, and improvements in function and mental health.
- In spite of the benefits, most people with rheumatoid arthritis are inactive.
- The greatest barrier for patients to engaging in physical activity and exercise may be the lack of specific instructions from healthcare providers.

frequency (number of sessions per week), and duration (length of sessions and length of program) but have in common that the programs were defined. More recently, less structured programs have been developed with the intent of increasing *physical activity*. These programs often focus on walking.

Until recently, observational and epidemiologic studies of physical activity have relied on self-report. Although there are a number of validated and widely used self-report measures, there is a general tendency for people to overreport their activity and exercise time, which has led to increasing use of accelerometers or other activity monitoring devices. These devices can provide data on the amount of activity and METs or kilocalories expended and often have other features. [MET refers to ''metabolic equivalent of task'' and is used to express the energy cost of physical activities. One MET is considered the energy required for quiet sitting. Sample values: sleeping (0.9 MET), walking at 2.5 mph (2.9 MET), pushing a stroller (4.0 MET), running at 6 mph (9.8 MET), jumping rope (12.3 MET). These are average values; actual METs vary by age, sex, height, and body mass[2]. Activity is often expressed as MET minutes, representing the time expended at a certain level of activity.]

Some studies have shifted focus from physical activity toward examining the impact of *physical inactivity*, or lack of moderate to vigorous physical activity (MVPA) [7,8], and *sedentary*, or 'sitting,' time [7,9,10]. Epidemiologic studies of self-reported sitting time estimate that US adults spend an average of 4.7 h/day sitting [11]. Researchers acknowledge, however, that this is probably an underestimate. Unlike many unhealthy behaviors, sitting time is greater among individuals with more education, probably reflecting the prevalence of increasingly sedentary occupations as education increases. Sitting time includes television viewing, time in cars, and, in some studies, computer time. There is compelling evidence that even after accounting for time spent in MVPA, sedentary time is an independent risk factor for obesity, metabolic syndrome, cancer, cardiovascular disease, and mortality [8,10].

The Centers for Disease Control and Prevention (CDC) has defined minimum standards for physical activity to improve health and reduce risk of disease: 150 min/week of MVPA, or 75 min/week of vigorous activity (http://www.cdc.gov/physicalactivity/everyone/guidelines/adults.html). Moderate-intensity activities are those that require 3–6 METs, or that an individual would rate as a 5 or 6 on 0–10 scale of

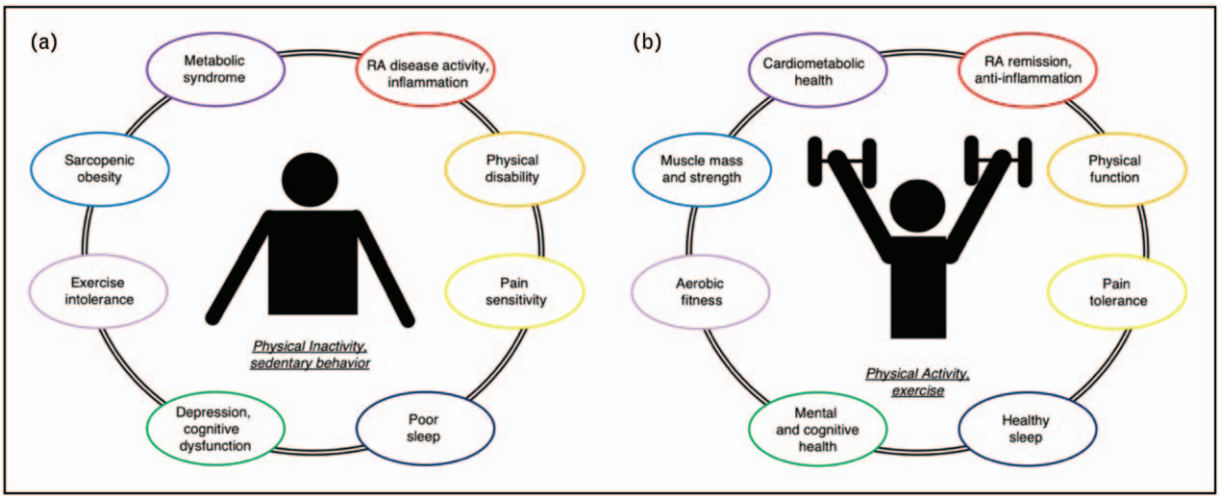

FIGURE 1. Overview of contrasting effects of physical inactivity and physical activity in Rheumatoid Arthritis. (a) Physical inactivity and sedentary behavior contribute to many important negative consequences in rheumatoid arthritis. (b) In contrast, physical activity and exercise help to mitigate and reverse these negative rheumatoid arthritis outcomes, leading to a state of generalized whole-person health. Rheumatologists and other care providers should discuss the potential hazards of physical inactivity and benefits of physical activity when outlining an exercise prescription plan for those with rheumatoid arthritis.

intensity. Vigorous-intensity activities require more than 6 METs. Converting the CDC recommendations to MET minutes yields about 600 MET minutes per week.

PHYSICAL ACTIVITY LEVELS IN PEOPLE WITH RHEUMATOID ARTHRITIS

In spite of recommendations, studies among individuals with rheumatic diseases have typically found low levels of physical activity [12–16]. For example, the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis study, which included 5235 rheumatoid arthritis patients from 21 countries, found that only 13.8% reported exercise at least 3 times/week [14]. Inactivity was higher among women, persons who were older, had lower education, were obese, had comorbidities, or had low functional capacity, high disease activity, pain, and fatigue. In a more recent US study, 29% of people with rheumatoid arthritis reported activity levels that met CDC guidelines [17]. Because people typically overestimate their activity levels, the actual percentage meeting guidelines is likely lower, as indicated in review of studies objectively measuring physical activity in people with rheumatoid arthritis [18]. This review showed daily MVPA time of 9–25 min/day and sedentary time of at least 9 h/day.

In contrast, CDC surveillance studies report that 48% of US adults meet current physical activity recommendations (http://www.cdc.gov/physicalactivity/data/facts.html) – a rate that is disappointing but is still higher than among individuals with rheumatoid arthritis. It is important to consider that the inflammatory backgrounds of rheumatoid arthritis may magnify the negative effects of inactivity.

EXERCISE, PHYSICAL ACTIVITY, AND RHEUMATOID ARTHRITIS DISEASE ACTIVITY

Contrary to previous fears that physical activity or exercise would worsen joint disease, studies show consistent associations of exercise and higher levels of physical activity with lower disease activity and lower levels of systemic inflammation [3▪▪]. For example, traditional aerobic/cardio exercise significantly improves disease activity measured by Disease Activity Score-28 joints (DAS28) [19]. Resistance/strength exercise without concurrent aerobic training also significantly improves DAS28 and erythrocyte sedimentation rate in patients with recent-onset rheumatoid arthritis [20]. Not surprisingly, combined aerobic and resistance exercise training programs improve rheumatoid arthritis disease activity as well, potentially to a greater extent than either modality alone [21,22]. In addition to traditional aerobic exercise programs, high-intensity interval training, where participants alternate bouts of near-maximal intensity aerobic exercise with bouts of lower intensity, significantly improves DAS28 and erythrocyte sedimentation rate [23▪]. In addition to improving disease activity, exercise does not increase radiographic joint damage [24,25].

Although exercise training generally improves rheumatoid arthritis disease activity, the benefit on inflammatory markers is inconsistent. [26] This inconsistency results from heterogeneity in multiple facets: disease activity and duration, intervention mode and amount, and inflammatory markers measured [26]. Also, these studies are complicated by design differences, specifically responses to acute exercise bouts versus training. In healthy persons, acute bout and chronic training responses differ [27–29], but regular physical activity and exercise improve inflammation, immunosenescence, and innate immune response efficiency [30–32,33▪▪, 34▪▪]. To better understand the impact of regular exercise on the rheumatoid arthritis immune profile, further randomized interventions should use carefully detailed, preferably supervised training interventions that include thorough cytokine and immune cell phenotyping.

PHYSICAL ACTIVITY AND RHEUMATOID ARTHRITIS SYMPTOMS

Previous exercise interventions among adults with rheumatoid arthritis have generally shown reductions in *pain* [1,35–37], regardless of the type of exercise or activity. This is particularly important given concerns that physical activity might aggravate rheumatoid arthritis disease activity and increase pain. The reasons that exercise affects pain are less clear. There have been suggestions that exercise increases the production of endorphins, which inhibit the transmission of pain.

There is also evidence that exercise modifies central pain processing [38], and that the intensity of activity may influence pain sensitivity [39]. Central processing modifications were invoked by Lofgren's recent study showing that one to two years of physical activity reduced rheumatoid arthritis pain ratings, but not pain sensitivity [36].

Fatigue is almost universally experienced by individuals with rheumatoid arthritis [40]. Only a handful of studies have examined the impact of physical activity on fatigue in rheumatoid arthritis, and in those, physical activity significantly improved fatigue levels [41–46,47▪]. Even moderate increases in walking appear to decrease fatigue [41]. A metaanalysis of

nonpharmacological interventions for rheumatoid arthritis fatigue concluded that exercise interventions reduce fatigue in rheumatoid arthritis, with effect sizes slightly smaller than those of a well-designed cognitive-behavioral program (~0.5 compared with 0.6–0.7) [48].

Self-reported *sleep disturbances* are common in rheumatoid arthritis [49–52]. In the general population, higher levels of physical activity are linked to better sleep quality, including less sleep fragmentation and better sleep efficiency [53,54]. Few studies have examined the relationship between exercise/physical activity and sleep specifically in rheumatoid arthritis, but emerging evidence suggests correlations between physical activity and improved sleep time and quality [46,49].

Higher levels of objectively measured physical activity are associated with fewer *functional limitations* and increases in physical activity have been linked to greater improvements in functioning in rheumatoid arthritis [23▪,35,41,49,55]. Conversely, lack of exercise or low physical activity has been associated with increased disability and loss of muscle mass [56]. Fitness and strength are improved with exercise, which may underlie the improvements in functioning [1,23▪,57]. Exercise can improve rheumatoid cachexia, which may also explain improvements in functioning [58,59].

In addition to the impact of increasing exercise or activity levels, reducing sedentary time also improves rheumatoid arthritis symptoms. Specifically, reductions in sitting time are associated with reductions in pain and fatigue and improvements in function [60].

PHYSICAL ACTIVITY AND MENTAL HEALTH

In the general population, observational studies have found a strong inverse relationship between physical activity and *depression* and consistent effects on reduction of depressive symptoms [61–63]. The effects of physical activity interventions on depression may be equivalent to the effects of psychological therapy and pharmacological treatment [64]. From a slightly different perspective, physical *inactivity* and sedentary behavior, particularly time spent watching television, also contribute significant risk for depression [65–68]. These findings are replicated in studies of persons with rheumatoid arthritis, with exercise interventions demonstrating statistically and clinically significant reductions in depressive symptoms, with effects similar to those found in general population studies [69].

Inactivity is linked to *cognitive impairment* in the general population [70–72], and, conversely, higher levels of physical activity and fitness are associated with better cognitive function, particularly executive function [71,73,74], which may be attributed to improved cardiorespiratory fitness [75]. Investigations into the mechanisms for physical activity's effect on cognitive function are relatively recent and appear to show that physical activity exerts structural effects on the brain [76]. Little work has explored the potential link between physical activity and cognitive impairment in rheumatoid arthritis, although a recent study reported that people with rheumatoid arthritis who are physically active are less likely to report cognitive problems [77].

BARRIERS TO PHYSICAL ACTIVITY

In spite of evidence supporting the benefits of physical activity, most individuals with rheumatoid arthritis are inactive. Some reasons for rheumatoid arthritis inactivity are similar to those expressed by the general population, such as female sex, older age, and less education (http://www.cdc.gov/physicalactivity/data /facts.html). Disease-specific barriers include disease activity and radiographic joint damage, each of which is associated with lower levels of physical activity [78]. Fatigue and pain levels may also be perceived as barriers to participation in activity.

Psychological and perceptual barriers may hamper uptake of physical activity, as well. Among a group of individuals with rheumatoid arthritis, 65% of excess inactivity was accounted for by lack of strong motivation and lack of strong positive beliefs related to benefits of physical activity [79]. Patients have reported concerns about exercise causing harm to joints, not knowing what exercises to do, and not wanting to exercise because joints hurt [80]. Inactive individuals tend to have more negative expectations of the effects of exercises [81].

Perhaps most importantly, individuals with rheumatoid arthritis may not be getting the message from their physicians or other healthcare providers that physical activity is beneficial [3▪▪,82]. Having a recommendation from a health professional may be the factor most strongly associated with engaging in physical activity or exercise [83]. This lack of advocacy for physical activity is not unique to rheumatology. An analysis of the 2011–2012 NHANES data found that over 50% of adults who were completely sedentary had not been told by a healthcare profession to increase their exercise [84].

Physicians and other providers may not have adequate information to guide their patients [85]. A survey from the Netherlands indicates that rheumatologists, clinical nurse specialists, and physical therapists believe physical activity is an important

rheumatoid arthritis health goal and moderate-intensity physical activity public health recommendations are attainable for persons with rheumatoid arthritis. Nonetheless, most of these providers did not feel competent in offering physical activity advice [86]. An additional barrier to regular physical activity may be that rheumatoid arthritis patients are confused by advice on how to manage disease symptoms. Pacing (e.g., taking breaks from activity) has traditionally been advocated as a way for people with arthritis to manage fatigue or pain [87]. Yet one author writes, 'Since patients with rheumatoid arthritis are already at risk for inactivity, further inactivation by activity pacing might potentially be harmful.' [88]

PROMOTION OF EXERCISE

Many types of programs have been developed to help people with rheumatoid arthritis increase physical activity. There is no strong evidence to favor one type of program over another. The primary criterion for success may be whether an individual will initiate and maintain it. With high-intensity exercise training, there is only a small risk of worsening previously damaged large joints, specifically glenohumeral and subtalar joints [25]. Thus, in the select rheumatoid arthritis population with these preexisting conditions and considering engaging in a relatively high-intensity regular exercise program, physical activity recommendations should focus on reduced-weight bearing exercise, such as pool therapy. Otherwise, rheumatoid arthritis patients should be encouraged to exercise without fear of worsening synovial inflammation or cartilage damage [89].

Walking may be the simplest way for many adults to increase their activity levels. Prescribing walking 5–7 days a week at a moderate pace, either in single or multiple sessions, may be the most effective way of increasing walking time [90]. For those who prefer the structure of an organized exercise program, the Arthritis Foundation's PACE and Walk with Ease programs are examples of such programs designed for people with arthritis.

Table 1. Recommendations for physical activity among individuals with rheumatoid arthritis

Type of activity	There is no clear evidence on what type of exercise is the most beneficial **Anything is better than nothing** The CDC guidelines are relevant: 150 min/week of moderate-to-vigorous physical activity, or 75 min/week of vigorous physical activity Aerobic activity can include activities such as walking, biking, or swimming Walking may be the most approachable form of physical activity for currently inactive individuals. However, some individuals may prefer engagement with exercise groups, which can provide both structure and social interactions CDC guidelines recommend two or more days/week of muscle-strengthening activities that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms)
Frequency	Frequency should be at least three times/week
Duration	Exercise bouts can be any length. Prior emphasis on 10-min bouts has evolved into recognition that even shorter periods of physical activity are beneficial New physical activity should be undertaken incrementally. Advise patients to start with what they know they can do, whether it is to walk for 15 min or for 2 min to get the mail and gradually increase The goal is to accumulate a minimum of 150 min/week
Intensity	Activity should be of at least moderate intensity. Moderate intensity can be gauged using the 'talk test.' If an individual can talk, but not sing, during the activity, the intensity can be considered of moderate intensity. In vigorous activity, an individual will not be able to say more than a few words without pausing for breath (http://www.cdc.gov/physicalactivity/everyone/measuring/index.html)
Sit less	'Sit less' is also an important message. Feehan and Westby point out that most people sit about 10 h/day, but could add 40 min of light activity by standing twice an hour [93]. Other suggestions they provide are standing up and stretching during television commercials or after a chapter in a book
Incorporate physical activity into lifestyle	Suggest that persons with rheumatoid arthritis make it a habit to take the stairs, park slightly farther from the grocery store or postoffice door, walk the dog, and lose the television remote control
Other	**Physical activity is safe for people with rheumatic conditions** Individuals who are depressed may need extra support in beginning a physical activity program and in maintaining it, at least in the initial stages Pedometers or other activity monitors can serve as useful guides to help quantify activity and monitor progress. They can also serve as motivation. Many new activity monitoring devices include on-line communities and self-monitoring and motivational tools. Some activity monitors can track exercise other than walking or running Careful selection of walking or other exercise shoes may be necessary for individuals with rheumatoid arthritis. Some individuals may benefit from shoe inserts or orthotics Support from healthcare providers and family/friends is an important facilitator for physical activity [83,94]

Use of pedometers is a simple means to measure and increase physical activity. Step counting can provide concrete evidence of activity and may serve as motivation. In addition to the mechanical aspect of counting steps, many devices have online components to offer guidance in setting goals, activity tracking, and development of walking 'buddies' or groups.

Physical activity guidelines for US adults call for 30 min/day of MVPA on at least five days per week [91]. Translating this to daily step counts yields a goal of approximately 8000 steps/day [92], about 3000 of which can be attributed to the 30-min exercise bout (assuming an average of 100 steps/min) and the remaining 5000 to 'background' daily activity [93]. Recognizing that the 'background' levels of activity are likely to be lower for older adults or those with chronic illness, initial goals of 5500 steps/day have been suggested [94]. Even 5500 steps/day may be daunting for individuals who have been inactive. Setting lower initial targets, with the intention of gradual increases in steps over time, may seem more attainable, and lead to greater adherence to activity. Typical exercise programs progress weekly by 10%, which at low levels of activity common in rheumatoid arthritis translates to a conservative metric for attainability.

CONCLUSION

Despite earlier hesitations about the safety and usefulness of physical activity and exercise for people with rheumatoid arthritis, research has consistently shown benefits for disease activity and symptoms. In spite of this, the vast majority of people with rheumatoid arthritis are inactive. Barriers to exercise include those typical to the population at large (e.g., lack of time), but also include rheumatoid arthritis-specific concerns such as fears that activity may worsen rheumatoid arthritis or harm joints. Understanding the benefits on symptoms may also be difficult when the symptoms themselves present barriers. However, the greatest barrier to healthy levels of physical activity among individuals with rheumatoid arthritis appears to be the lack of direction from healthcare providers. Providers are encouraged to give patients positive messages about the benefits of physical activity and the extremely low risks of harm. Specific recommendations are shown in Table 1 or at https://www.exerciseismedicine.org/assets/page_documents/EIM_Rx%20for%20Health_Rheumatoid%20Arthritis.pdf

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Conflicts of interest

There are no conflicts of interest.

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Treatment of immune checkpoint inhibitor-induced inflammatory arthritis

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Purpose of review
This review summarizes the current evidence on treatment strategies for inflammatory arthritis because of cancer treatment with immune checkpoint inhibitors (ICI), prognosis of ICI-induced arthritis, and management of patients with preexisting inflammatory arthritis receiving ICI therapy.

Recent findings
Inflammatory arthritis is the most common rheumatic immune-related adverse event observed in patients receiving ICI therapy. Most patients can successfully be treated with low doses of corticosteroids or conventional synthetic disease modifying anti-rheumatic drugs (DMARDs). A small minority will develop severe symptoms requiring biologic therapy including TNF inhibitors and IL-6 receptor inhibitors. Many cases of inflammatory arthritis will resolve with cessation of ICI therapy. Some patients will develop persistent arthritis despite discontinuation. Patients with preexisting inflammatory arthritis (e.g. rheumatoid arthritis) commonly flare on ICI therapy, but can usually be managed with corticosteroids.

Summary
Inflammatory arthritis following ICI therapy for cancer is relatively common and the practicing rheumatologist should be able to recognize and manage it in conjunction with Oncology. The majority of patients respond to corticosteroids, but some will need treatment with conventional synthetic or biologic DMARDs. Additional studies should investigate the effects of immunosuppression on tumor response and the use of ICI therapy in patients with preexisting autoimmune disease.

Keywords
cancer, immune checkpoint inhibitor, inflammatory arthritis

INTRODUCTION

The emergence of immune checkpoint inhibitors (ICI) has revolutionized the treatment of cancer. Improved survival and prolonged responses are now being seen for previously difficult to treat malignancies [1–3]. ICIs primarily work by blocking inhibitory interactions between T cells and other cells and tissues, thus allowing for unchecked T-cell activation with resultant antitumor effect. The Food and Drug Administration (FDA) has approved to date seven ICIs for a myriad of malignancies, including for mismatch repair-related cancers regardless of origin, which represents the first tissue agnostic approval of an antineoplastic agent [4]. Currently approved ICIs target CTLA-4, PD-1, and PD-L1. Other checkpoint pathways are under investigation for development of targeted drugs include lymphocyte-associated gene 3 (LAG-3), T-cell immunoglobulin mucin 3 (TIM-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT) [5–7]. The consequence of generalized immune activation is inflammatory damage of healthy tissues, referred to as immune-related adverse events (irAE) [8▪▪]. The pathogenesis of irAEs is not fully characterized but is likely related to the effect of ICIs on T-cell activation and functioning [9–11]. Inflammatory arthritis is a well described complication from ICI therapy and estimates of incidence vary from 1 to 7% of patients treated [12▪]. Many more patient will suffer from arthralgias, up to 40% in some clinical trials [13]. Uniquely, whereas the vast majority of irAEs will resolve with holding treatment and glucocorticoids, inflammatory arthritis may persist despite these measures in a subset of patients [14▪].

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KEY POINTS

- Immune checkpoint inhibitors (ICI) can cause a variety of immune-related adverse events, including inflammatory arthritis.
- Systemic corticosteroids are required for most patients referred to rheumatology for ICI-induced inflammatory arthritis; conventional synthetic DMARDs or biologic DMARDs may also be used.
- In limited studies, immunosuppression for ICI-induced inflammatory arthritis does not seem to affect tumor response negatively.
- Collaboration with the treating oncologist is critical for successful care of inflammatory arthritis because of ICIs.
- Patients with preexisting inflammatory arthritis commonly flare on ICIs but most of these flares can be managed with corticosteroids.

The epidemiology and clinical presentation of inflammatory arthritis secondary to ICI therapy has previously been reviewed in this journal [15]. To summarize, multiple phenotypes of inflammatory arthritis have been reported in the literature and including small joint predominant polyarthritis similar to rheumatoid, large joint oligoarthritis frequently involving the lower extremities, tenosynovitis, psoriatic-type arthritis, and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) [15]. Patients treated anti-PD1 monotherapy are more likely to develop a small joint polyarthritis whereas patients treated with anti-CTLA4 therapy alone or in combination most commonly present with knee arthritis [16]. Inflammatory markers are variably elevated and the majority of patients will be seronegative for rheumatoid factor and anticitrullinated protein antibodies [16–19]. Imaging findings include Doppler-positive synovitis on ultrasound, joint effusions and synovitis on MRI, as well as erosions in severe cases [18]. Tendon involvement, with tenosynovitis and enthesitis, is also appreciated with musculoskeletal ultrasound [20,21]. This review will focus on current treatment strategies.

OVERARCHING PRINCIPLES

In managing patients with inflammatory arthritis, close collaboration with the treating oncologist is essential. According to the oncologic practice guideline for the management of immune-related adverse events (irAE), treatment should be dictated by the grade of the irAE. In oncologic practice, treatment-related side effects are classified on a scale of 1–5 [22–24,25▪]. In the context of inflammatory arthritis, grade 1 is defined as mild pain with erythema, inflammation, or joint swelling; grade 2 as moderate pain and limiting instrumental activities of daily living (ADLs), and grade 3 and 4 as severe pain resulting in irreversible joint damage and limiting self care ADLs. Most patients will experience grade 1 or 2 severity. Per oncologic guidelines, for grade 1 inflammatory arthritis, most patients will not be seen in a rheumatology practice as symptoms can be managed with analgesics, such as acetaminophen or NSAIDs and ICI therapy can be continued. If these conservative measures are not effective, or symptoms persist, rheumatology consultation is appropriate. Additionally, grade 2 events and above should be referred to rheumatology for evaluation [23,24,25▪]. ICIs are not typically held unless events are grade 3 or higher. In patients who cannot perform ADLs, especially if they have already received a long course of ICIs, it is reasonable for rheumatologists to recommend holding the ICI to the oncologist.

INITIAL TREATMENT

The initial treatment strategy for patients with ICI-induced inflammatory arthritis should be NSAIDs for mild disease (grade 1) followed by glucocorticoids. In patients with limited large joint involvement, intra-articular glucocorticoids can be considered. This is in accordance with major oncologic society guidelines for management of rheumatic irAE [23,24,25▪]. The overwhelming majority of patients in case series of inflammatory arthritis are initially treated with glucocorticoids, likely because these patients developed severe enough arthritis to be referred to rheumatology. In our center's experience, for patients with moderate symptoms with impairments in instrumental ADLs, prednisone 10–20 mg daily is a reasonable starting dose of steroids. Patients with more severe arthritis and significant functional limitation may require doses of 40–60 mg daily initially with a plan to taper. In patients at risk for adverse effects from glucocorticoids or unable to taper below 10 mg of prednisone daily, we suggest initiating a conventional synthetic disease modifying anti-rheumatic drug (csDMARD), such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine, all of which have been used successfully in various case series [13,16,17,19]. There have been no comparative effectiveness studies assessing the response to these various agents and the choice should be guided by severity of arthritis and patient comorbidities.

BIOLOGICS

There are two scenarios where biologic therapies may be used. First, patients who have been treated

with glucocorticoids and csDMARDs and who have persistent severe arthritis should be escalated to biologic therapy to prevent long-term joint damage and regain functional status. Second, patients where a faster time to arthritis improvement is needed may benefit initial treatment with a biologic therapy as a steroid-sparing agent. These may be patients in whom ICI therapy has been temporarily held because of toxicity with a subsequent plan to re-challenge or a patient with progressive cancer and a limited life span who wishes to achieve functional improvement to enjoy activities at the end of life. In our center's experience, patients typically note improvement after two to three doses of a subcutaneous TNF inhibitor for ICI-induced arthritis whereas response to csDMARDs tends to be slower.

Data with regard to biologic use in patients with ICI-induced inflammatory arthritis is limited to case reports and small case series. TNF inhibitors have been used with success in a number of case series [17,18]. Although small in size, previous studies have not found that treatment of inflammatory arthritis with either csDMARDs or TNF inhibitor impacts overall survival or progression of tumor [14▪,16] In melanoma, short courses of TNF inhibitors (one to two doses) had no effect on tumor response [26]. Beyond TNF inhibition, a case series of three patients with severe persistent arthritis demonstrated efficacy of IL-6 inhibition with tocilizumab [27]. All three patients demonstrated improvement in arthritis and one patient maintained a durable tumor response from ICI therapy despite tocilizumab treatment and two of the three patients receiving concomitant ICI therapy and tocilizumab. In reports of treatment for inflammatory arthritis, ICIs are almost always held while biologics are administered. There is increasing interest about whether patients with severe arthritis and an indication for ongoing ICI therapy can be co-treated with ICIs and biologic therapies. In immune-related enterocolitis, one of the most frequent irAEs requiring discontinuation of ICI, a small case series of five patients demonstrated that colitis could successfully be treated with infliximab while continuing ICI therapy [28▪]. Patients demonstrated both clinical and pathologic improvement with regards to colitis and there was no cancer progression on restaging studies.

IMMUNOSUPPRESSION AND TUMOR RESPONSE

There are theoretical concerns that treating irAEs with immune-modulating agents will negatively affect tumor response to ICI therapy. The data from irAE treatment are mixed. Short-term glucocorticoid exposure has not been associated with attenuated antitumor efficacy in melanoma and other tumors [26,29,30]. Additionally, short-term TNF inhibition with one to two doses of infliximab did not negatively affect response to ipilimumab in melanoma [26]. Patients who receive high dose corticosteroids for hypophysitis, however, had a worsened overall survival than those who only received adrenal replacement-dosed corticosteroids [31]. Baseline immunosuppression may also be detrimental as those receiving prednisone 10 mg or higher had worsened response to anti-PD-1 and anti-PD-L1 agents for nonsmall cell lung cancer [32].

PERSISTENT ARTHRITIS

A recent study reported a significant percentage of patients will have a persistent arthritis despite cessation of ICI therapy. Of 41 patients with ICI-induced inflammatory arthritis followed longitudinally for at least 6 months, 20 patients had active arthritis at 6 months from ICI- discontinuation [14▪]. Patients with persistent arthritis were more like to have been treated with treated with combination immunotherapy and have experienced two or more irAEs versus those patients whose arthritis resolved. Those with persistent arthritis also had longer duration of ICI therapy. The results of this study suggest that patients receiving combination immunotherapy should undergo more frequent and prolonged monitoring. Interestingly, numerous studies across various malignancies have associated the development of an irAE with durable tumor response [30,33–36]. Similarly, in the aforementioned study on persistence of inflammatory arthritis, there was a nonsignificant trend toward better tumor responses in patients whose arthritis persisted.

OTHER CONSIDERATIONS

Good practice guidelines for patients with inflammatory arthritis should be extended to the treatment of ICI-induced inflammatory arthritis. Infection screening for chronic hepatitis and tuberculosis should be performed prior to starting immunosuppressive medication and may not have previously been completed as part of routine oncologic care. With regard to duration of treatment and tapering patients off immunosuppressive medications, there is no data to guide management so treatment should be individualized to the patient. Many patients will experience

an additional irAEs in conjunction with inflammatory arthritis, up to 40% in our center's experience [14▪]. In general, management decisions and monitoring response to therapy should be discussed with the treating oncologist and the relevant subspecialist.

PREEXISTING INFLAMMATORY ARTHRITIS

The preponderance of data suggests that patients with preexisting autoimmune disease including inflammatory arthritis receiving ICI therapy are likely to flare as a result of checkpoint inhibitors but that these flares can generally be managed. As these patients were excluded from clinical trials, the data is exclusively derived from retrospective cohort studies [37▪▪,38,39]. Early data from melanoma patients with preexisting autoimmune disease treated with anti-CTLA-4 therapy found that disease flares occurred relatively frequently (27% of patients) but could generally be managed with corticosteroids. Fifty percent of patients experienced neither a flare nor disease nor an irAE requiring treatment [40]. Similarly, treatment with PD-1-targeted therapy in patients with autoimmune disease resulted in flares in 38% of patients that again could be managed with immune suppression [41]. A study from the Mayo Clinic identified 16 patients with preexisting autoimmune disease prior to receiving ICI therapy out of 700 patients receiving ICI therapy from 2011 through 2016. Five of these patients had rheumatoid arthritis. Six out of 16 patients experienced an irAE; however, only one experienced a flare of their preexisting autoimmune disease [42]. In a multicenter case series from Australia, 10 out of 12 patients with patient receiving ICI-therapy experienced a flare of their disease, including four with inflammatory arthritis [43]. The largest study to date analyzed outcomes from ICI therapy in 112 patients in France with a preexisting autoimmune disease; 20 of the 112 patients had rheumatoid arthritis while the most common autoimmune disease was psoriasis. Only 24 of the patients were receiving any immunosuppression at the start of ICI treatment although 65% of these patients with rheumatoid arthritis (13 patients) were on immunosuppression. A flare of preexisting autoimmune disease and/or development of a separate irAE occurred in 71% of patients, with 47% of patient experiencing a flare of their preexisting autoimmune disease [44▪]. Immunosuppressive therapy was required in 43% of patients for management of flare and/or new irAE. Interesting, median progression free survival was shorter among patients receiving immunosuppression at start of ICI therapy compared with those who were not immunosuppressed (3.8 versus 12 months). The authors raise the question of whether immunosuppressive treatment of stable preexisting autoimmune disease should be discontinued prior to starting ICI therapy to maximize chance of tumor response. Although this is currently not the standard practice, this observation underscores the need for close and regular communication between the treating oncologist and rheumatologist in managing these patients. Additional research is needed to identify, which patients with preexisting rheumatic disease are at greatest risk for flare with ICI therapy and medical management prior to cancer therapy. There is no evidence currently supporting any particular immunomodulatory regimen for prophylaxis against flare or autoimmune disease.

CONCLUSION

Inflammatory arthritis secondary to ICIs is a well established clinical entity that rheumatologists should be familiar with in light of increasing use of these agents as first line therapy for a wide variety of malignancies. Although the presentation of inflammatory arthritis can vary, principles from the management of classic inflammatory arthritis may be applied. Initial treatment should consist of NSAIDs and glucocorticoids with a low threshold to start conventional synthetic DMARDs in patients with persistent arthritis and inability to taper steroids. Biologic therapy with TNF inhibitors is effective for refractory arthritis and does not appear to decrease antitumor effect of ICI therapy, although long-term studies of patients treated with these agents are needed. Patients with preexisting inflammatory arthritis are likely to experience a flare of their disease with initiation of ICI therapy; however, most cases can successfully be managed with the above treatment strategies and should not be an indication to withhold potentially lifesaving cancer treatment. As immunotherapy expands both in terms of the number of patients treated as well as the drug targets, more prospective research is needed to understand optimal management of patients both de novo inflammatory arthritis and those with preexisting autoimmune disease.

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Conflicts of interest

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