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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

Kenneth G. Saag

Kenneth G. Saag, MD, MSc, is *Jane Knight Lowe* Professor of Medicine, Division of Clinical Immunology and Rheumatology, at the University of Alabama at Birmingham (UAB) in Birmingham, Alabama, USA and Professor of Epidemiology, at the UAB School of Public Health.

Dr Saag is a native of Chicago, and following studies in engineering at the University of Michigan, USA, he returned to Chicago for medical school and Internal Medicine Residency at Northwestern University, USA. He then traveled to the University of Iowa, USA, for his rheumatology and epidemiology training and remained on the faculty there until moving to UAB in 1998.

Dr Saag is the founding Director of the Agency for Health Care Research and Quality Deep South Center for Education and Research on Therapeutics, the UAB Center of Research Translation in Gout and Hyperuricemia, and the UAB Outcomes Research Center. He also serves as a Vice Chair for the UAB Department of Medicine. He has published over 300 peer reviewed manuscripts; has also authored more than 100 reviews, editorials, and book chapters. Recently he published the first edition of the clinical handbook *Diagnosis and Management of Osteoporosis*.

Dr Saag is the Secretary of the American College of Rheumatology (ACR) and Past President of the Board of Trustees of the National Osteoporosis Foundation.

Sara K. Tedeschi

Dr Tedeschi is a Rheumatologist at Brigham and Women's Hospital and an Assistant Professor of Medicine at Harvard Medical School, both in Boston, Massachusetts, USA. She completed medical school at Vanderbilt University School of Medicine in Nashville, Tennessee, USA. Dr Tedeschi then completed both her internal medicine residency and rheumatology fellowship training at Brigham and Women's Hospital and received her MPH from the Harvard T.H. Chan School of Public Health. Her clinical research focuses on risk factors for and outcomes in rheumatic diseases. Dr Tedeschi's current work which focuses on calcium pyrophosphate crystal deposition disease is funded by the National Institutes of Health. She is Co-Chair of the OMERACT CPPD Working Group and serves on the leadership team of the ACR/EULAR CPPD Classification Criteria working group.

George C. Tsokos

Dr George C. Tsokos, MD is Professor of Medicine at Harvard Medical School and Chief, Rheumatology Division, Beth Israel Deaconess Medical Center in Boston, USA. He trained in Rheumatology at the National Institutes of Health, USA. He has served various leadership positions including President of the Clinical Immunology Society, Chair of the Council of the University of Athens and Member or Chair of multiple federal study sections and Editor or Member of editorial boards of scientific journals.

Dr Tsokos holds a MERIT Award from the National Institutes of Health and has received several prestigious awards including the Kirkland, Howley, Evelyn Hess awards and the Distinguished Basic Investigator Award from the American College of Rheumatology, the Lupus Insight Award, the Carol Nachman International Prize in Rheumatology and the Marian Ropes Physician Achievement Award. Dr Tsokos' laboratory has opened and led the field of molecular abnormalities on immune cells in patients with SLE and identified previously unknown pathways which have served as the basis for novel treatments which are currently in various phases of development.

Review of publications evaluating opioid use in patients with inflammatory rheumatic disease

Christine Anastasiou and Jinoos Yazdany

Purpose of review
This article discusses publications assessing the prevalence, efficacy, and safety of opioid analgesics in patients with rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, and systemic sclerosis.

Recent findings
Recent studies show long-term opioid use is common in patients with inflammatory rheumatic disease. We did not find any studies demonstrating improved function or pain control with long-term opioid use in people with rheumatic diseases. Some data shows potential adverse effects including increased risk for fractures and opioid poisoning hospitalizations. There is evidence demonstrating an association of opioid use with mental health disorders, fibromyalgia, obesity, and disability, although causative links have not been established. Only minimal reductions in opioid use were observed after initiation of biologic disease modifying antirheumatic drugs (DMARDs). Studies have shown delayed DMARD initiation and reduced DMARD use in patients on opioids, raising concerns that these analgesics may delay care or initially mask symptoms of active disease.

Summary
Available literature highlights high levels of opioid use in people with rheumatic disease, without scientific evidence to support efficacy for chronic pain control and increasing evidence of adverse events. These findings strongly suggest that opioids do not have a routine role in the chronic management of inflammatory rheumatic diseases.

Keywords
inflammatory arthritis, opioid, pain

INTRODUCTION

Patients with inflammatory rheumatic diseases are often afflicted with acute and chronic pain. Chronic noncancer pain can be due to a variety of factors including active inflammatory disease, accumulated damage from disease or treatment, injury, neurologic or neuropathic disease, central pain disorder, or other conditions [1–4]. The Centers for Disease Control and Prevention (CDC) have developed guidelines for chronic pain treatment, and appropriate opioid use in the general population [2]. Based on the CDC review of the literature through 2016, there was no evidence of long-term benefit of opioids for chronic noncancer pain and function, and they recommended against routine use of opioid medications for chronic musculoskeletal pain because of concerns regarding safety and inefficacy [2].

Addressing pain in inflammatory rheumatic diseases can present unique clinical challenges but is essential. Pain relief has historically been rheumatoid arthritis (RA) patients' highest priority [5]. All practitioners treating patients with inflammatory rheumatic disease are faced with the difficult responsibility of identifying the underlying cause of each person's pain and compassionately trying to improve patient comfort with a combination of nonpharmacologic therapy and a limited number of pharmacologic options.

In this review, we examine the most recent publications evaluating opioid use in patients with inflammatory rheumatic disease, including any evidence for efficacy, associated risk factors, relation to disease modifying antirheumatic drug (DMARD) therapy, and potential adverse effects. We divide

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KEY POINTS

- Chronic opioids are commonly prescribed for patients with RA, SLE, psoriasis or psoriatic arthritis, and ankylosing spondylitis, with evidence of associated adverse effects.
- Opioid use minimally decreased but remained high after biologic DMARD medications were initiated.
- There is no data reporting improved function, quality of life, or pain control with long-term use of opioids for patients with inflammatory rheumatic diseases, making this an important area for future research.

the review article into sections evaluating opioid use in each of 5 inflammatory rheumatic diseases commonly clinically associated with pain: RA, systemic lupus erythematosus (SLE), psoriasis and psoriatic arthritis, ankylosing spondylitis, and systemic sclerosis.

RHEUMATOID ARTHRITIS

Prevalence of opioid use in rheumatoid arthritis

Chronic opioids are prescribed to 17% to 67% of US patients with RA. The highest recent estimate is from a study of Social Security Disability Insurance beneficiaries less than 65 years of age (Table 1) [6▪–8▪,9▪▪,10–14]. A cross-sectional study of the National Ambulatory Medical Care Survey examining data from 2011 to 2016 showed that one-fourth of US office visits for RA involved an opioid prescription; opioid prescribing for outpatient RA visits increased from 15% to 34% ($P < 0.0001$) over the time frame; and primary care physicians were the most common prescribers [6▪]. Among US rheumatologists, there is likely high variability in prescribing patterns between physicians, such that RA patients cared for by the same rheumatologist are more or less likely to be opioid users based on their physician's practice [11,15].

Efficacy and safety of opioid use in rheumatoid arthritis

There is no evidence to support the efficacy and safety of long-term opioid use for RA. The most relevant study of interest was a randomized trial examining chronic opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis [16]. This trial was conducted between 2013 and 2015 at Veterans Affairs primary care clinics where patients were randomized to receive opioid or nonopioid analgesics. There was no significant difference in pain-related function over 12 months, and pain intensity was significantly better in the nonopioid group with less adverse medication-related symptoms. Although the results of this study may not fully capture opioid treatment outcomes for patients with inflammatory arthritis, it is striking to note that chronic opioid therapy was associated with higher pain intensity with no improvement in pain-related function, supporting the notion that opioids should not be routinely used for chronic musculoskeletal pain.

Limited evidence exists to support treating RA pain short-term (<6 weeks) with weak opioids, with evidence of adverse effects [17–18]. Among patients with RA, opioid use has been associated with increased risk of fracture (adjusted hazard ratio [aHR] 1.37 [95% CI 1.18–1.59] for weak opiates, aHR 1.53 [95% CI 1.24–1.88] for strong opiates) [19]. Increased fracture risk from opioids may be a result of cognitive side effects, more falls, or opioid-induced endocrinopathies [20–21] as identified in other patient populations. Recent evidence also demonstrates that hospitalizations for RA patients have a higher risk of primary diagnosis of opioid poisoning compared to the general population [22], emphasizing that the risks of adverse outcomes from opioids may be magnified in RA patients.

Factors associated with chronic opioid use in rheumatoid arthritis

Chronic opioid use in RA has been associated with fibromyalgia [6▪,11], anxiety [11], antidepressant use [11,14], and smoking [8▪]. However, antidepressants are sometimes used as a treatment modality for pain [23–24] which complicates the interpretation of antidepressant use in these studies. There is also evidence that RA patients with mental health conditions may be at higher risk for receiving chronic opioid therapy. A retrospective cohort of veterans with RA initiating opioids between 2001 and 2012 evaluated the association between mental health conditions including anxiety, depression, bipolar disease, posttraumatic stress disorder, and substance use disorder with risk of being treated with chronic opioids [25▪▪]. Veterans with mental health conditions were at higher risk than those without mental health conditions to receive long-term opioid therapy [aHR 1.18, 95% CI 1.09, 1.29], with the risk being highest for those with a history of substance use disorder. This study emphasizes the importance of evaluating and treating comorbid mental health conditions concomitantly with patients' autoimmune disease as part of a comprehensive treatment approach.

Disability has also been associated with long-term opioid use in multiple studies [7▪,8▪,14]. Baker

Table 1. Selected studies reporting opioid use among patients with rheumatic diseases

Reference	Data source	Study design	Patients	Summary of opioid use
Rheumatoid arthritis (RA)				
Baker *et al.* [8▪]	FORWARD databank	Cohort study, 1/1999–2/2019	37,868 patients with RA	27% Any opioid use
Chen *et al.* [29]	Truven Health MarketScan claims data	Retrospective observational study of US claims data, 2003–2014	181,710 patients with RA	19% Chronic opioid use
Curtis *et al.* [11]	US Medicare data	Retrospective observational study of US Medicare data, 2006–2014	240,750 patients with RA	41% Chronic opioid use, 19% Intermittent opioid use in 2014
Huang *et al.* [6▪]	National Ambulatory Medical Care Survey, 2011-2016	Cross-sectional survey, 2011–2016	Estimated 4.5 million encounters with primary diagnosis of RA	Proportion of visits with opioid prescription: 24.3%
Lee YC *et al.* [14]	Corrona RA registry	Cohort study, 2002–2016	33,739 patients with RA	16.9% Chronic^{+} opioid use in 2015
Navarro-Millán *et al.* [7▪]	Medicare and Medicaid services claims data	Retrospective observational study of US claims data, 2007, 2011, 2014	43,563 patients with RA <65 years old receiving SSDI Medicare and Medicaid	63.7% Chronic opioid use in 2014
Park *et al.* [10]	IQVIA^{TM} Health Plan Claims Data	Retrospective observational study of US claims data, 2007–2015	2,330 patients with RA	51.0% Any opioid use
Systemic lupus erythematosus (SLE)				
Birt *et al.* [30▪]	IBM MarketScan Databases	Retrospective observational study of US claims data, 1/2012–5/2018	49,413 patients with SLE	52.6% Any opioid use 34.6% Chronic opioid use
Chen *et al.* [29]	Truven Health MarketScan claims data	Retrospective observational study of US claims data, 2003–2014	45,834 patients with SLE	16% Chronic opioid use
Lee J *et al.* [32▪]	Single institution chart review	Retrospective observational chart review, 2013–2016	77 SLE patients who had persistent frequent ED visits	37.7% Chronic opioid use
Somers *et al.* [28]	MILES Cohort	Prospective cohort, 2/2014–9/2015	462 SLE patients	31.0% Any opioid use 21% Chronic^{++} opioid use
Psoriasis and psoriatic arthritis (PsA)				
Chen *et al.* [29]	Truven Health MarketScan claims data	Retrospective observational study of US claims data, 2003–2014	30,307 patients with PsA	15% Chronic opioid use
Hunter *et al.* [9▪▪]	HealthCore Integrated Research Database	Retrospective observational study of US claims data, 1/2013–7/2019	921 patients with psoriatic arthritis	33.8% Any opioid use 12 months after initiation of biologic
Loft *et al.* [34▪]	Danish Skin Cohort	Prospective cohort study	4016 patients with psoriasis, 847 with concomitant PsA	13–25.6% Any opioid use within the past year
Noe *et al.* [38]	Optum Electronic Health Records Database	Retrospective study of US claims data, 1/2007–6/2017	99,830 patients with psoriasis	1.9% of opioid-naïve patients with psoriasis received an incident opioid prescription over one year.
Taylor *et al.* [35]	National Ambulatory Medical Care Survey (2006-2016) & National Hospital Ambulatory Medical Care Survey (2006–2011)	Cross-sectional survey, 2006–2016	1148 encounters for psoriasis and PsA evaluated, weighted to a US national estimate of 27 million visits	Proportion of visits with opioid prescription: 10%
Walsh *et al.* [36]	Optum Research Database	Retrospective study of US claims data, 1/2012–4/2016	1,235 patients with PsA	48.6% Any opioid use

Table 1 (*Continued*)

Reference	Data source	Study design	Patients	Summary of opioid use
Ankylosing spondylitis (AS)				
Chen *et al.* [29]	Truven Health MarketScan claims data	Retrospective observational study of US claims data, 2003–2014	7,686 patients with AS	25% Chronic opioid use
Dau *et al.* [40]	Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS)	Prospective cohort study	706 patients with AS	31.2% Any opioid use 9.5% Chronic^{+++} opioid use
Hunter *et al.* [9▪▪]	HealthCore Integrated Research Database	Retrospective observational study of US claims data, 1/2013–7/2019	188 patients with AS	36.2% Any opioid use after initiation of biologic
Hwang *et al.* [39]	PSOAS	Prospective cohort, 2003–2017	991 patients with AS	19.0% Any opioid use
Sloan *et al.* [41]	Truven Health MarketScan claims data	Retrospective observational study of US claims data, 1/2012–3/2017	12,862 patients with AS (ICD 720.0)	Commercial claims: 23.5% Chronic opioid use Medicaid claims: 57.1% Chronic opioid use

AS, ankylosing spondyliti; BMI, body mass index; SLE, systemic lupus erythematosus.
Unless otherwise specified, chronic opioid use can be summarized as ≥ 90 days of opioid prescription or opioid use.
Chronic +: opioid use at ≥ 2 consecutive study visits which are ≥ 3 months apart. Chronic ++: Opioid use for ≥ 1 year. Chronic +++: Daily opioid usage > 6 months. Legend. MILES: Michigan Lupus Epidemiology and Surveillance Program.

and colleagues [8▪] reported results from the FORWARD databank between 1999 and 2019 showing that obese RA patients had greater comorbidities, pain, and disability. Higher BMI in this study was associated with higher risk of chronic opioid use, and severe obesity was associated with a higher risk of strong opioid use [aHR 2.1, 95% CI 1.6–2.7]. Reducing obesity rates could be one potential intervention to decrease disability, pain, and chronic opioid use among patients with RA and deserves further investigation.

Initial opioid prescription duration may also be a risk factor for chronic opioid use [26]. Liberman, *et al.* reported that RA patients prescribed a longer initial opioid prescription duration had a higher risk of being on chronic opioids thereafter compared to patients receiving initial 0–7-day prescriptions [aHR 1.52, 95% CI 1.16–2.01 for 16–29-day prescriptions; aHR 1.78, 95% CI 1.53–2.08 for 30 days prescriptions] [25▪▪]. Almost 60% of patients were given a 30-day supply at onset of therapy. One possible explanation is that patients receiving shorter duration prescriptions had acute pain anticipated to resolve quickly, whereas patients who received longer prescriptions were being treated for chronic pain processes. Alternatively, longer duration of initial prescriptions may increase the risk of opioid dependence.

Higher disease activity [14] or longer disease duration [8▪] are also associated with opioid use which raises the question of whether these patients' RA is sufficiently treated. Administrative data from the US military TRICARE program showed that patients prescribed opioids for incident RA had greater delays until initiation of DMARD therapy (mean 212 days) compared to patients with incident RA who did not use opioids (mean 77 days, $P < 0.0001$ for the difference) [27]. Another study evaluating RA patients with commercial insurance plans or a Medicare Advantage Prescription Drug Plan, found that opioid use was associated with lower DMARD use [13]. These study results suggest that early opioids may improve pain in the short-term, resulting in delayed DMARD therapy or lower DMARD use. Furthermore, different studies have shown that opioid use only modestly decreased after initiation of biologic therapies (Table 2). The most recent publication on this topic found that although opioid use significantly decreased 12 months after RA patients initiated biologic medications, the overall prevalence of opioid use remained high at 40% [9▪▪]. It is unknown whether these patients use opioids after biologic initiation because of persistent inflammatory disease activity not sufficiently controlled on therapy, persistent pain not due to active RA, patient reluctance to stop opioids, or lack of physician initiative to taper opioids after initiating biologic therapy.

SYSTEMIC LUPUS ERYTHEMATOSUS

Prevalence of opioid use in SLE (Table 1)

Patients with SLE are more likely to receive long-term opioid prescriptions compared to patients without the rheumatic disease [28–29]. Retrospective analysis from the Truven MarketScan

Table 2. Changes in opioid use after starting biologic therapy for rheumatoid arthritis

Reference	Population	Time frame	Major results
Accortt *et al.* [12]	Truven Health MarketScan claims data	2010–2013	Opioid use (y/n) modestly decreased from 54.8% to 52.2% within the 12 months after initiation of etanercept (P <0.001).
Hunter *et al.* [9▪▪]	HealthCore Integrated Research Database claims data	2014–2017	Opioid use (y/n) decreased 12 months after initiating biologic therapy in patients with rheumatoid arthritis (52.0 vs. 40.4%, $P < 0.001$).
Park *et al.* [10]	IQVIA Health Plan Claims Data	2007–2015	Opioid use (y/n) modestly decreased from 54.0% to 51.0% ($P=0.006$) after initiation of TNFi. 38.8% used chronic opioids over entire 24-month study. Twenty-eight percentage of patients who had opioid use prior to TNFi initiation discontinued opioids thereafter, but 26.5% not prescribed opioids prior to TNFi initiated opioids after TNFi was started. The proportion of patients receiving $\geq$ 50 mg median daily morphine equivalent dose modestly decreased from 12.6% to 10.6% in the 12 months after TNFi initiation ($P = 0.005$).

TNFi, tumor necrosis factor inhibitor; y/n, Yes/No.

administrative claims database from 2012 to 2018 showed that 53% of SLE patients used opioids in one year, with 18% chronic use [30▪]. There was no difference in the prevalence of opioid use in the 6 months prior to compared to the 6 months after initiation of belimumab, despite a decrease in oral corticosteroids after belimumab [30▪]. The underlying reason for persistent opioid use after therapy was not identified.

Efficacy and safety of opioid use in SLE

There is no evidence to support chronic opioid therapy in SLE, and increased opioid utilization may lead to worse outcomes for SLE patients. In 2016, US hospitalizations for SLE patients had over a 2-fold higher estimated risk of a primary diagnosis of opioid overdose compared to other hospitalizations [22].

Factors associated with chronic opioid use in SLE

Focusing on SLE ED encounters may help identify risk for and prevent some chronic opioid use in SLE patients. SLE patients using opioids were more likely to have had an emergency department (ED) visit within the preceding 12 months [28]. Lee and colleagues evaluated SLE patients with frequent ED visits at one tertiary academic medical center [31,32▪]. They found that one-third of these patients were on long-term opioid therapy, 55% had pain-related diagnoses on ED discharge, opioids were administered during 38% of encounters, and 17% of the ED discharges included an opioid prescription. Future research can identify potential outpatient and ED interventions to reduce visits for chronic pain and to prevent long-term continuation of opioids started for acute pain.

PSORIASIS AND PSORIATIC ARTHRITIS

Pain in psoriasis and psoriatic arthritis

Psoriatic arthritis is diagnosed in a fourth of patients with psoriasis and can cause painful arthritis or enthesitis [33]. Psoriatic skin lesions can also be painful [34▪]. Approximately half of patients with psoriasis and without diagnosed psoriatic arthritis report moderate to severe joint pain, a greater proportion than controls [34▪], which could potentially indicate underdiagnosed and undertreated psoriatic arthritis, or noninflammatory processes which are causing joint pain in this population.

Prevalence of opioid use in psoriasis or psoriatic arthritis (Table 1)

A recent study from the Danish Skin Cohort reported that patients with psoriasis and psoriatic arthritis are more likely to use opioids than the general population (18–25% of patients with psoriatic arthritis, 13–15% of patients with psoriasis, and 9% of control patients used an opioid within a year) [34▪]. Furthermore, the rate of outpatient opioid prescribing for patients with psoriasis or psoriatic arthritis has increased over time in the US from an estimated 4.9% of outpatient visits in 2006–2011 up to 16.3% of outpatient visits in 2012–2016 [35].

Patients prescribed biologic therapy also have a high rate of opioid use. Psoriatic arthritis patients

taking a tumor necrosis factor inhibitor (TNFi) or antiinterleukin (IL)-12/23 inhibitor have frequently (17%) been prescribed opioid medications [36]. Moreover, Hunter and colleagues showed that opioid use only decreased a small amount (38.1% vs. 33.8%, $P = 0.013$) after biologic initiation in an analysis of 2013–2019 claims data [9▪▪].

Factors associated with opioid use in psoriasis or psoriatic arthritis

As noted in other rheumatic diseases, depression and anxiety are common comorbidities for patients with psoriasis or psoriatic arthritis [36–37]. Depression may be associated with opioid prescription among patients with psoriasis [38].

ANKYLOSING SPONDYLITIS

Prevalence of opioid use in ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the axial spine and commonly associated with stiffness and pain. Few publications evaluate opioid use in patients with AS. Despite a lack of evidence, opioid use is common among patients with AS with an estimated prevalence of 19–57% (Table 1) [39–41]. In a recent retrospective analysis, opioid use only slightly decreased without statistical significance in the 12 months after biologic initiation (42.6 vs. 36.2%, not significant) [9▪▪].

Factors associated with opioid use in AS

An increased association between chronic opioid use and anxiolytic or muscle relaxant use has been described in different AS cohorts [40–41]. These medication combinations could potentially raise the risk for oversedation.

SYSTEMIC SCLEROSIS

Our literature search did not identify relevant recent publications examining the efficacy, tolerability, or side effects of oral opioids among patients with systemic sclerosis. There is sparse prior literature in systemic sclerosis discussing the efficacy of opioid analgesics to manage painful skin ulcers [42–43]. Since these patients often experience pain from inflammatory arthritis and other disease manifestations, we suspect a large proportion of patients with systemic sclerosis may be receiving chronic opioids.

DISCUSSION

Although there is no available data showing benefit of long-term opioid use in patients with inflammatory rheumatic diseases, there is a high rate of opioid use in these patients, and high persistent use even after initiating biologic therapy. Chronic opioid therapy for noncancer noninflammatory musculoskeletal pain has been associated with increased pain intensity and no improvement in pain-related function long-term [16]. Chronic opioids can also cause nausea, altered mental status, dependence, addiction, and opioid induced hyperalgesia [44–46]. Available evidence suggests potential adverse effects of opioids in patients with rheumatic disease, including increased fracture risk, increased opioid overdose hospitalizations, and delayed or diminished use of appropriate DMARD therapy.

Nevertheless, in select patients the benefits of chronic opioid therapy may outweigh the risks. Randomized controlled trials or observational studies evaluating the efficacy of chronic opioid therapy, specific indications, and the full spectrum of potential adverse effects in patients with inflammatory rheumatic disease is lacking and warrants further exploration.

Expert committee recommendations provide some guidance regarding pain control for certain rheumatic conditions. The European League Against Rheumatism (EULAR) [47] recommendations for pain control for inflammatory arthritis and osteoarthritis focus on a patient-centered approach, with treatment including a combination of education, orthotics, psychosocial interventions, sleep hygiene education, physical activity, weight management, and pharmacological therapies first considering paracetamol and intra-articular injections as well as treating active inflammation with DMARDs to prevent damage accumulation. The guidelines from the Assessments in Spondyloarthritis International Society/EULAR notes a lack of formal evidence for opioids in AS and makes a weak recommendation by expert opinion to consider opioid medications for residual pain if recommended treatments for AS have failed or were poorly tolerated [48]. Given the high prevalence of chronic pain among patients with rheumatic disease, future task forces in rheumatology may consider investigating and providing additional formal guidance regarding appropriate pain management and opioid use.

Prior to initiating opioids in patients with inflammatory rheumatic conditions, treating practitioners may consider the origin of a patient's pain to treat the underlying disease process appropriately (e.g. undertreated active inflammatory arthritis, irreversible joint damage, fibromyalgia or other pain syndrome, etc.) preserving opioids for severe acute pain, and aiming to minimize routine long-term use. Moreover, the therapeutic objective of treatment, whether improved function or quality of life

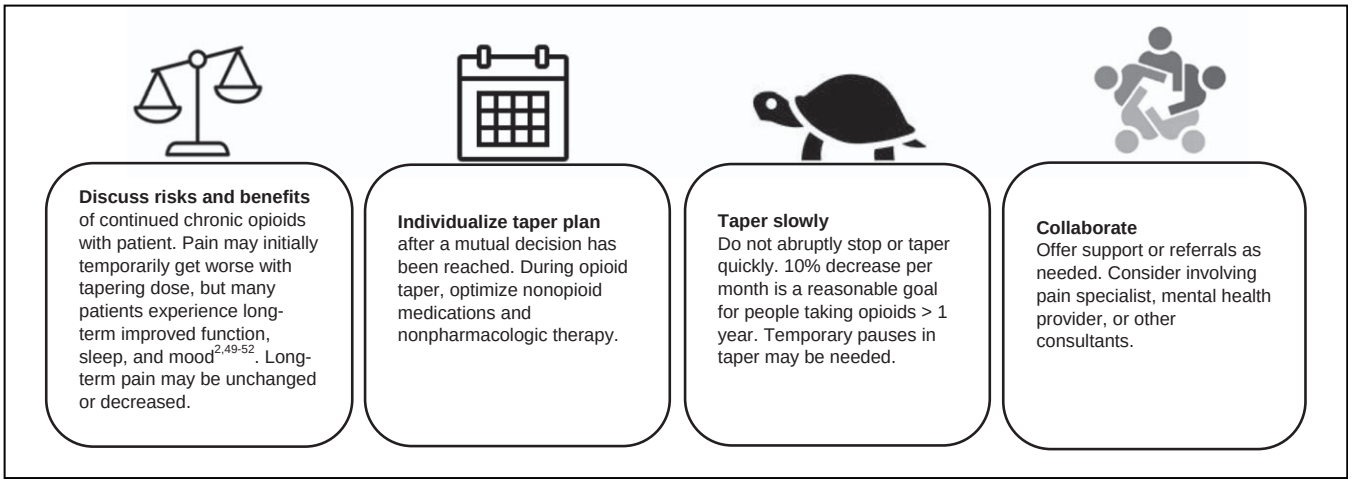

FIGURE 1. Steps for opioid tapering.

or other reason needs to be determined prior to initiation, and with the understanding that there is currently no evidence showing improved function or pain in patients with inflammatory rheumatic diseases on long-term opioids.

Resources are available to help patients and providers who jointly thoughtfully decide to initiate opioid tapering. Taper may not be appropriate for all patients. Reducing opioid use is not an authoritative process, but instead individualized through shared decision-making and based on patient goals and comorbidities. Although short-term pain often increases during taper, tapering opioids may be associated with improved function, sleep, mood, and either unchanged or reduced pain long-term for many patients [49–52]. Figure 1 provides a summary of selected steps in opioid tapering [2,49,50] and additional resources can be obtained from the CDC [2,49]. Opioid tapering has inherent risks (withdrawal symptoms, worsened pain, patient opioid seeking behaviors either within or outside the healthcare system, overdose with reinitiation of prior high doses), and often requires a pain specialist and multidisciplinary involvement to improve patient outcomes.

CONCLUSION

Future research should evaluate whether chronic opioids have efficacy, even for narrow indications, in patients with inflammatory rheumatic disease and should identify alternative nonpharmacological and pharmacological tools for pain management in rheumatic diseases with a goal to reduce initial opioid prescriptions for nonacute pain.

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Conflicts of interest

There are no conflicts of interest.

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

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Dual-energy computed tomography in crystalline arthritis: knowns and unknowns

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Purpose of review
To give an overview of what can reasonably be considered as known about dual-energy computed tomography (DECT) in crystal-related arthropathies, and what still needs to be explored.

Recent findings
Recent studies suggest an overall superiority of DECT over ultrasound in gout in terms of sensitivity (89 vs. 84%) and specificity (91 vs. 84%), except in early disease. Additional studies are needed to optimize DECT postprocessing settings in order to improve the specificity of the technique and eliminate all artifacts. Evidence has been controversial concerning DECT's ability to detect monosodium urate (MSU) crystal deposits on vessel walls, or whether or not MSU-coded plaques are artifacts. DECT can be used to monitor MSU crystal depletion during urate-lowering treatment; MSU crystal volume is associated with cardiovascular risk and disease activity. There are some reports on calcium-containing crystal deposition diseases (calcium pyrophosphate and basic calcium phosphate) demonstrating that DECT can characterize and discriminate between the different types of crystals.

Summary
Our knowledge about the use of DECT in crystal-related arthropathies continues to expand. Some unknowns have been clarified but there's still lots to learn, particularly concerning gout management and the potential use of DECT in calcium-containing crystal-related arthropathies.

Keywords
calcium pyrophosphate deposition disease, dual-energy computed tomography, gout

INTRODUCTION

Dual-energy computed tomography (DECT) continues to be an exciting novelty in the field of crystal-related musculoskeletal disorders since it was first used in gout patients more than a decade ago [1▪▪]. The impressive images generated by DECT led to its adoption by researchers and physicians with an interest in gout. The first questions to be answered were related to how useful DECT could be for the diagnosis of gout, and more recently whether repeated explorations could contribute usefully to disease management, an area still largely unknown. Today, both the European Alliance of Associations for Rheumatology (EULAR) guidelines and the 2015 American College of Rheumatology (ACR)/EULAR classification criteria of gout recognize DECT as a useful tool for the diagnosis of gout [2▪▪,3▪▪]. The development of DECT protocols for calcium-containing crystal diseases, namely calcium pyrophosphate deposition disease (CPPD) and basic calcium phosphate (BCP) deposition disease, started only recently, raising many new questions on how the technique could be useful. So far, only a few have been answered.

The objective of this narrative review is to recall what can be reasonably considered as known about the use of DECT in crystal-related arthropathies, and what still needs to be explored.

DUAL-ENERGY COMPUTED TOMOGRAPHY IN GOUT: A GROWING BODY OF EVIDENCE FOR MORE THAN A DECADE

The first reports that DECT could be used in gout were made before 2010 in series of tophaceous gout patients [1▪▪]. These studies included the now famous 3D color-coded images visualizing clumps

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KEY POINTS

- DECT is the imaging technique with the best diagnostic performances in gout, except in very early disease.
- DECT is useful to monitor MSU crystal dissolution during treatment and exhibits persistent crystal loads even after 2 years of treat-to-target therapy.
- DECT is helpful in characterizing and discriminating calcium-containing crystals, so far mostly with research applications.

of MSU crystal deposits displayed in a color different from that of bone. The underlying principle of the technique is that the X-ray beam attenuation (i.e. tissue absorption) in a tissue containing a sufficient quantity of monosodium urate (MSU) crystals, unlike the same crystal-free tissue, varies with the level of the X-ray energy (usually 80 and 140 kV).

Specifically, X-ray attenuation (measured in Hounsfield units, HU) is increased in the presence of MSU crystals, in comparison with crystal-free tissue. A convenient way of understanding what happens is to represent X-ray attenuation on a graph with the attenuation values (in HU) on the *y*-axis, and the X-ray beam energy (kV) values on the *x*-axis (Fig. 1). In soft tissue, attenuation increases proportionally to X-ray energy, whether MSU is present or not (dashed line), yet the presence of MSU increases electronic density (Rho), and therefore, 'pushes' attenuation dots along the line. The interaction between MSU and X-ray relies on the Compton effect, whereas the photoelectric effect is not significant. Compton scattering predominates at high energies and is related to the tissue volumetric mass and provides an assessment of the electron density (Rho) of considered voxel. Typically, monosodium urate deposits have a low atomic number and their presence has a neutral effect on the photoelectric effect while increasing the tissue volumetric mass, and therefore, has the same Zeff as surrounding soft tissue but an increased Rho detected with DECT. The photoelectric effect occurs in biological materials with higher atomic number values (*Z*), such as calcium (calcium pyrophosphate, basic calcium phosphate, bone), and increases the slope of the line. As a consequence, attenuation properties measured at 80 and 140 kV define the position of the dots on the graph and makes it possible to characterize the tissue based on its biochemical signature.

Diagnostic performance of dual-energy computed tomography in gout

The diagnostic relevance of DECT has been investigated in gout patients for more than a decade. The

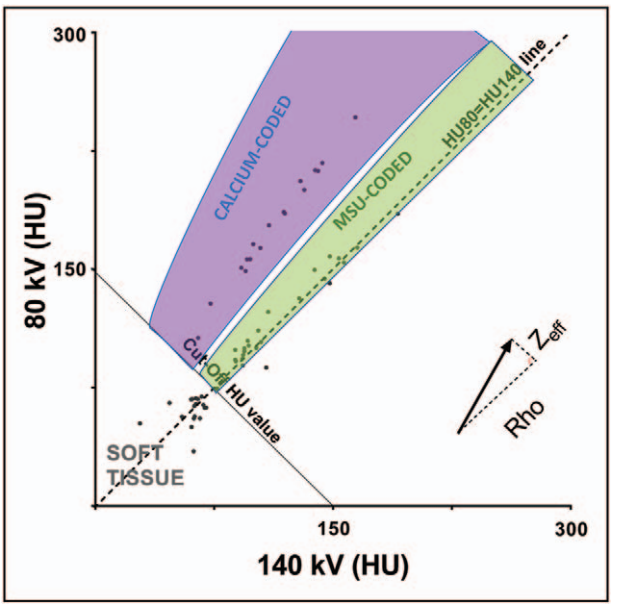

FIGURE 1. Principle of monosodium urate-coding by postprocessing software of dual-energy computed tomography scans. Combined effects of volumetric mass density (Rho) and effective atomic number (Zeff) on computed tomography (CT) numbers at 80 and 140 kV for tophi. Each dot representing a combined value of attenuations at 140 and 80 kV will be coded as MSU (green box) if situated above the cut-off line and around the line where attenuations at both energies are equal. Dots below the cut-off line will be coded as soft-tissue, and dots above the bow will be coded as calcium (purple box). HU, Hounsfield unit; MSU, monosodium urate.

performance level has been excellent, particularly in patients with established disease. The real question is DECT's performance level compared with ultrasound, the established imaging technique commonly used in clinical practice [4].

Performance level: dual-energy computed tomography versus ultrasound

Several studies have reported systematic assessment of gout patients with both DECT and ultrasound. Most of these studies were retrospective, with small sample sizes and uneven disease duration; observer blinding was inconsistent and gold standards varied [5–9,10]. The results of these comparisons between the two techniques varied from one study to another, depending on disease duration, and/or, which joints were assessed because of a lack of standardization in routine practice leading to various center-dependent protocols. One group performed a pooled meta-analysis that showed an overall superiority of DECT detection of MSU deposits over ultrasound in terms of sensitivity (89 vs. 84%) and specificity (91 vs. 84%)

when both the ultrasound double contour sign and tophi were included in the assessment [11]. Our group recently reported comparative and combined performances of systematic scanning of knees and ankles/feet both with DECT and ultrasound in a cohort of 147 patients. Our diagnostic gold standards were: presence of MSU crystals in synovial fluid, and fulfilment of the 2015 ACR/EULAR gout classification criteria (i.e. $\geq$8 points) while not scoring points for imaging features, that is, fulfilling classification criteria by clinical items alone [12,13▪]. The results of this study also favored the performance of DECT over ultrasound, mainly because of the questionable reliability of the double contour sign in the foot (especially for the first metatarsalphalangeal joint). Of note, combining the two techniques did not provide significant improvement in diagnostic performance over DECT alone [13▪]. However, in early disease (symptom duration <1 or 2 years), DECT sensitivity may be insufficient, owing to a spatial resolution of several hundred microns at best, precluding detection of small deposits. A recent cohort study of 196 patients compared the diagnostic performance of DECT alone according to disease duration [14]. DECT demonstrated poor sensitivity (38%) in very early disease (<1 year), a situation where ultrasound usually displays better performance.

To sum up, we may not yet be in the 'fully known' section but DECT seems to perform better than ultrasound in terms of diagnosis, particularly for the ankles and feet (results are more uneven for the upper limbs), except for very early disease where false-negative DECT is frequent (whereas the ultrasound double contour sign has better chances of being positive) [10,14].

Optimizing dual-energy computed tomography settings to improve specificity and avoid artifacts

Surprisingly, many unknowns in DECT are related to the postprocessing settings, which are decisive in making MSU-coded lesions appear or disappear [15]. Most postprocessing software default settings were chosen based on the results of small cadaver studies and may not always reflect the real volume of crystals observed at the histopathological examination, which can only provide a two-dimensional assessment [16]. Several attempts have been made to optimize these default settings but the gold standard of a histopathological examination is still lacking, for obvious ethical reasons, except in cadaver studies [17]. Most DECT artifacts are well known, as they can be misidentified as MSU occurrence (mainly nail beds for feet, skin thickening, tendon reflection zone, bone surfaces), and attempts are made to optimize software settings to avoid these misleading images before assessing total MSU volume [18,19▪].

Artifacts are often small, and more and more authors tend to select only lesions at least 2 mm in diameter to preserve specificity (the 2015 ACR/EULAR classification criteria only exclude submillimeter lesions as artifacts [3▪▪]). In addition, DECT parameters depend on the type of machine used and its brand. Most of the published literature contains reports of studies using Siemens and to a lesser extent General Electric machines, and it is still largely unknown whether results from a certain type of machine can be reproduced on another.

Beyond joints: dual-energy computed tomography detection of monosodium urate crystal deposition in organs

MSU crystal deposition is an issue not only inside and around joints, but also in organs. In situations of dramatic global deposition for instance, MSU crystals can be found abundantly with DECT in kidneys [20]. The key question however remaining at stake is whether MSU crystal deposition within the cardiovascular system is relevant – with the potential of a contributing explanation for the increased number of cardiovascular events in gout patients – and whether DECT is able to detect and quantify such deposition which has been suggested by histological studies [21]. So far, the available data on the issue have been controversial. The first published study comparing coronary and aorta DECT scans from 59 gout patients and 47 controls showed that MSU-coded plaques were more frequently found in gout patients (86.4 vs 14.9%, $P < 0.001$) [22▪▪]. These deposits were found in patients with the highest calcium scores. The same results were found by the same group in a similar study separating the control group into hyperuricemic and non-hyperuricemic controls [23]. Our group provided conflicting data from a study of popliteal artery plaques in 126 gout patients and 26 controls, showing that MSU-coded plaques were equally prevalent between groups [24▪▪]. Contrary to the study from Klauser *et al.*, prevalence of calcified plaques was similar between gout patients and controls. A follow-up substudy including 17 patients showed that MSU-coded plaques persisted despite extensive MSU crystal dissolution in joints under urate-lowering therapy. Finally, the analysis of plaques exhibited differences with classical MSU crystal deposition with unusually high Zeff values [reflecting the presence of a photoelectric effect which MSU is not supposed to create (Fig. 1)], suggested that these plaques could be early calcified plaques. This hypothesis was supported by the observation of

an initially MSU-coded plaque which was later on coded as a calcified plaque during follow-up. Other studies are needed (some are under way) to provide new data to determine if all of these MSU-coded plaques should be considered as artifacts or not, in which case DECT would provide additional significant information for the management of cardiovascular disease in patients with gout.

While it is still unknown whether these MSU vascular plaques are real or not, DECT has already provided insight into the importance of measuring the initial crystal load for predicting cardiovascular risk. Cross-sectional studies showed an association linking the volume of MSU crystal deposits measured with DECT at the knees and feet with chronic heart failure and diabetes, irrespectively of usual cardiovascular risk factors [25–27]. A prospective cohort study of 128 patients followed-up for up to 3 years with baseline DECT scans of the knees and feet showed that patients with the higher crystal burdens at baseline had the highest mortality and cardiovascular risks [28▪]. The volume of MSU crystals measured with DECT (HR 1.02, 95% CI 1.002–1.03) and serum urate levels (HR 1.04, 95% CI 1.003–1.06) at baseline were the only two factors significantly associated with mortality, mainly from cardiovascular causes.

Quantifying monosodium urate crystals at baseline and during follow-up

Although the use of DECT for the diagnosis of gout has been explored since the emergence of this application of the technique, its usefulness for predicting and managing the disease is of more recent interest [4]. One of the main advantages DECT is its ability to quantify directly the crystal load of the scanned location. Indeed, although ultrasound has the advantage of giving a clue about the tophi's inflammatory cellular response, something DECT cannot do, ultrasound cannot distinguish MSU from calcification in a mature tophus. The two techniques, therefore, provide different volumes for the same measured tophi [29▪].

A cohort study of 78 patients from our group showed that the baseline MSU crystal volume at the feet was a predictor of upcoming flares in the following 6 months. Each 1 cm^3 increase in MSU crystal volume increased the risk of flare with an odds ratio of 2.03 (1.15–4.38) [30▪]. Such data need to be reproduced in other studies to determine if complete/significant MSU crystal depletion in DECT should indicate when to stop anti-inflammatory prophylaxis, such as colchicine when ULT is at a steady dose. This question in particular needs to be answered, given that recent data on the kinetics of crystal load depletion under urate-lowering therapy monitored with DECT displayed significant remaining volumes of MSU crystals even after 2 years of well conducted (treat-to-target) treatment [31▪,32,33▪]. Our group's experience is that patients with significant deposits at baseline (>1 cm^3) and treated-to-target deplete more than 90% at least of their initial deposits at 2 years (Fig. 2). These studies also brought insight on the 'knowns and unknowns' of gout itself in explaining why so many patients reaching serum urate targets still kept on flaring for several months – simply as they still have substantial amounts of crystals for a long time [34]. What is starting to be known on the use of DECT for gout management has probably raised as many questions as answers. Although serum urate is and will remain the central landmark for long-term management of the disease in most patients, DECT may be useful in managing patients requiring more intensive urate-lowering and/or anti-inflammatory therapy but also more attention to their comorbidities.

DUAL-ENERGY COMPUTED TOMOGRAPHY IN CALCIUM-CONTAINING DEPOSITION DISEASES: AN EMERGING ERA PAVING THE WAY FOR PHOTON-COUNTING COMPUTED TOMOGRAPHY

As always, calcium-containing crystal arthropathies are second-in-line in terms of scientific progress, and usually benefit from the discoveries made in gout. It is, therefore, not a surprise that DECT was applied to CPPD (as well as BCP disease) only recently, first in crystal-containing phantoms [35].

Dual-energy computed tomography in calcium pyrophosphate deposition disease

DECT posttreatment algorithms, which were designed to distinguish urate from calcium in gout patients, are not applicable to patients with calcium-containing crystal arthropathies. This means that researchers and clinicians have had to go back to the fundamental physics and basic DECT parameters. Although in gout, DECT mostly exploits the fact that MSU crystals, via Compton scattering, increase the electronic density (Rho) of the tissue they are deposited in, the characterization and discrimination of calcium crystals with DECT depends on the quantity of the photoelectric effect [quantified in Zeff and dual-energy index (DEI) values] produced by the tissue (Fig. 3). The photoelectric effect predominates at low energies and highly relates to the chemical composition of the tissue exposed to the energetic beam and provides an averaged atomic

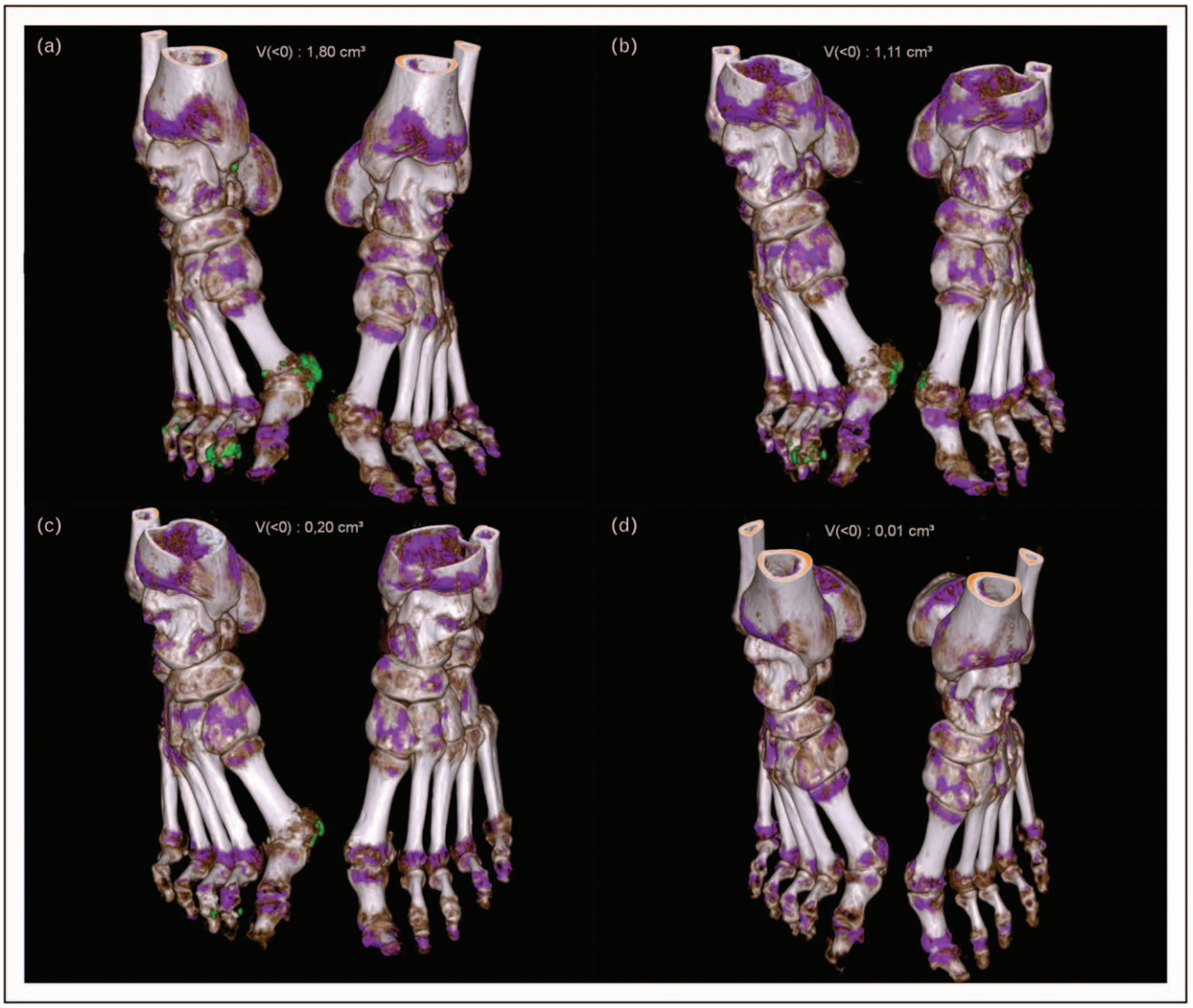

FIGURE 2. Monitoring monosodium urate crystal dissolution volume in a 75-year-old woman undergoing treat-to-target urate-lowering therapy. DECT scans of the ankles/feet at (a) baseline, (b) 6 months, (c) 12 months and (d) 24 months, with removal of known artifacts (mostly nail beds).

number of the considered voxel (Zeff). The higher the atomic number (e.g. calcium), the more sensitive to photoelectric effect the compound is [36▪▪]. The DEI provides an information combining predominantly the photoelectric effect and Compton scattering to a lesser extent. Our group published the proof-of-concept study including 21 patients with chondrocalcinosis and 19 controls, demonstrating that menisci with calcium pyrophosphate crystal deposits exhibited specific DECT parameters different from calcification-free menisci but also from the hydroxyapatite contained in subchondral and trabecular bone [36▪▪]. Using postprocessing settings provided by the manufacturer based on DEI values, a pilot study including 10 CPPD patients showed 90% sensitivity versus 40% for plain X-rays [37]. Further validation of postprocessing settings for the automatic quantification of CPP crystals using predefined ranges of DEI values could include cadaver studies (such as what had been performed for MSU crystals), and/or probably more easily through a comparison with volumes obtained from manual selection of chondrocalcinosis on conventional CT images. It was, however, still unclear whether DECT would be able to improve the sensitivity for chondrocalcinosis detection provided by conventional (mono-energetic) CT. A study including 132 patients with ($n = 82$) or without ($n = 50$) chondrocalcinosis was designed to determine the ability of DECT to detect modifications of DECT parameters of menisci from patients with CPPD on prespecified slices where chondrocalcinosis was not visible on conventional CT [38▪▪]. Despite a numerical trend towards increased DEI values for menisci in

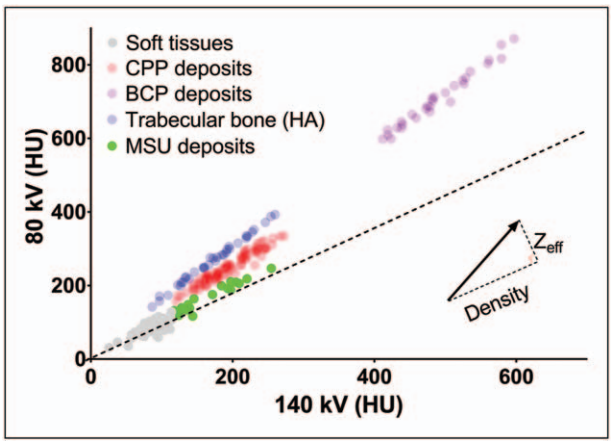

FIGURE 3. Discrimination of calcium-containing structures and monosodium urate with dual-energy computed tomography scans. Combined effects of volumetric mass density (Rho) and effective atomic number (Zeff) on computed tomography (CT) numbers at 80 and 140 kV for tophi, trabecular bone, calcium pyrophosphate (CPP) crystal deposits, basic calcium phosphate (BCP) deposits and soft tissue. The slope of each material is correlated with its Zeff and photoelectric effect; the steeper the slope, the higher the discrimination potential using DECT. HA, hydroxyapatite; HU, Hounsfield unit.

the CPPD group, the difference did not reach statistical significance ($P = 0.09$). Moreover, a large overlap of values between the CPPD and the control group supported the conclusion that DECT would be unable to detect 'CT-invisible chondrocalcinosis'.

Discriminating calcium pyrophosphate from basic calcium phosphate crystals using dual-energy computed tomography

The proof-of-concept study of DECT in CPPD had shown that calcium pyrophosphate deposits exhibit different DECT characteristics from the hydroxyapatite contained in bone [36▪▪]. A further study, using Raman spectroscopy as the gold standard, investigated whether BCP deposits in tendons also differed from calcium pyrophosphate deposits in terms of DECT parameters [39]. The study compared the DECT parameters of calcifications from 13 patients with BCP deposition disease and 11 CPPD patients. The results showed that BCP deposits exhibited higher Zeff ($P < 0.05$) and DEI values ($P < 0.01$) than calcium pyrophosphate crystals once adjusted on calcification density. Most of the time, DECT is not needed to distinguish BCP from calcium pyrophosphate deposits in clinical practice given that in general radiographic signs associated with crystal topography make it easy to identify both crystals. The cervical spine is probably the only location where the nature of the incriminated crystal can be challenging, and specific studies are needed to determine if DECT can be helpful in such circumstances. To date, knowing that DECT is able to discriminate between calcium pyrophosphate and BCP crystal deposits is probably most interesting in the research setting (Fig. 4).

Although many unknowns remain regarding how and whether DECT might add to the diagnosis and management of CPPD and BCP deposition, particularly compared with conventional CT, exploring and demonstrating the concept that such

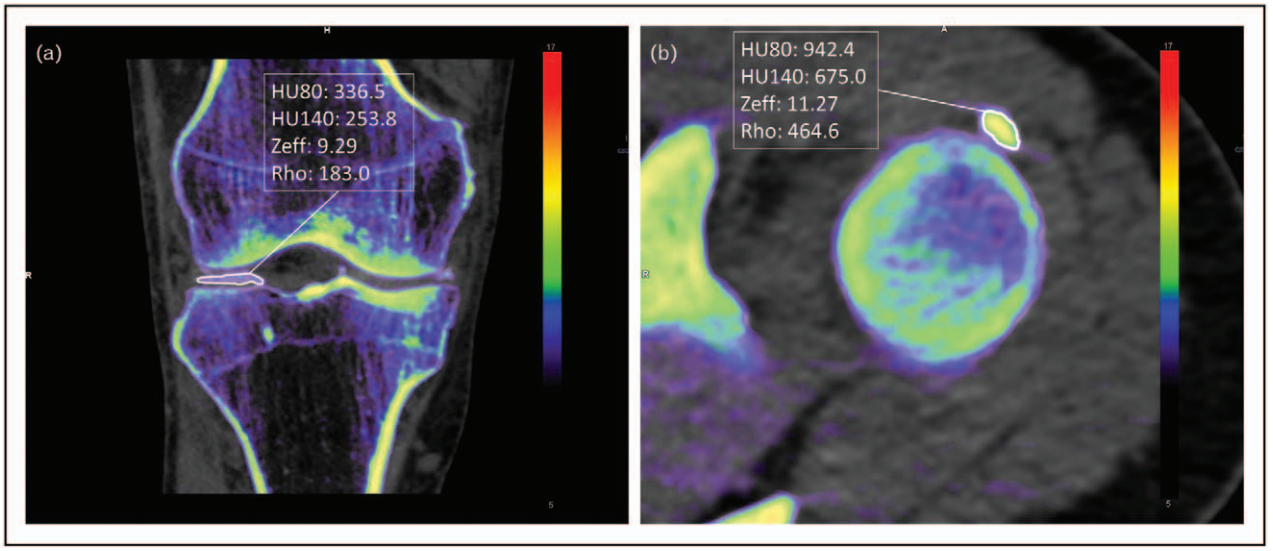

FIGURE 4. Measurements of dual-energy computed tomography parameters in (a) calcium pyrophosphate crystal deposition and (b) basic calcium phosphate deposition. HU, Hounsfield unit; Rho, electron density; Zeff, effective atomic number.

CTs can help characterize (and discriminate) calcium-containing crystals is of importance in basic research, particularly in osteoarthritis in which the involvement of calcium-containing crystals is highly suspected. Furthermore, the development of photon-counting CTs will certainly rely on the advances made in DECT to reach reliable statistical and clinical relevance in detecting, characterizing and discriminating calcium-containing crystals [40,41▪,42]. Not only will photon-counting CTs improve the spatial resolution compared with DECT but will provide a continuous range of energy-dependent HU values, which will increase the specificity of material characterization [41▪].

CONCLUSION

Knowledge on DECT in crystal-related arthropathies remains young but is moving fast. Some unknowns have been clarified but there's still lots to explore. For the diagnosis of gout, the role of DECT and its hierarchy with other imaging techniques is getting clearer. Data on DECT in the management and follow-up of the disease is starting to be gathered but a standardized use, if any, has not yet been agreed upon. Applying DECT to calcium-containing crystal deposition brought in interesting concepts about crystal discrimination and potential quantification. Many may already be applicable in certain specific diagnostic situations, and may be a significant asset by providing an in-vivo tool for research on the pathogenicity of calcium crystals, particularly discussed in osteoarthritis.

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Conflicts of interest

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Gout and the COVID-19 pandemic

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Purpose of review
This review gives an overview of recently published articles on COVID-19 and gout.

Recent findings
People with gout are likely to be at an increased risk of poor outcomes after COVID-19 infection due to comorbid cardiometabolic conditions. The effects of chronic hyperuricemia on trained immunity, and the hyperinflammatory state induced by gout itself may also play a role. Frequent courses of glucocorticoids for gout flares may be associated with adverse outcomes after COVID-19 infection and reduced immunogenicity to the COVID-19 vaccination. Similarities between the pathophysiology of gout flares and the dysregulated inflammatory response of severe COVID-19 have been identified. Medications used in the treatment of gout, including colchicine and interleukin-1 inhibitors, have shown promise in the treatment of COVID-19 in clinical trials. Overall, the COVID-19 pandemic has had a negative impact on gout care, with patients reporting more difficulty with disease control, accessing medications and healthcare, and poorer quality of life.

Summary
The COVID-19 pandemic has created many challenges for people with gout. At present, there is a lack of guidance on the management of gout during the pandemic and paucity of research assessing outcomes of COVID-19 infection in people with gout.

Keywords
colchicine, COVID-19, gout, interleukin-1 inhibitor, SARS-CoV-2

INTRODUCTION

The COVID-19 pandemic has caused significant morbidity and mortality worldwide, and impacted the care of people with rheumatic diseases. Gout is the most common inflammatory arthritis in adults, affecting approximately 9.2 million Americans, and is a rheumatic disease of public health importance [1]. People with gout are likely to have a high absolute risk of poor outcomes after COVID-19 infection due to coexistent cardiometabolic comorbidities and their underlying biology, with a tendency to a hyperinflammatory state [2]. Similarities between the pathophysiology of gout flares and the dysregulated inflammation of severe COVID-19 have also led to interest in the use of gout medications in the treatment of COVID-19 [3]. Like other people with rheumatic diseases, people with gout have had their medical care disrupted during the pandemic [4▪▪]. In this review, we examine and discuss the current literature on gout and its management during the COVID-19 pandemic.

GOUT AND COVID-19 OUTCOMES

An analysis of the UK Biobank cohort by Topless *et al.* [5▪▪] in the early phase of the COVID-19 pandemic (March–August 2020) found that gout was associated with a 1.5-fold [95% confidence interval (95% CI) 1.2–1.8] increased risk of COVID-19 infection and a 1.7-fold (95% CI 1.2–2.4) increased risk of COVID-19-related death in a model adjusting for age, sex, ethnicity, deprivation index, BMI and smoking status. However, in a model further adjusting for comorbidities, including diabetes, cerebrovascular diseases, cardiovascular diseases (CVDs), chronic kidney disease, pulmonary conditions, dementia, cancer, rheumatoid arthritis and osteoarthritis, gout was no longer associated with COVID-19 infection [odds ratio (OR) 1.01,

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KEY POINTS

- People with gout are likely to have a high absolute risk of poor outcomes after COVID-19 infection due to coexistent cardiometabolic comorbidities, the effects of chronic hyperuricemia on trained immunity and the hyperinflammatory state induced by gout itself.
- People with gout should receive priority for the COVID-19 vaccination, alongside other people with autoimmune and inflammatory rheumatic diseases.
- Anti-inflammatory agents commonly used in the treatment of gout, including colchicine and interleukin-1 inhibitors, have been studied for the treatment of COVID-19 infection to dampen the dysfunctional inflammatory response.
- The COVID-19 pandemic has had a negative impact on healthcare provision for people with gout.
- Gout remains under-represented in publications describing COVID-19 outcomes in people with rheumatic diseases and in guidelines addressing management of rheumatic diseases during the pandemic.

95% CI 0.83–1.24] or COVID-19-related death (OR 1.18, 95% CI 0.84–1.65) [5▪▪]. These findings suggest that gout itself is not an independent risk factor for COVID-19 infection or mortality, but that the cardiometabolic conditions frequently coexistent with gout are significant contributors to the increased risk of COVID-19 infection and COVID-19-related death observed in people with gout [5▪▪]. Other contributing factors to the increased risk in people with gout could include the pro-inflammatory effects of hyperuricemia and the inflammatory milieu induced by gout itself. In addition, frequent courses of glucocorticoids for management of gout flares may also contribute to adverse outcomes after COVID-19 infection.

Cardiometabolic comorbidities

People with gout frequently have cardiometabolic comorbidities such as overweight or obesity, CVD, diabetes and chronic kidney disease [6], which are all established risk factors for hospital admission and mortality in COVID-19 infection [7▪]. These risk factors are even more pronounced for people with gout who are referred to secondary or tertiary rheumatology clinics. For example, a prior analysis in a secondary care rheumatology clinic in Aotearoa/New Zealand demonstrated that more than half of people with gout had a very high risk of a CVD event (≥20% risk of CVD events in 5 years), mostly due to existing CVD or diabetic nephropathy; one-third had type 2 diabetes; and 95% had overweight or obesity [8].

In the past year, algorithms have been developed to help clinicians estimate the risk of poor outcomes in people infected with COVID-19. The QCOVID and ALAMA COVID-19 Medical Risk Assessment calculators are validated population-based prediction models developed in the UK, which estimate the risk of COVID-19 associated hospital admission and COVID-19 associated death considering patients' demographic factors and medical comorbidities [9,10]. A similar risk prediction calculator for COVID-19 mortality has also been developed in the USA [11]. In the following scenarios, applying the QCOVID and ALAMA calculators to people with gout with cardiometabolic comorbidities highlights the increased risk of poor outcomes in this patient group. It should be noted, however, that gout is not included as a risk factor in the QCOVID or ALAMA calculators.

Patient 1: A 76-year-old woman with tophaceous gout and allopurinol intolerance. She has atrial fibrillation, heart failure and stage 3 CKD. BMI is 23.9 kg/m^2. She has not received prednisone in the last 6 months and is not taking immunosuppressive therapy. According to the QCOVID calculator, she is in rank 90 out of 100, where 100 is most at risk of a COVID-19 associated death. According to the ALAMA calculator, her COVID-age is more than 85 with a mortality estimate between 30 and 119/1000, placing her in a 'very high vulnerability' category.

Patient 2: A 58-year-old man with recurrent gout flares. He has type 2 diabetes, hypertension and dyslipidaemia, and has required two courses of high-dose prednisone to treat gout flares in the preceding 6 months. BMI is 39.2 kg/m^2. He is not taking immunosuppressive therapy. According to the QCOVID calculator, he is in rank 90 out of 100, where 100 is most at risk of a COVID-19 associated death. According to the ALAMA calculator, his COVID-age is more than 85 years with mortality estimate between 30 and 119/1000, placing him in a 'very high vulnerability' category.

Pro-inflammatory effects of hyperuricemia

Hyperuricemia is a prerequisite to the development of gout [6]. Recently, there has been growing interest in the pro-inflammatory effects of serum urate, in particular its ability to induce trained immunity to set up a state of chronic, maladaptive inflammation [12,13]. Studies have demonstrated that high concentrations of soluble urate alter the transcriptional programme of cells to modulate cytokine production and activate the NLRP3 inflammasome to induce production of interleukin-1β (IL-1β), a potent inflammatory cytokine [14,15]. In addition, high concentrations of soluble urate can drive

epigenetic reprogramming in myeloid cells, with both in-vitro and in-vivo models demonstrating that cells primed with soluble urate have persistently elevated levels of inflammatory cytokines with increased responsiveness to secondary stimuli [15,16]. Moreover, soluble urate induces the production of chemokine ligand 2, a monocyte chemoattractant that increases levels of circulating monocytes and primes them to respond rapidly to inflammatory stimuli [17]. Severe COVID-19 is characterized by an excessive and dysregulated inflammatory response to the SARS-CoV-2 virus. People with gout may therefore be at an increased risk of severe COVID-19 due to the trained immunity induced by longstanding hyperuricemia.

Interestingly, observational studies of serum urate in patients with COVID-19 have demonstrated that the prevalence of hypouricemia increases following hospital admission for COVID-19 due to proximal renal tubule dysfunction. An inverse association between serum urate levels and disease severity has also been observed in these studies [18,19]. Further research in people with gout and COVID-19 infection are needed to understand whether serum urate levels decline during COVID-19 infection and whether this is associated with adverse outcomes.

The inflammatory milieu of gout

Gout itself is caused by an exuberant autoinflammatory IL-1β driven innate immune system response to monosodium urate (MSU) crystals [20]. This tendency to a hyperinflammatory state has the potential to lead to an increased immune response to the SARS-CoV-2 virus. Poorer COVID-19 outcomes have also been associated with elevated serum levels of interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor α (TNF-α) [21▪], raising the possibility that people with gout may be at risk of a poor outcome because they also have higher circulating levels of these factors [22]. Although theoretically an exuberant innate immune response might pose a risk of developing dysregulated inflammation to the SARS-CoV-2 virus and a poorer outcome, emerging data in children suggest that a robust innate immune response may in fact be associated with better outcomes [23]. Further research into the role of the innate immune response on COVID-19 outcomes is required.

Glucocorticoid use

Glucocorticoids are used in the management of gout, with short courses of high-dose prednisone (20–40 mg daily) frequently prescribed for the management of acute flares. Glucocorticoid treatment is associated with a dose-dependent risk of opportunistic and serious bacterial infections [24]. This latter concern may be particularly important, as case series in China have demonstrated that up to half of all COVID-19 deaths were attributable to secondary bacterial infection [25]. A cross-sectional observational study assessing factors associated with COVID-19-related death in people with rheumatic diseases found that prednisone-equivalent doses more than 10 mg per day were associated with an increased risk of COVID-19 mortality compared with no glucocorticoid use (OR 1.69, 95% CI 1.18–2.41) [26▪]. However, this association was potentially confounded by the higher disease activity observed in patients on higher doses of prednisone, which itself is a risk factor for COVID-19 mortality. Further studies are needed to clarify the impact of glucocorticoids on COVID-19 outcomes and whether people with poorly controlled gout are at an increased risk of adverse outcomes from COVID-19 infection [26▪,27]. Currently, international rheumatology guidelines recommend that glucocorticoids, if indicated, should be used at the lowest possible dose to control rheumatic disease activity, regardless of COVID-19 exposure or infection status [28▪,29].

GOUT AND COVID-19 VACCINATION

The American College of Rheumatology (ACR) has recommended that people with autoimmune and inflammatory rheumatic diseases (AIIRDs) be prioritized for COVID-19 vaccination before the general population based on their increased risk for COVID-19 and adverse outcomes from COVID-19 infection [30▪]. Gout was not included in the ACR guidance. However, it seems appropriate that people with gout should also be prioritized for vaccination as they are at increased risk of poor outcomes from COVID-19 infection. The use of glucocorticoids in people with inflammatory diseases has been associated with reduced immunogenicity to vaccines [31]. A recent study demonstrated that the seropositivity rate following BNT162b2 mRNA COVID-19 vaccination in people with AIIRDs treated with glucocorticoids (mean dose 6.2 mg/day) was only 66% [32▪]. In view of this, maintaining disease control in people with gout to avoid frequent courses of glucocorticoids and using alternative anti-inflammatory therapies for gout flares should be emphasized during the COVID-19 pandemic. Recently, the Centers for Disease Control and Prevention has recommended an additional dose of the mRNA COVID-19 vaccine for patients who are moderately to severely immunocompromised including those receiving active treatment with high dose corticosteroids (≥20 mg per day) [33]. Patients with poorly controlled gout who

are taking frequent courses of glucocorticoids should be considered for an additional mRNA COVID-19 vaccine dose.

GOUT MEDICATIONS IN THE TREATMENT OF COVID-19

The development of severe COVID-19 is characterized by prolonged and exaggerated interactions between the innate and adaptive immune systems. This results in the unrestrained secretion of many pro-inflammatory cytokines, including IL-1, IL-6, IL-18, TNF-α and interferon-γ, resulting in a cytokine storm that causes acute respiratory distress syndrome and multiorgan failure [3,34,35]. Gout flares are characterized by a hyper-inflammatory state induced by MSU crystals, with elevated levels of IL-1β, IL-6, IL-8 and TNF-α observed in the affected joint [36]. Anti-inflammatory agents commonly used in the treatment of gout, including colchicine and IL-1 inhibitors, have been studied for the treatment of COVID-19 infection to dampen the dysfunctional host inflammatory response.

Colchicine

Colchicine is an anti-inflammatory agent used in the prevention and treatment of acute gout [6]. Its main mechanism of action is the inhibition of tubulin polymerization with consequent reduction of cellular adhesion molecule expression, neutrophil chemotaxis and migration, NLRP3 inflammasome activation, and production of inflammatory cytokines [37]. These properties have led to interest in its role in preventing the dysregulated inflammatory response seen in patients hospitalized with COVID-19. The Greek Effects of Colchicine in COVID-19 (GRECCO-19) trial was the first prospective open-label randomized trial evaluating colchicine versus usual care in early hospitalized patients. This study of 105 patients found a significant reduction in the primary clinical outcome of a two-point deterioration on WHO disease severity scale in patients receiving colchicine [38▪]. Subsequently, a randomized placebo-controlled trial conducted in 72 people hospitalized with moderate to severe COVID-19 found that patients receiving colchicine had less need for supplemental oxygen at day 7 (9 versus 42%, log rank; $P = 0.001$) and had a shorter duration of hospitalization than those receiving placebo [median (IQR) 7.0 (5.0–9.0) days versus 9.0 (7.0–12.0) days] [39▪]. On the contrary, the RECOVERY trial, a large randomized controlled open-label trial conducted in more than 11 000 adults hospitalized with COVID-19, found that colchicine use was not associated with reductions in 28-day mortality, duration of hospitalization or risk of progressing to invasive mechanical ventilation or death compared to usual care [40▪▪]. The role of colchicine in the outpatient setting has been studied in the COLCORONA trial (>4400 participants), which demonstrated that colchicine use (0.5 mg twice per day for 3 days then once per day for 27 days thereafter) led to a lower rate of the composite of death or hospital admission compared with placebo (OR 0.75; 95% CI 0.57–0.99, $P = 0.042$) among people with PCR-confirmed COVID-19 and risk factors for complications related to COVID-19 [41▪▪]. The potential benefits of colchicine in nonhospitalized patients, together with the known risks of corticosteroids, suggest that colchicine may be the preferred option for the management of gout flares during the pandemic [2].

Interleukin-1 inhibitors

IL-1β is an important mediator of acute gouty inflammation and also plays a central role in the cytokine storm of severe COVID-19 [3,6]. In recent years, agents inhibiting IL-1 action have been developed for the treatment of gout flares. Anakinra, a recombinant IL-1 receptor antagonist, is an effective treatment for gout flares [42] and is primarily used when there is intolerance or contraindication to first-line therapies. Canakinumab, a fully humanized mAb blocking IL-1β signalling, is highly effective in treatment and prevention of gout flares [43,44]. Both anakinra and canakinumab have been studied in the treatment of COVID-19 with variable results. Initial observational studies suggested possible efficacy of anakinra for mild-to-moderate, severe, or critical COVID-19 [45–48]. The SAVE-MORE multicentre randomized trial found that anakinra was associated with improved clinical status and mortality among people hospitalized with moderate to severe COVID-19 pneumonia with elevated serum urokinase plasminogen activator level [49▪]. However, in a randomized controlled trial nested in the CORIMUNO-19 cohort, anakinra did not improve mortality or the need for noninvasive or mechanical ventilation in those hospitalized with mild-to-moderate COVID-19 pneumonia [50▪]. Observational studies have also suggested that canakinumab improves oxygenation and decreases the systemic inflammatory response in people with COVID-19 [51,52]; however, in a randomized controlled trial conducted among people hospitalized with severe COVID-19, canakinumab did not improve mortality or reduce the need for invasive mechanical ventilation [53▪].

GOUT CARE DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has had a major impact on healthcare delivery for people with rheumatic

diseases. Social distancing requirements and 'lockdowns' have led to a significant increase in the use of telemedicine and a decrease in face-to-face clinic reviews [54]. During the pandemic, people with rheumatic diseases have had more difficulty accessing healthcare, experienced medication shortages, experienced increased levels of anxiety and depression and displayed adverse health behaviour changes (such as medication rationing and reluctance in attending face-to-face healthcare and laboratory monitoring appointments) [55▪]. In addition, a rise in unemployment and a decrease in full-time employment was observed among people with rheumatic diseases in the early stages of the pandemic [56▪]. People with gout have been similarly affected. An online survey undertaken in 122 people with gout found that 41% had more difficulty with their gout overall, including the management of gout flares, gout-related pain, performing activities at work and participating in social activities, during the pandemic. Thirty-seven percent had difficulty in accessing healthcare for gout in the outpatient clinic, and 17% had difficulty in accessing healthcare for gout in the emergency room or hospital. Twenty percent also reported difficulty in getting gout medication refills from the doctor. Overall, gout-specific health-related quality of life was worse compared with the prepandemic period and patients exhibited higher levels of psychological distress [4▪▪]. These observations are concerning as poorly controlled gout is associated with both articular and extra-articular complications. There is therefore an urgent need for strategies to improve gout care during the pandemic. Examples include a proactive approach to ensuring patients receive regular urate-lowering therapy, developing individualized action plans for gout flares, allowing easier access to telehealth appointments, and utilizing peer support groups. The encouraging results of the COLCORONA study may also lead to increased demand for colchicine and safeguards need to be put in place to ensure people with gout can access colchicine when required.

UNDER-REPRESENTATION OF GOUT IN THE CURRENT LITERATURE AND FUTURE RESEARCH

Despite the prevalence of gout, few studies have examined the impact of the COVID-19 pandemic on people with gout, and management of gout during the pandemic has not been specifically addressed in guidelines published by international rheumatology societies. Although people with gout are at an increased risk of poor outcomes following COVID-19 infection, gout has also been underrepresented in publications describing COVID-19 outcomes in people with rheumatic diseases to date [2]. As the pandemic continues, further research needs to be undertaken in the gout population. Specific areas to address include

(1) Identifying risk factors in people with gout that predict poor outcomes in COVID-19 infection.
(2) Re-evaluating the role of glucocorticoids in the management of gout flares given a possible association with poor COVID-19 outcomes and reduced response to COVID-19 vaccination.
(3) Assessing the role of colchicine and IL-1 inhibitors in the management of gout flares given the potential for improved outcomes in COVID-19 infection.
(4) Developing new models of care to improve the management of gout during the COVID-19 pandemic.

CONCLUSION

The COVID-19 pandemic has created many challenges for people with gout. Not only are they at an increased risk of poor outcomes after COVID-19 infection due to associated comorbidities, but also their access to healthcare and medications has been disrupted during the pandemic, with negative effects on disease control, quality of life and mental health. At present, there is a lack of guidance on the management of gout during the pandemic and a lack of research assessing outcomes of COVID-19 infection in people with gout.

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- ■ of special interest
- ■■ of outstanding interest

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This is an observational study examining factors associated with COVID-19-related death in a large dataset of more than 3700 people with rheumatic diseases (data for gout could not be extracted as gout was not reported separately). The study found that older age, male sex, CVD, chronic lung disease, moderate/high disease activity and certain medications (rituximab, sulfasalazine and immunosuppressants) were associated with COVID-19-related death.

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This study is a prospective, open-label, randomized clinical trial ($N = 105$) conducted in 16 tertiary hospitals in Greece evaluating the effect of treatment with colchicine on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with COVID-19. Participants who received colchicine had improved clinical outcomes compared with those who received standard medical treatment.

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This is a large phase III multicentre randomized controlled trial (>4400 participants) investigating the effect of colchicine on the composite of COVID-19-related death or hospital admission in community treated patients with COVID-19. The trial found that among patients with PCR-confirmed COVID-19, colchicine use led to a lower rate of the composite of death or hospital admission compared with placebo.

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This is a multicentre randomized clinical trial ($N = 116$) conducted across 16 university hospitals in France assessing the use of anakinra in patients hospitalized with mild to moderate COVID-19 pneumonia. Anakinra did not improve clinical outcomes in this group of patients compared with usual care.

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This is a randomized, double-blind, placebo-controlled phase III trial ($N = 454$) conducted across 39 hospitals in Europe and the USA evaluating the efficacy of canakinumab in patients hospitalized with severe COVID-19. Canakinumab did not significantly increase the likelihood of survival without invasive mechanical ventilation or improve COVID-19 mortality in this patient group.

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This qualitative study evaluated the impact of the COVID-19 pandemic on people with RMDs by analysing Twitter messages posted by people with RMDs across several countries from March to July 2020. The study focused on inflammatory-driven RMDs, including ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus; however, gout was not specifically included.

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This study presents results from the COVID-19 Global Rheumatology Alliance Patient Experience Survey of more than 12 000 people with rheumatic diseases worldwide (data for gout could not be extracted as gout was not reported separately). The study found that patients with rheumatic diseases adopted protective behaviours during the early phase of the COVID-19 pandemic and that the pandemic had a negative impact on patients' ability to access healthcare and a negative impact on their employment status, with a rise in unemployment.

Update on gout management: what is old and what is new

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Purpose of review
The global burden of gout is rising, as are the prevalence of associated comorbidities, all-cause mortality and societal costs. In this review, we discuss recent advances in epidemiology and treatment strategies for gout.

Recent findings
Genetic factors and obesity are prominent contributors to hyperuricemia and gout, while dietary factors contribute to less variance in serum urate, though can still have some contribution to population attributable risk. A consensus statement by the Gout, Hyperuricemia and Crystal-Associated Disease Network outlined appropriate terminology regarding gout, which will aid in communication about various aspects of the disease. The 2020 American College of Rheumatology gout guideline offers comprehensive evidence-based recommendations for the management of hyperuricemia using urate-lowering therapy, prophylaxis when initiating urate-lowering therapy, treatment of gout flare and adjunctive management strategies. There is improved understanding of risk factors for allopurinol hypersensitivity syndrome and well tolerated use of allopurinol in chronic kidney disease. Trial data have provided new insights regarding cardiovascular risk with febuxostat. Several new drug therapies are being tested for both urate-lowering efficacy and gout flare management.

Summary
Although there have been significant advances in understanding of risk factors and treatment approaches, gout remains suboptimally managed. There is substantial need for improving gout management efforts and gout education among patients and clinicians.

Keywords
gout, hyperuricemia, management, update

INTRODUCTION

Gout is the most common inflammatory arthritis and is caused by monosodium urate crystals deposited in the joints in people with hyperuricemia. In this review, we summarize the current understanding of the epidemiology of gout, recent treatment guideline recommendations, management considerations in special populations and treatments in the pipeline.

RISING PREVALENCE AND BURDEN OF DISEASE

Over the last 30 years, there was a 100% increase in prevalence of gout, which is out of proportion to the 42% increase in the world population or the rise in life expectancy [1▪]. The Global Burden of Disease Study in 2017 estimated that approximately 41.2 million adults are living with gout worldwide, more than double the number of people living with rheumatoid arthritis [1▪,2]. The prevalence of gout in the USA alone is 9.2 million (3.9% of USA adults) [3]. The incidence and prevalence of gout are higher in racial/ethnic minorities and in older adults [4▪].

Gout is associated with a 17% higher all-cause mortality risk than those without gout, with cardiovascular disease (CVD) being the most common cause of death [5]. In addition, renal disease was associated with 1.78 times higher risk of cause-specific mortality in those with gout compared with those without [5]. Although a decrease in excess risk

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KEY POINTS

- Gout is a common condition that is associated with higher all-cause mortality risk compared with the general population and significant healthcare costs.
- Diet alone is typically insufficient for management of hyperuricemia in patients with gout.
- The 2020 ACR Gout Guideline has provided a strong recommendation for a treat-to-target strategy for those in whom management of gout is indicated, with a target serum urate of less than 6 mg/dl.
- Novel drug therapies for urate-lowering, including xanthine oxidase inhibition and harnessing renal or gastrointestinal urate excretion, minimizing immunogenicity of uricase-based therapy and additional anti-inflammatory therapeutic targets are being developed and tested in trials.

of premature mortality compared with the general population has been observed in rheumatoid arthritis over time [6], this trend has not been observed in gout, with similar excess risk of mortality for patients diagnosed with gout in 1999–2006 as compared to 2007–2014 [7].

Gout contributes to tremendous healthcare costs. A 2015 meta-analysis estimated all-cause annual direct costs among employed patients ranging from $4733 to $9353 per capita [8]. Costs are higher for older adults ($16 925) and patients with treatment refractory gout ($18 362) [8]. Emergency department visits for gout increased from 2006 to 2012 by 14%, and healthcare charges increased by 80% in the USA [9]. Whereas hospitalization rates for rheumatoid arthritis patients declined by 67% from 1993 to 2011, hospitalization rates doubled for patients with gout [10]. Furthermore, patients with gout incur high indirect costs related to the work impairment and productivity loss [8].

GOUT MANAGEMENT

The terms 'acute' and 'chronic' gout have contributed to a false dichotomy in regards to decisions about timing and indications for urate-lowering therapy (ULT), leading to a misconception that only patients with 'chronic' gout require ULT. A consensus statement by the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) to clarify labels for gout disease elements has highlighted that terms such as 'acute' and 'chronic' gout should not be used, and instead, the terms 'gout flare', 'intercritical gout' and 'chronic gouty arthritis' are recommended [11]. Accordingly, the 2020 ACR gout guideline does not use the terms 'acute gout' and 'chronic gout' in its discussion of gout management.

Management of hyperuricemia: urate-lowering therapy

The cornerstone of gout treatment is the reduction of urate using ULT, which includes xanthine oxidase inhibitors (XOI) (allopurinol and febuxostat), uricosuric agents (probenecid, benzbromarone, lesinurad, dotinurad) and recombinant porcine-like uricase that metabolizes urate to allantoin, pegloticase. Not all therapies are available in all markets.

Indications for urate-lowering therapy

The 2020 American College of Rheumatology (ACR) gout guideline strongly recommends initiating ULT in patients with one or more clinically evident tophi, radiographic damage reflecting gouty bony erosion or two or more gout flares annually. ULT was also conditionally recommended for patients with more than one gout flare annually, and for patients with comorbid stage at least 3 chronic kidney disease (CKD), serum urate level more than 9 mg/dl or kidney stones [12▪▪]. Allopurinol is strongly recommended as the preferred first line agent for all patients, including those with moderate to severe CKD, unless there are contraindications such as hypersensitivity to prior allopurinol exposure or consideration of potential high risk due to HLA-B*5801 [12▪▪]. Dosing considerations for various ULTs available in the USA are outlined in Table 1.

Starting ULT during a gout flare is conditionally recommended by the 2020 ACR gout guideline, reflecting the need for shared decision making [12▪▪]. This is similar to the 2012 ACR gout guideline, with additional studies considered in the updated 2020 guideline in which some trial data did not suggest a large risk for the theoretical concern about prolonging a flare [13–15]. Ensuring appropriate patient education and follow-up may be challenging when a patient is in the midst of an intensely painful flare. On the contrary, patients may be more motivated to make significant changes immediately while seeking care for a flare.

Treat-to-target strategy

Titrating ULT to achieve a target serum urate level of less than 6 mg/dl is strongly recommended over fixed dosing in the ACR gout guideline [12▪▪], supported by data from a number of randomized controlled trials (RCTs) regarding clinical benefits. In the pegloticase RCT, there was a significant reduction in flares and tophi at 6 months [16]. In a febuxostat RCT in early gout, there was a significant reduction in gout flares noted only after 6 months [17]. In a UK RCT, patients randomized to a target-to target strategy (T2T) nurse-led intervention were significantly more likely to achieve a serum urate

Table 1. Approved urate-lowering therapies currently available on the market in the USA

Drug (FDA approval date)	Dosing and considerations in CKD	Select side effects	Select drug interactions/ considerations
Allopurinol (1966)	Start at dose ≤100 mg/day and titrate by ≤100 mg every 2–4 weeks to goal serum urate; max FDA recommended dose 800 mg/day GFR<30: start at 50 mg/day and titrate by 50 mg every 2–4 weeks to goal serum urate. Okay to use in patients with ESRD on dialysis	• Mobilization gout flares when initiating ULT • Rash • Haematologic abnormalities • Hepatotoxicity • AHS/DRESS syndrome especially if HLA-B58 : 01 positive	• Potentiation of immunosuppressive effects of azathioprine and 6-mercapropurine • Increased likelihood of ampicillin induced rash
Febuxostat (2009)	Start at 40 mg/day and titrate to 80 mg/day if serum urate not at goal GFR 15–29 ml/min: doses above 40 mg/day not recommended per FDA label, but studies indicate that doses up to 80 mg/day may be safe Limited data on febuxostat use in patients with ESRD on dialysis	• Mobilization gout flares when initiating ULT • Nausea • Arthralgias • Rash • Unclear potential cardiovascular risk • Hepatic abnormalities • Hypersensitivity reactions/ DRESS	• Potentiation of immunosuppressive effects of azathioprine and 6-mercapropurine
Probenecid (1979)	Start at 250 mg twice daily with dose titration to maximal effective dose of 2000 mg/day GFR<30 ml/min: probenecid not recommended due to lack of efficacy in setting of inadequate renal function	• Mobilization gout flares when initiating ULT • Rash, flushing • GI intolerance • Urolithiasis	• Prolonged half-life of penicillin and ampicillin • High dose aspirin may reduce probenecid's uricosuric effect
Pegloticase (2010)	8 mg i.v. every 2 weeks Check serum urate prior to each infusion after first dose, and stop if serum urate > 6 mg/dl No dose adjustment needed in patents with CKD or ESRD on dialysis *Discontinue all ULT prior to initiation of pegloticase to avoid masking loss of urate response	• Contraindicated in G6PD deficiency (haemolysis, methemoglobulinemia) • Mobilization gout flares • Nausea, vomiting • Anaphylaxis and serious infusion reactions related to antidrug antibodies • Caution in patients with CHF	

of less than 6 mg/dl and have lower flare frequency and greater tophus resolution at 2 years [18]. Other studies have also been supportive of a T2T approach, including pharmacy led T2T programmes that were more effective than usual care in patients achieving target urate levels [19,20]. In patients who do not achieve target urate level despite XOI, uricosurics and other interventions and who continue to have frequent flares or nonresolving tophi, pegloticase is recommended [12▪▪]. For patients on therapy, it is conditionally recommended to continue ULT indefinitely [12▪▪].

Prophylaxis when starting urate-lowering therapy

When initiating ULT, the 2020 ACR gout guideline strongly recommends administering prophylactic antiinflammatories such as NSAIDS, colchicine or prednisone to prevent gout flares [12▪▪]. A stepwise dose escalation of febuxostat from 10 to 40 mg/day has been demonstrated to be comparable with addition of colchicine prophylaxis to fixed-dose febuxostat 40 mg daily for the prevention of gout flares during ULT titration [21].

Gout flare management

The ACR guideline strongly recommends NSAIDs, colchicine or glucocorticoids (oral or intra-articular) as first-line therapy for the management of gout flares, without differentiating between particular agents, over anti-IL-1 therapy [12▪▪]. Of note, in patients who are already on colchicine prophylaxis, colchicine could be used for flare treatment as long as liver and kidney function permit, and there are no major contraindications or drug-drug interactions. IL-1 inhibitors, anakinra and canakinumab, though currently not FDA-approved for such use, are reserved for those unresponsive to therapy or who are unable to tolerate NSAIDS, colchicine and steroids.

Data on direct comparative effectiveness of interventions for gout flare management are minimal. A 2021 network meta-analysis reported that canakinumab has a potential advantage compared with other anti-inflammatory interventions for pain reduction and joint tenderness at day 2 [22▪▪]. Intravenous (i.v.) and intramuscular (i.m.) steroids may also be superior to ibuprofen, COX-2 inhibitors, colchicine and oral corticosteroids in pain reduction at day 2. Acetic acid derivative NSAIDs are probably superior to ibuprofen NSAIDS for joint swelling reduction at day 2.

Dietary and lifestyle modifications

Recent studies have highlighted the importance of genetic factors and obesity as being prominent determinants of hyperuricemia. A 2018 meta-analysis reported that the variance in urate levels due to genetics was higher than dietary factors [23]. However, although variances in hyperuricemia explained by obesity, nonadherence to the DASH diet, alcohol use and diuretic use were overall low, the population attributable risk of obesity was estimated to be 44%; in contrast, for the DASH diet and alcohol use, the population attributable risks were 9 and 8%, respectively [24▪▪].

Although ULT is the mainstay of gout management, dietary and lifestyle modifications may be useful adjuncts to ULT. Dietary interventions alone often do not lead to significant urate reduction in patients with gout and caution should be undertaken when discussing dietary factors to avoid patient blaming [25]. Nonetheless, weight loss may improve urate levels and risk of flares, and is recommended by the ACR gout guideline, which also conditionally recommends limiting consumption of alcohol, purines and high fructose corn syrup. No recommendations could be made regarding cherry/cherry extract, omega-3 fatty acids and dairy due to a paucity of data [12▪▪].

SPECIFIC CONDITIONS OR TREATMENT CONSIDERATIONS

Allopurinol hypersensitivity syndrome

Allopurinol hypersensitivity syndrome, AHS, is a rare, but highly fatal, adverse reaction to allopurinol. Starting dose is an important risk factor for AHS [26,27]; as such, allopurinol should be started at 100 mg/day for those with normal or mildly impaired renal function (up to CKD stage 3), or at 50 mg/day for those with CKD stage 4 or worse; this lower starting dose approach also mitigates risk of flares [12▪▪]. Another important risk factor for AHS is the HLA-B*58 : 01 allele, which is associated with a 80 to 580-fold increased likelihood of AHS [28,29]. Prevalence of HLA-B*58 : 01 allele is nearly 7.4% in Han Chinese, Korean and Thai populations, nearly 3.8% in African–Americans and 0.7% in whites [30]. However, numerous ethnic groups have not had prevalence of HLA-B*58 : 01 reported. Nonetheless, testing for HLA-B*58 : 01 allele is conditionally recommended in Southeast Asian and African–American patients [12▪▪].

In settings wherein HLA-B*5801 testing is not available or cost-prohibitive to patients, starting at a low dose and slowly titrating up with close monitoring is a feasible approach [12▪▪]. It should also be recognized that febuxostat is associated with drug rash with eosinophilia and systemic symptoms (DRESS), through a different mechanism than HLA-B*5801.

Management of gout in chronic kidney disease

In addition to the dosing recommendations regarding allopurinol in CKD summarized above, patients on haemodialysis or peritoneal dialysis can also safely receive allopurinol [31]. Febuxostat does not require dose adjustments for CrCl at least 30 ml/min; for CrCl 15–29 ml/min, it is recommended to use no more than 40 mg/day according to the FDA label. RCT data suggest that febuxostat may be well tolerated to use in patients with GFR at least 15 ml/min [32], but there are limited data on its use in advanced CKD, dialysis and transplant [31,33▪▪]. Uricosurics are not effective at low CrCl levels; probenecid is not recommended for those with CrCl less than 30 ml/min [12▪▪]. Pegloticase can be used in patients with advanced CKD, including patients on dialysis, without dose adjustment [31]. For prophylaxis while initiating ULT, NSAIDs and often colchicine may not be an option for patients with CKD; in such case, low-dose steroids may need to be used, though not ideal; consideration of anti-IL-1β therapy may be reasonable.

There has been substantial interest in whether ULT may have a beneficial effect on renal function among people with CKD outside of the context of gout. However, two recent RCTs suggested that allopurinol use was not associated with reduction in renal disease progression in patients with CKD who were at high risk, though questions remain about appropriateness of study sample given the underlying cause of CKD in one RCT (type 1 diabetes) and potential issues with power in the other RCT [34,35].

Cardiovascular risk and XOI

Although there are biologic hypotheses supporting potential detrimental effects of serum urate on CVD, ULT RCTs have not supported these hypotheses and have in fact raised concerns about potential adverse cardiovascular consequences of febuxostat in particular. The FDA-mandated postmarketing Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities Trial, CARES, raised concerns about potential higher all-cause and cardiovascular mortality with febuxostat compared with allopurinol [36]. However, valid interpretation of these findings is challenging due to 57% dropout, 45% lost-to-follow-up and 85% of events occurring after drug discontinuation, including 23–28% of deaths occurring within 30 days of drug discontinuation [37]. In contrast, the EMA-mandated postmarketing Febuxostat versus Allopurinol Streamlined Trial, FAST, did not find an elevated risk of cardiovascular events in the febuxostat group compared with allopurinol and had excellent follow-up and much lower drug discontinuation [38▪▪]. The FDA placed a black box warning on febuxostat in light of the results of the CARES trial. The 2020 ACR gout guideline took the CARES trial results and the FDA black box warning into account and made a conditional recommendation to switch therapy in patients on febuxostat with a history of CVD or a new cardiovascular event [12▪▪]. Subsequently, with the FAST trial results providing some reassurance about lack of elevated risk with febuxostat, it is anticipated that the next treatment guideline will take these newer data into consideration [39▪▪].

Pegloticase and immunogenicity

A challenge in the use of pegloticase is the development of antidrug antibodies with resultant risk for infusion reactions and anaphylaxis [16,40]. A rise in serum urate levels in between pegloticase infusions above 6 mg/dl signals a risk for infusion reaction or anaphylaxis. Only about 42% of patients maintain serum urate levels below 6 mg/dl over a 6-month treatment course with pegloticase [16]. A prospective clinical trial enrolled 14 patients who were treated with methotrexate 15 mg per week for 4 weeks prior to and during pegloticase treatment and reported that 79% of patients maintained therapeutic response at 6 months [41▪]. Mycophenolate mofetil (MMF) was also demonstrated to be effective in mitigating immunogenicity of pegloticase: at 12 weeks, serum urate below 6 mg/dl was achieved in 86% of participants in the MMF group as compared to 40% in placebo; maintenance of serum urate below 6 mg/dl at 24 weeks was achieved in 68 versus 30% in the MMF and placebo groups, respectively [42▪]. The optimal immunosuppressive regimen with pegloticase to prevent antidrug antibody formation remains to be determined.

HOW IS GOUT MANAGED IN THE REAL WORLD?

Despite availability of effective therapy, ULT is greatly underutilized in gout management. On the basis of a study of commercial health insurance enrolees from the USA, the number of ULT users per 1000 gout patients was estimated to be 567 in 2009, and this number increased only slightly to 656 in 2019 [43▪]. Another claims-based analysis reported that less than 80% of patients with gout, including those with tophaceous gout, received prescriptions for ULT, and prescription coverage was for less than 50% of the year [44▪]. Adherence is also poor at about 46%, with 54–87% of patients experiencing a gap in therapy [45].

Among ULT options, patients are almost exclusively prescribed allopurinol. Febuxostat's use peaked at nearly 10% of all ULT prescriptions in 2013–2014; following the CARES trial data and addition of the FDA black box warning, its use diminished [43▪]. Probenecid is prescribed infrequently, accounting for less than 5% of all ULT prescriptions [43▪]. Pegloticase prescriptions represent less than 0.1% and the same was true for lesinurad prior to it coming off the market [43▪].

Gout is often managed by primary care physicians. The 2017 American College of Physicians (ACP) gout management guideline differs from all Rheumatology specialty guidelines from the past decade, including ACR, European League against Rheumatism and British Society of Rheumatology [12▪▪,46–48]. Specifically, the ACP guideline does not offer clear recommendations for initiation of ULT, serum urate target levels or T2T [49]. Although the bulk of gout care occurs in primary care, a recent study showed that having a visit with a rheumatologist reduces patients' emergency room utilization, emphasizing that there is a tremendous room for improvement of gout management outside of rheumatology [44▪].

DRUGS IN THE PIPELINE

There are numerous drugs that are currently in the pipeline for gout management, some of which are summarized in Table 2. The general categories of drug mechanisms being explored are related to renal urate excretion, minimizing immunogenicity of uricase-based therapy, additional targets on the purine metabolism pathway and leveraging the gastrointestinal system for urate excretion. In addition, IL-1

Table 2. Ongoing clinical trials in gout[a]

Drug	Mechanism of action	Study phase
Urate-lowering therapy		
Inhibition of urate reabsorption in the kidney		
Dotinurad	Inhibitor of urate transporter 1 (URAT1)	Phase 3
SHR4640	Inhibitor of URAT1	Phase 3
SAP-001	Inhibitor of URAT1	Phase 2
D-0120	Inhibitor of URAT1	Phase 1/2
XNW3009	Small molecule hURAT1 inhibitor	Phase 1
AC-201[b]	Inhibitor of production and activity of caspase-1 and Il-1b and selective inhibitor of re-absorption transporters in kidney	Phase 2
Xanthine oxidase inhibitors		
ABP-671	Novel xanthine oxidase inhibitor	Phase 2
LC350189	Novel xanthine oxidase inhibitor	Phase 1
Metabolizers of serum urate		
SEL-212	Combination product of pegadricase, proprietary pegylated uricase, coadministered with ImmTOR, designed to mitigate formation of antidrug antibodies	Phase 3
ALLN-346	Engineered urate oxidase that acts in the gastrointestinal tract	Phase 2
SSS11	PEGylated recombinant candida urate oxidase	Phase 1
Gout flare management		
RPH-104	Novel heterodimeric fusion protein that inhibits IL-1	Phase 2
AC-201[b]	Inhibitor of production and activity of caspase-1 and Il-1b and selective inhibitor of re-absorption transporters in kidney	Phase 2
Anakinra in CKD or renal transplant	IL-1 receptor antagonist	Phase 2/3
Adrenocorticotropic hormone (ACTH)	Activation of melanocortin type 3 receptor; adrenal corticosteroid release	n/a

[a]Based on clinicaltrials.gov search until September 2021.
[b]Dual mechanism for flare and ULT.

inhibition and inflammasome targets are among the programmes in development for gout flare management.

CONCLUSION

Overall, although knowledge about the pathophysiology of gout and management principles has been augmented greatly, there is tremendous room for improvement in practice implementations as well as patient and clinician education.

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Conflicts of interest

There are no conflicts of interest.

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B cells in systemic lupus erythematosus

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Purpose of review
New insight into altered B cell distribution including newly identified subsets and abnormalities in systemic lupus erythematosus (SLE) as well as their role in immune protection are summarized in this review.

Recent findings
SLE carries characteristic B cell abnormalities, which offer new insights into B cell differentiation and their disturbances including discoveries of pathogenic B cell subsets and intrinsic B cell abnormalities. A recent study in SLE found that antigen-experienced B cell subsets lacking expression of CD27 and IgD defined by their lack of CXCR5 and CD19low expression are expanded in SLE and represent plasmablasts likely escaping proper selection. In terms of therapeutic targeting with broader coverage than rituximab, second-generation anti-CD20, anti-CD38 and CD19-CART treatment experiences have advanced our understanding recently. However, the key role of qualitative and quantitative B cell requirements in connection with T cells became apparent during SARS-Cov2 infection and vaccination, especially in patients with gradual B cell impairments by rituximab, mycophenolate mofetil and cyclophosphamide.

Summary
Identification and characterization relevant B cell subsets together with altered regulatory mechanisms in SLE facilitates new approaches in targeting pathogenic B cells but require consideration of preservation of protection.

Keywords
anti-CD20, CD19 targeting CAR T cell therapy, COVID-19 vaccination, extrafollicular B cell activation, systemic lupus erythematosus

INTRODUCTION

Various B cell abnormalities described in systemic lupus erythematosus (SLE) such as autoantibody formation, plasmacytosis, and an anergic/post activated phenotype [1], demonstrate the key role of this cell lineage in this condition. Due to various and heterogeneous B cell abnormalities in SLE, finding a clear classification of pathogenic versus protective B cells has been challenging and remains elusive. Substantial depletion of the B cell compartment as therapy using anti-CD20 [2–4] in patients with SLE appeared to be effective in refractory patients [5], while associated with a higher risk of infection [6,7]. However, BAFF inhibitor belimumab approved for SLE since 10 years [2] and recently for lupus nephritis [8] does not deplete B cells and does not impair immune protection or vaccination responses [9] but highlights the pathogenic role.

Overall, it appears attractive to target pathogenic B cell subsets more selectively, avoiding side effects caused by global B cell depletion. Double-negative B cells, a subset that has been identified to be associated with SLE [10], has been repeatedly described as heterogeneous [11,12], suggesting it comprises distinct populations. Apart from altered composition of the B cell compartment, intrinsic abnormalities mirror an alternative state of B cells in SLE patients making B cells a prominent target for immunomodulation. Another characteristic of SLE is the IFN signature wherein impact on B cells is not fully understood. The interrelationship between type I IFN and B cell abnormalities has been subject of recent studies, results of which will be discussed in this review.

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KEY POINTS

- Two distinct B cell subsets CD11c+CD19high and CD19lowCD27+/- both lacking CXCR5 expression are expanded in SLE.
- New insights in regulation of ASCs induction reveal new potential treatment targets, like BTLA, FOXM1, IL-17RA/RC and sFas ligand. CD52 may candidate as another diagnostic marker of anergic/postactivated SLE B cells.
- B cell targeting CAR T cell therapy is an innovative approach for long-term B cell depletion with a potential broader and deeper coverage of CD19+ B cell abnormalities in SLE.
- Immunosuppressive therapies, for example by rituximab, MMF or cyclophosphamide substantially alter the immune system of SLE patients leading to diminished immunization responses and higher risk of hospitalization due to COVID-19 pandemic.

ALTERED B CELL SUBSETS DISTRIBUTION: SUBSETS LACKING CXCR5 AND CD21 SUGGEST EXTRAFOLLICULAR B CELL ACTIVATION AND DIFFERENTIATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

The development of better readout techniques, such as multicolour flow cytometry and mass cytometry, to identify B cell subsets based on surface marker expression led to detailed decoding of the diversity of B lymphocytes in healthy individuals and patients. There are several B cell subsets that gained attention recently after being initially identified in SLE [13].

CD11c+ B cells are expanded in systemic lupus erythematosus and correlate with disease activity

CD11c, also known as Integrin α-X, gained attention as a marker for age associated B cells in mice [14,15] as well as a marker of activation in various leucocytes such as macrophages [16] and T cells [17]. In the B cell lineage, CD11c+/++ and CD21low mark populations with an activated phenotype. Those subsets were found increased in autoimmunity and acute infection [18]. Increased CD11c expression can be found across various differentiation states of B cells from activated naive B cells (aNAV) [19], naive-like [15], atypical memory or double-negative B cells [15,20].

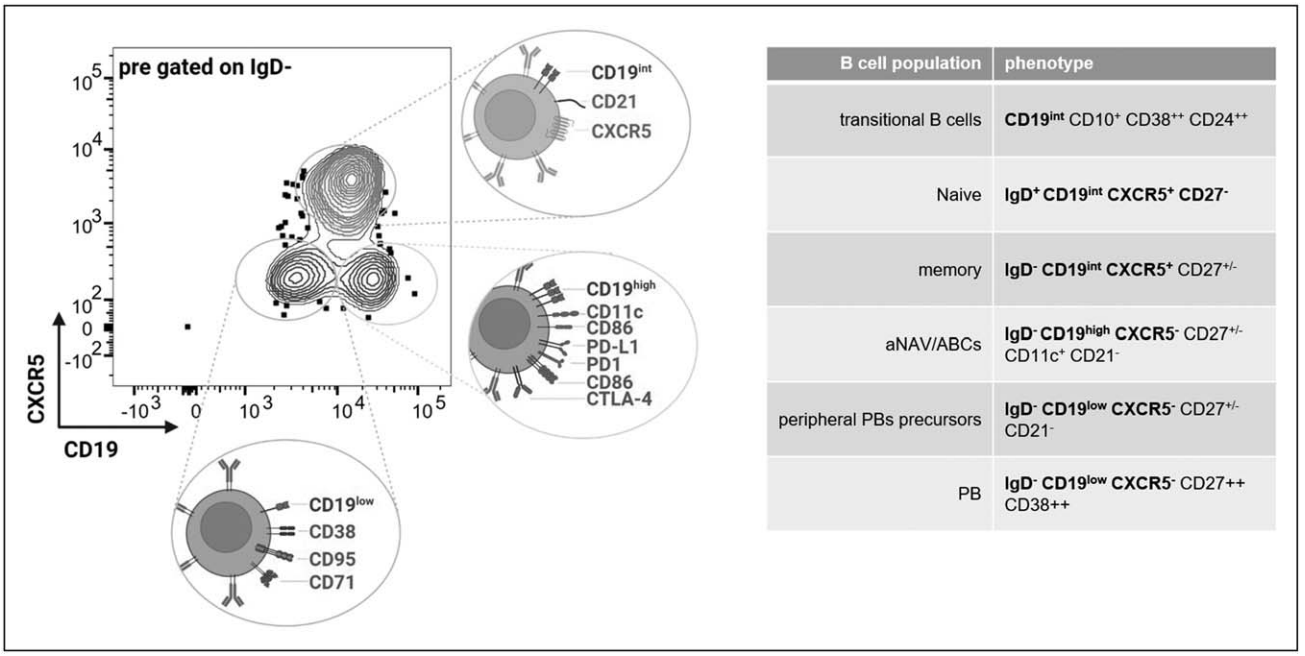
A possible mechanism of induction of CD11c+ cells was proposed recently by Yu *et al.* [21▪▪], using human primary B cells edited with Cas9 RNP. They knocked out lncRNA (named XIST), which initiates inactivation of the second X chromosome in XX females. XIST knockout resulted into increased expression of TRL7 on chromosome X and subsequent expansion of CD11c+ cells. Additional Gene Set Enrichment Analysis in patients with SLE and acute COVID-19 infections also shows overexpression of other XIST-silenced genes especially in IgD-CD27-CD11c+ cells [21▪▪]. This expanded our understanding of the role of TLR7-dependent B cell activation coinciding with CD11c expression.

aNAVs B cells defined as IgD-CD27-CD21-CXCR5-CD11c+ are increased in SLE, especially enriched by B cells reactive to dsDNA mimetope DWEYSVWLSN peptide. In addition, aNAV tetramer-binding B cells correlate with clinical parameters such as SLEDAI-2K, ESR and antidsDNA antibody levels [19]. The activated phenotype of CD11c+ B cells was found to express a distinct profile of regulatory molecules and activation markers. Thus, CD21low CD11c+ populations enriched in naive-like or double negative (DN) B cell compartment in patients with SLE downregulate inhibitory receptors Siglec-10, CD32 and FcRL4 [15], while CD19, CD69, Ki-67, CD45RO, CD45RA as well as checkpoint molecules (CPMs) CD86, PD1, PDL1, CD137, VISTA and CTLA-4 were found highly expressed [20]. Analysis of intrinsic pathway activation of CD21low B cells shows reduced phosphorylation of ERK1/2 in IgG memory B cells and reduced phosphorylation of BCR related kinases such as SYK and phospholipase PLCγ2 as well as absent canonical NF-kB response and reduced Ca2+ influx [15]. All these data are consistent with the notion that anergic postactivated B cells occur characteristically under chronic immune stimulation.

Notably, inconclusive expression of activation marker CD69 [20] and heterogeneous BCR responsiveness [15,22▪▪] suggest overlapping but not identical subsets of antigen-/T cell inexperienced (naive) and experienced (memory) subsets. Although there are overlapping phenotypical characteristics of CD11c+ B cells and CD21low CD19++ CXCR5- B cells, a clear understanding addressing coexpression of various markers is still lacking.

CD19low B cell subsets increased in systemic lupus erythematosus with similarities to plasmablasts

CXCR5 and CD21 low expression is seen as potential marker for extrafollicular/germinal centre independent route of B cell differentiation, a characteristic also found on CD11c-CD19low B cells. Recently, CD19low subsets were identified in both memory and double-negative B cells [22▪▪]. Those



B cell population	phenotype
transitional B cells	**CD19^{int}** CD10^{+} CD38^{++} CD24^{++}
Naive	**IgD^{+} CD19^{int} CXCR5^{+} CD27^{-}**
memory	**IgD^{-} CD19^{int} CXCR5^{+}** CD27$^{+/-}$
aNAV/ABCs	**IgD^{-} CD19^{high} CXCR5^{-}** CD27$^{+/-}$ CD11c^{+} CD21^{-}
peripheral PBs precursors	**IgD^{-} CD19^{low} CXCR5^{-}** CD27$^{+/-}$ CD21^{-}
PB	**IgD^{-} CD19^{low} CXCR5^{-}** CD27++ CD38++

FIGURE 1. B cell subsets described in recent studies question CD27 as reliable marker for B cell differentiation and effector function and rather imply a new way of nomenclature based on IgD, CD19 and CXCR5 expression. IgD- B cells can be identified regarding their CD19 and CXCR5 expression as GC memory B cells, ABCs or plasmablast precursors with distinct phenotypes.

subsets correlated with canonical gated plasmablast (CD27++CD38++) and share the expression of CD95, CD38, CD71, reduced BCR responsiveness and express plasmablast associated transcription factors. Thus, both populations share characteristics of plasmablasts with intermediate or absent CD27 expression raising questions about CD27 as identifier [22▪▪]. Sub-segmentation of switched memory and double negative B cells into three distinct populations (Fig. 1) may permit a new classification of B cells based on CXCR5 and CD19 independently of CD27. This new definition could contribute to a better understanding, resolve the heterogeneity seen in memory and atypical memory B cells especially with their abnormalities seen in certain autoimmune conditions, such as SLE.

REGULATORY MECHANISM OF EXPANSION OF ANTIBODY SECRETING CELLS AND POTENTIAL TARGETS

The pathology of SLE is characterized by breakdown of self-tolerance [23] accompanied by plasmacytosis [24], autoantibody production [25] and type I interferon production [26]. A profound understanding of how induction of antibody secreting cells is regulated is needed in order to target autoantibody producing cells.

Altered expression profile of regulatory checkpoint molecules on plasmablasts in patients with systemic lupus erythematosus

The CPM BTLA is considered to inhibit plasmablast induction in healthy individuals. In a recent study, naive B cells of SLE patients showed reduced BTLA expression and lack this inhibitory role, which could explain expansion of or lack of appropriate selection of ASCs [27]. Apart from BTLA expression, other CPMs are also altered in SLE, such as increased PD-1, PD-L1, PD-L2 and CD86. This B cell activation correlates with laboratory and clinically parameters suggesting a potential pathogenic involvement. Interestingly, cells enriched for CPM expression were CD20−, thus probably not targeted by anti-CD20 therapies [28]. These data suggest that the emergence of certain B cell abnormalities in SLE including autoreactive B lineage cells derive directly from impaired regulatory mechanisms which remain to be delineated.

Distinct CD19+CD20+CD38++ B cells in quiescent state predicts plasmablast-associated flares

Identifying patients at risk to develop flares would help to timely adapt therapy strategies. Therefore, studies investigating biomarkers and predictors are of great importance. Kotliarov *et al.* [29] found that high antibody responders in primary yellow fever

and repetitive influenza vaccinations as well as SLE patients with flares share a predictive B cell population expressing CD19+CD20+CD38++, a signature independent of CD20-CD38++ plasmablasts, prior to vaccination or during clinically quiescent SLE. An independent study that confirms the clinical value of this subset for flare prediction is warranted.

Identification of new targets associated with plasmablasts and plasma cells induction in systemic lupus erythematosus patients

Instead of B cell depletion using anti-CD20 treatment by rituximab (type I anti-CD20), a phase II study in lupus nephritis using obinutuzumab (type II) suggested that deep tissue depletion of B cells may result in better outcome [3]. An alternate approach co-targeting was reported by daratumumab (anti-CD38) with promising results in two patients with refractory SLE [30▪▪]. This approach targets not just CD38 expressing plasmablasts, but also activated B and natural killer (NK) cells expressing CD38. IgG levels and NK cells are significantly diminished by daratumumab, which may increase infectious risks [31]. Therefore, more selective approaches targeting ASCs remain to be of key interest and under investigation in multiple myeloma studies.

In this context, transcription factor FOXM1 was found significantly higher expressed in CD38+ CD43+ B cells than naive or memory B cells and especially elevated in plasmablast from SLE patients and may candidate as molecular target of plasmablasts [32]. An IL-17RA/RC-expressing plasma cell subset found in SLE shows antidsDNA IgG-secretion and correlates with increased frequencies of Th17 cells. Treatment with IL-17 markedly increased frequencies of antidsDNA producing cells, whereas anti-IL-17R neutralizing antibody was able to reduce autoantibody secretion by lupus plasma cells promoting anti-IL17 as a potential approach [33▪].

An unbiased large-scale library of secreted proteins tested on B cells revealed soluble FAS ligand as potential plasmablast inducer. Stimulation with sFAS ligand downregulated PAX5 while increasing Blimp-1 expression [34] known for physiologic plasma cell differentiation. In line with increased soluble FAS ligand levels detected in patients with active lupus nephritis [35], sFAS ligand may represent a driver of plasmacytosis in SLE.

EFFECT OF INTERFERON SIGNATURE ON B CELLS AND BIOMARKER ASSOCIATED WITH INTERFERON EXPOSITION OF B CELLS

Known drivers for ASC induction are cytokines of the interferon family [34,36,37▪,38]. Interferons are subdivided in three groups, all upregulated in SLE [39]. Increased type I IFN signature is a known characteristic for SLE and correlates with disease activity [40,41]. Targeting IFN pathways by modulating Jak/STAT signalling [42,43] is a promising approach for therapeutic interventions. Recently, increased levels of signalling molecule STAT1 downstream of IFN receptors but not phosphorylated pSTAT-1 were detected in naive, memory B cells and plasmablasts of SLE patients and correlated with interferon induced Siglec-1 expression on monocytes and disease activity [44]. Ex-vivo stimulation with IFNalpha led to increased STAT1 phosphorylation in plasmablasts of SLE patients suggesting a hyperresponsiveness to IFN [44].

Clinical trials and treatment strategies aiming at modulating the IFN system require reliable, cell type specific and easy to detect biomarkers for monitoring. Although markers such as Siglec-1 or IP-10 expressed by monocytes [45] have been well established, no marker has been identified for B cells exposed to IFN. In this context, a recent gene expression analysis identified CD137 (tetherin) expression as a surface marker for IFN-exposed memory B cells. CD137 levels respond to type I IFN in a dose-dependent manner and was evaluated as predictive marker for clinical flares [46].

In contrast to type I and II IFNs and their role in autoimmunity, only little is known about type III IFNs and their role in SLE [38]. Increased serum levels of INF-λ1 were detected in SLE [39] and lupus nephritis [47]. In this context, new studies investigating the effect of IFN λ on B cells are of particular interest. A recent study showed that BCR combined with INF-λ stimulation of naive B cells activates mTORC1 pathway and cell cycling, which induces plasmablast formation directly from naive B cells [37▪].

It remains to be of interest how targeting type I IFN by recently approved mAbs against the receptor, anifrolumab and blockade of BAFF/BLyS by belimumab may target distinct SLE patients. Here, IFN is considered an inducer of BAFF/BLyS and recent analyses suggest better belimumab responses in patients with increased type-1 IFN mRNA expression [48].

B CELL INTRINSIC ABNORMALITIES ALTERED SIGNALLING TRANSDUCTION AND METABOLOMICS

B cells can respond to various signals in their microenvironment leading to activation of signalling pathways, metabolic changes and cell fate decisions.

CD52 as inhibitor of B cell receptor signalling

Signalling via B cell receptor (BCR) is crucial to B cell activation. Imbalance in BCR regulation leads

to dysfunction and can cause autoimmunity. SLE B cells undergo an anergic/post activated state with reduced BCR responsiveness [49]. Consistently, a recent study found elevated levels of CD52 and soluble CD52 in B cells in lupus. CD52 is cleaved upon BCR stimulation and sCD52 inhibits BCR signalling and downregulates IgM, IgD, CD19 and CXCR5 expression [50].

B cell immunometabolism in systemic lupus erythematosus

Pyruvate kinase M2 (PKM2), a kinase involved in glycolysis is elevated in monocytes, dendritic cells, and B cells of SLE patients. Induction of CD86 and CD40 cell surface expression, activation of MAPK and NF-kB pathway as well as mRNA transcripts of IL-6 and TNF-alpha upon TLR4/TLR7/TLR9 were reduced in B cells from PKM2 inhibitor treated mice. Those findings suggest that PKM2 has a role in TLR signalling. Inhibition of PKM2 improved splenomegaly in two lupus mouse models and reduced antidsDNA antibody titres and glomerular deposition of IgG and IgM [51]. Analogously, treatment of MRL/lpr mice with PKM2 inhibitor alleviated cognitive impairment and brain damage through decreased microglial activation [52].

B CELL DIRECTED CAR T CELL THERAPY

Although there are exciting clinical developments and approvals, a substantial medical need remains to improve outcome in SLE. Apart from small molecule compounds (e.g. tyrosine kinase inhibitors) and a variety of biologicals aiming to control disease activity, current cellular strategies, such as autologous stem cell transplantation and genetically engineered CAR T cells preferentially aim to modulate more profoundly underlying disease mechanisms. Here, NZB/W and MRL-lpr mice undergoing anti-CD19 CAR T cells show successful depletion of B cells and thus reduction of autoantibodies [53]. Among CAR-T cells featuring either CD28 or 4-1BB costimulatory motif, the later shows better therapeutic efficiency in MRL-lpr mice [54]. On the basis of these preclinical experiences, a recent first application of CD19-CART in a case of otherwise refractory SLE led to rapid serological and clinical remission including signatures of lupus nephritis [55▪▪]. Further promising approaches to modulate the B cell compartment, anti-CD19 and anti-CD38, bi-specific anti-CD19/CD22 [56] or BCMA/CD38 [57] CAR T cells are currently under investigation.

B LINEAGE CELLS AND COVID-19: WHAT TO CONSIDER REGARDING IMMUNOSUPPRESSION THERAPY AND IMMUNIZATION IN PATIENTS?

Studies investigating acute COVID-19 infections and safety and efficacy of vaccination against COVID-19 in vulnerable patients, including individuals suffering from SLE provided very clear evidence that B lineage cells play critical roles in host protection. Patients with SLE do not seem to be at a higher infectious risk for COVID-19 [58] but seem to develop more severe progression [59] and increased need of hospitalization [60]. Whether COVID-19 infection might trigger flares [61,62] or new onset of SLE [63] remains a matter of debate. Nevertheless, elevated levels of anti-SSA/Ro antibodies [64] and increased antiphospholipid antibodies [65] and other specificities have been reported in COVID-19 patients without prior autoimmune disease. These observations may permit to study characteristics of these autoantibodies and their impact on induction of autoimmunity.

The most potent way of protection against severe COVID-19 is immunization. A self-reported cross-sectional survey investigated side effects and risk of flares across different vaccines independent of mode of action and observed rare occurrence of flares with just 3% in SLE suggesting vaccination as important and well tolerated [66]. A study just focusing on mRNA vaccine BNT162b2 screened 126 SLE patients and found impaired humoral response in patients with reduced naive B cells and low baseline IgG levels prior to vaccination and patients treated with mycophenolate mofetil (MMF) and methotrexate (MTX). Rituximab-treated patients with autoimmune conditions including SLE resulted in reduced humoral immune response in acute infection with SARS-CoV-2 [67] as well as diminished vaccination response [68,69]. Overall, no increased risk of flares was detected upon vaccination with BNT162b2 in SLE [9,66].

CONCLUSION

The critical role of B cells in SLE remains undisputable. New insight into B lineage diversity (Fig. 2) can be drawn from recent studies, which identify new B cell subsets associated with ASC induction in SLE. Here, a hitherto unknown CD19low B cell subset has been recently identified and shares similarities with peripheral plasmablasts apart from lacking CD27 expression. Along with widely accepted notion that CD27-IgD- (double-negative) B cells represent a heterogeneous population of antigen-experienced, nonnaive B cells the question should be raised

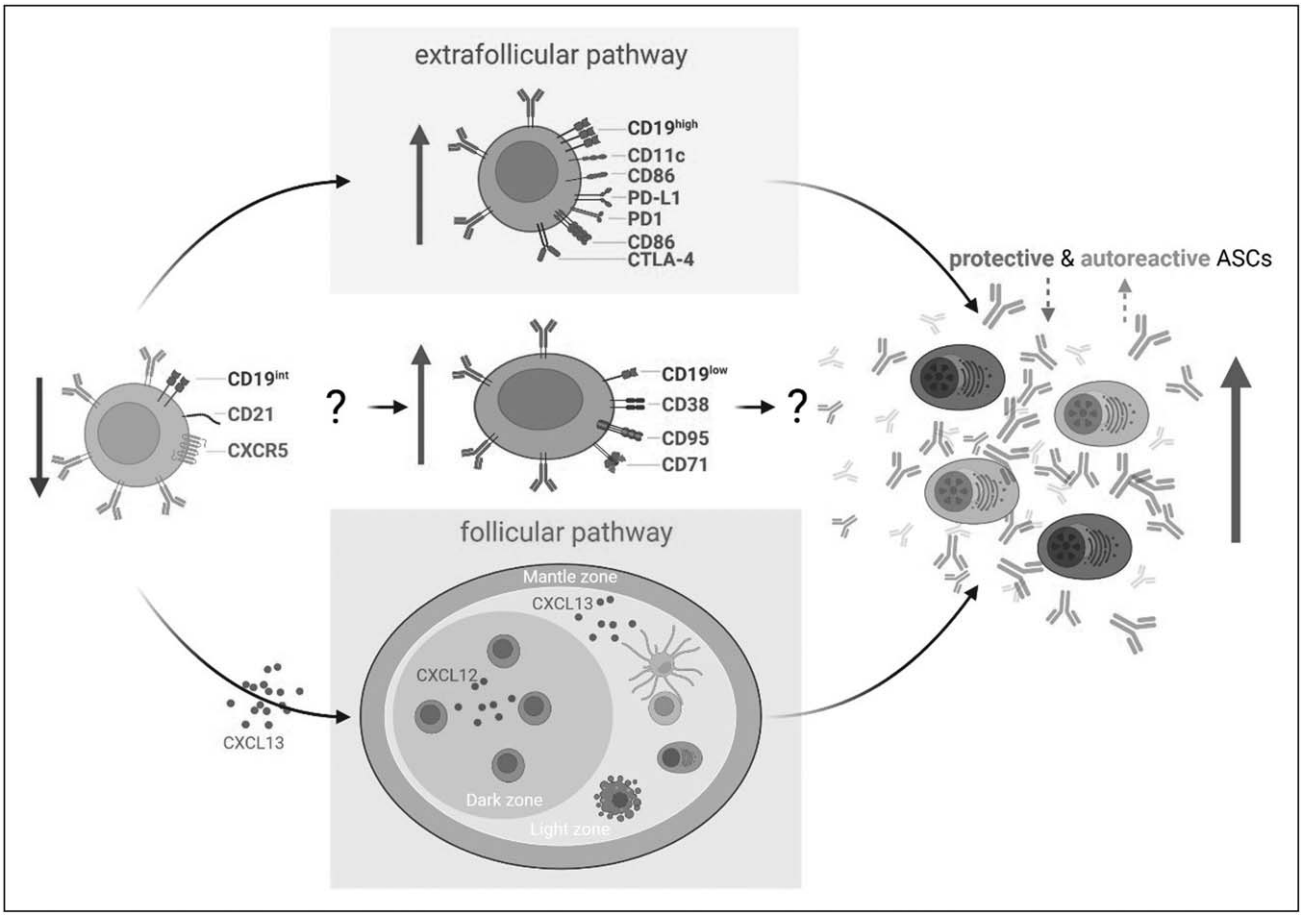


FIGURE 2. Altered B cell distribution in systemic lupus erythematosus with decrease in CXCR5-expressing cells and increase in CXCR5- B cells and expansion of antibody secreting cells. Suggesting a misbalance between the extrafollicular and follicular route. Patients exhibit increased titres of autoantibodies, while protective titres upon immunization can be decreased as a possible bystander effect of immunosuppressive therapy.

whether CD27 is a sufficient marker for all memory and ASC stages, although these deviations become apparent in patients with systemic autoimmunity, such as SLE.

Recent anti-B cell strategies comprise anti-CD20 second generation, anti-CD38 and CAR T cell therapies efficiently targeting CD19, which may provide broader coverage of the substantial B cell abnormalities in SLE. The current pandemic threat by SARS-CoV-2 provides evidence that treatments, such as MMF, cyclophosphamide and rituximab with a substantial effect on B cells may not only impact on course of an infection but also for vaccination response, possibly reconsideration of immunization protocols.

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Conflicts of interest

There are no conflicts of interest.

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Advances in understanding and examining lymphatic function: relevance for understanding autoimmunity

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Purpose of review
The aim of this review is to give insights into how novel lymphatics functions may influence autoimmunity.

Recent findings
The lymphatic system connects peripheral tissues to draining lymph nodes to regulate adaptive immunity and directly interfaces with leukocytes in lymph vessels and in the lymph node. Here, we discuss recent findings showing evidence of dysfunctional lymphatics in autoimmune disease, new understanding of how afferent lymphatic regulation can modulate immunity, lymph node lymphatic heterogeneity and how these lymphatics can directly modulate lymphocyte function, how this understanding can be harnessed for new therapeutics, and new tools for the investigation of lymphatic and immune biology.

Summary
Lymphatics have an active role in the regulation of inflammation and the adaptive immune response. Here, we review recent findings in lymphatics biology in peripheral tissues and lymph nodes and emphasize the relevance for better understanding autoimmune diseases.

Keywords
autoimmunity, lymph node, lymphatics, stromal

INTRODUCTION

The nonhematopoietic tissue 'stromal' compartment is increasingly appreciated as having more than a bystander role in shaping immune responses in the study of autoimmune diseases. Among the stromal structures, lymphatic vessels play a unique role in directly connecting peripheral tissues to draining secondary lymphoid organs wherein primary and secondary adaptive immune responses take place. The signals, including cells, antigens, and cytokines, that lymphatic vessels do or do not transmit thus play critical roles in shaping immunity and autoimmunity. Lymphatic vessels begin as blind-ended capillaries in tissue, which reabsorb interstitial fluid and molecules (see [1,2] for recent reviews on lymphatic ontogeny, function and signalling). Vessels are dynamic and can change their permeability and undergo lymphangiogenesis under different stimuli. Immune cells enter afferent lymphatics via migrating through chemokine gradients that lymphatics create and through direct interaction with cell adhesion molecules on lymphatic endothelial cells (LECs). Collecting lymphatic vessels are surrounded by smooth muscle cells and have valves, which actively pump lymph unidirectionally. Lymph is collected in draining lymph nodes wherein lymph node LECs actively regulate lymphocyte egress, compartmentalization and function [3]. The role in inflammation has focused mostly on tissue clearance, presumably of inflammatory cells and inflammatory cytokines [4]. In addition to these important and well established roles of tissue drainage, lymph node compartmentalization and chemokine production, lymphatics more recently have been described to have novel additional immunoregulatory roles that could have

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KEY POINTS

- LECs are a heterogeneous population of cells that have dynamic functions under different environmental stimuli.
- LECs dynamically regulate leukocyte egress from tissue and alter their activation. Lymph node LECs present antigen and can alter shape CD8 and $CD4^+$ responses.
- Novel delivery of lymphangiogenic factors and a new mouse model with increased number of lymphatics are promising new methods to study lymphatics in autoimmune models.

implications in autoimmune disease (Fig. 1). In this article, we will briefly review relevant recent findings on lymphatics in autoimmune disease models or patients with rheumatic disease, LEC function and regulatory mechanisms in peripheral and secondary lymphoid tissues, and approaches to study lymphatics.

LYMPHATICS IN RHEUMATOID ARTHRITIS MODELS AND PATIENTS

Lymphatics in rheumatologic diseases have arguably been most studied in the context of clearance of inflammatory mediators from affected joints and flow to the draining lymph nodes in the context of rheumatoid arthritis. Edward Schwarz and colleagues have shown that dysfunction of lymphatic flow from joints to lymph nodes contributes to joint inflammation and they delineated the role of immune cells in contributing to the dysfunction [5]. Recently, the group showed that tumour necrosis factor transgenic (TNF-Tg) mice that overexpress TNF and develop inflammatory arthritis have altered lymphatic vessels in peripheral tissues with decreased branching, increased diameter and poor smooth muscle cell coverage, all suggesting poor

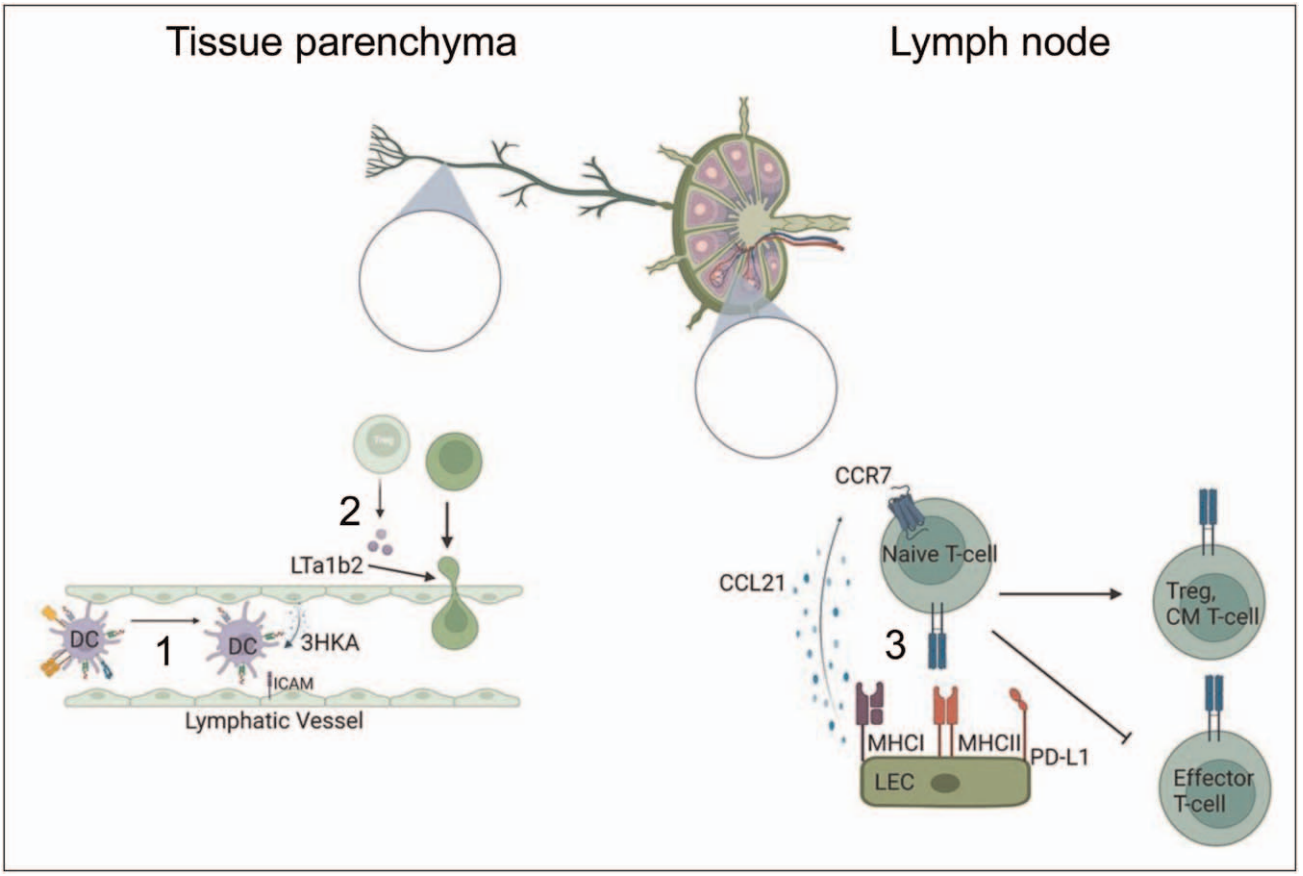

FIGURE 1. Recent finds in immune cell modulation by lymphatic endothelial cells. Afferent lymphatic vessel demonstrating effects on trafficking immune cells from tissue parenchyma to draining lymph node. These include the induction of tolerogenic dendritic cells and Treg mediated licensing of immune cell egress. LEC interaction with T cell in the lymph node paracortex. LECs attract CCR7-naive T cells via secreting its cognate chemokine CCL21. LECs alter the phenotype and fate of T cells (both CD8 and $CD4^+$) by presenting antigen on MHCI and MHCII along with lack of costimulation.

drainage function [6]. TNF was shown to induce apoptosis of lymphatic-associated smooth muscle cells by inducing LECs to produce nitric oxide. These results suggest the possibility that TNF inhibition improves inflammatory arthritis in part by restoring lymphatic drainage function. Furthermore, direct interrogation of lymphatic dysfunction using near infrared lymphangiography in patients with rheumatoid arthritis and active synovitis [7▪▪] showed delayed lymphatic drainage and altered lymphatic vessel anatomy with fewer and shorter lymphatic vessels. Interestingly, there were not differences in the contractility of the lymphatic vessels as were seen in preclinical murine models. This may be due to a difference in cytokine levels, increased susceptibility of smooth muscle damage in murine models or differences in the sites assayed between murine models and human subjects. The documentation of lymphatic dysfunction in patients with rheumatologic disease is an exciting complement to the mechanistic studies in murine systems and it will be interesting to ask the extent to which lymphatic dysfunction correlates with disease activity and lymphatic manipulation could improve disease activity.

AFFERENT LYMPHATIC FUNCTION, MOLECULES AND REGULATION

Several recent studies have provided new insights into immune cell trafficking via lymphatics. Dendritic cell migration through afferent lymphatics has previously been thought to only take place in the Lyve1+ capillaries via a CCR7 and integrin dependent manner. Afferent capillaries have slow flow and dendritic cells actively migrate through them to reach collecting lymphatics, which have higher flow rates. This is likely why most dendritic cells take several days to migrate from tissue to draining lymph node, while soluble antigen arrives much faster. However, Arasa *et al.* [8▪] demonstrated that dendritic cells can enter directly through cutaneous lymphatic collecting vessels, thus reaching draining lymph nodes faster. Transcriptomic analysis, immunofluorescence and FACS all demonstrated selective upregulation of cell adhesion molecules, such as VCAM1, on Lyve1- collecting vessels. Intravital microscopy visualized direct dendritic cell entry. Rapid migration was dependent on CCR7, integrin binding via VCAM1 and basement membrane and extracellular matrix degradation by matrix metalloproteinases. DC-LEC interactions have been shown to reduce dendritic cell maturation, thereby making them less able to activate effector T cells [9]. If rapid migration is upregulated in inflammatory conditions, this could further lead to decreased LEC-DC interaction, which can contribute to greater T cell activation.

Piao *et al.* [10▪▪] demonstrated a role for regulatory T cells in conditioning LECs to promote abluminal-to-luminal trans-endothelial migration (TEM) that brings leukocytes into lymphatic vessels. The authors showed that TLR2 signalling on Tregs stimulated lymphotoxin alpha1 beta2 (LTa1b2) expression that acted on LEC LTb receptor to induce endothelial cell adhesion molecule and chemokine expression. This process promoted graft survival of allogeneic pancreatic islets, attributable to both clearance of tissue inflammation as well as migration of regulatory T cells to the draining node to promote tolerance. Regulatory T cells have been found to be less potent at regulating effector T cells in autoimmune diseases that include type 1 diabetes, multiple sclerosis, SLE and rheumatoid arthritis [11], and it is tempting to speculate that regulatory T cells are also dysfunctional in promoting lymphatic vessel entry and subsequent immune regulation.

At steady state, LECs, by interacting with dendritic cells and T cells, have the important function to help maintain peripheral tolerance. Tryptophan (Trp) is an essential amino acid whose catabolism generates a cascade of over fifty molecules in a cell-specific manner. Three major Trp metabolic pathways have been described: synthesis of serotonin, synthesis of melatonin and generation of kynurenines. In mammalian cells, 90% of Trp is processed through the kynurenine pathway and kynurenine metabolites are regarded as one of the most powerful mechanism for immune regulation. Tryptophan (Trp) catabolism plays a major role in the modulation of immune responses [12–14]. By metabolizing Trp and thus depleting an essential amino acid required for protein synthesis and proliferation, dendritic cells strongly inhibit T cell proliferation [15]. In addition, metabolites from the Trp pathway have regulatory functions in several experimental models of autoimmunity and chronic inflammation by favouring the generation of regulatory dendritic cell and Tregs [12,16]. The limiting enzyme in Trp catabolism is IDO1 and LECs have been shown to be IDO1+ [17▪,18,19▪]. We recently reported that LECs generate a previously unidentified biogenic amine, 3HKA, which derives from a lateral pathway of Trp catabolism [19▪]. 3HKA exhibits a clear anti-inflammatory profile by inhibiting the STAT1/NF-kb pathway in both mouse and human dendritic cells with a consequent decrease in the release of pro-inflammatory chemokines and cytokines; most notably, IL-6, IL12p70 and TNF; *in vivo*, 3HKA exerted protective effects in the experimental model of psoriasis by decreasing skin thickness, erythema, scaling and fissuring. In a model of nephrotoxic lupus, 3HKA

improved proteinuria and serum urea nitrogen, overall ameliorating the immune-mediated glomerulonephritis and renal dysfunction. As such, IDO1 and Trp metabolites from the canonical and lateral pathway are important components of LEC-mediated immune tolerance. Together, these new studies emphasize the complex and dynamic role of afferent lymphatics in modulating the relationship between peripheral tissues and subsequent activity in draining nodes.

LYMPH NODE LYMPHATICS FUNCTION, REGULATION AND THERAPEUTIC TARGETING

New articles using single cell transcriptomic techniques to examine lymph node LECs continue to underscore the subset and location-specific nature of LEC subsets. Fujimoto *et al.* [20▪] and Xiang *et al.* [21▪] both examined murine lymph node LECs by single cell RNA sequencing and delineated four major subsets, similar to an earlier single cell analysis of human lymph nodes [22]. Two of the subsets were ceiling and floor LECs of the subcapsular sinus that receives afferent lymphatic input and modulates dendritic cell migration into the parenchyma. The remaining two subsets were medullary and/or cortical LECs, and Fujimoto *et al.* [20▪] showed that this latter subset mediated egress of lymphocytes from lymph nodes. Remarkably, Xiang *et al.* [21▪] could use the transcriptomic data to map the physical location of LEC subsets, identifying cells that appeared to physically bridge the floor and ceiling subcapsular sinus cells, for example. Similar to human lymph node LECs, both groups could delineate LECs that had more structural vs. immune function that included expression of molecules that involved in immune cell recruitment, scavenger functions and T cell tolerance [20▪,21▪]. Xiang *et al.* [21▪] also showed that 48 h of oxazolone painting on the skin, lymph node LECs showed subset-specific changes that appeared to at least in part type I interferon responses, underscoring the critical connection between skin and lymph nodes as a modulator of immune function in health and disease. Sibler *et al.* [23▪] also used scRNAseq analysis to examine murine lymph node LECs, asking about the changes that occur with 7 days of the TLR7 agonist imiquimod (IMQ). Although the 7-day regimen is used as a model for psoriasis, 4 weeks of IMQ is used as an SLE model [24], suggesting that these results could have implications for better understanding this SLE model. The authors were able to distinguish the subcapsular sinus ceiling and floor and medullary LECs and these subsets showed distinct magnitudes and type of responses to the IMQ. Notably, the authors compared these changes with changes induced by 48 h of oxazolone painting and saw that some of the LEC changes were common to both stimuli, suggesting that there may be a framework of stereotypical LEC responses to skin inflammation with additional aspects of the response that are stimulus-specific. These data present exciting opportunities to better understand how lymphatic vessels or sinuses in lymph nodes impact autoimmunity in disease.

Recent studies have also further established the role of lymph node LECs in modulating CD8 T cell function. The oncology literature has elucidated an immunosuppressive role of LECs by looking at $CD8^+$ T-cell responses in tumour draining lymph nodes (TDLNs). Lymph node LECs express the T-cell inhibitory protein PD-L1, which is upregulated by IFN-gamma. In two different orthotopic murine cancer models, knocking out PD-L1 in LECs increased the frequency of tumour-specific $CD8^+$ T-cells [25▪]. Lack of PD-L1 prevented apoptosis specifically in tumour antigen specific $CD8^+$ central memory T-cells. These had more inflammatory and cytotoxic capabilities compared with $CD8^+$ T-cell than those that survived in wild type controls. In addition, these mice had improved survival and less cancer progression. On the contrary, Melody Swartz's group showed LECs also promote central memory $CD8^+$ T-cells education and development by MHCI cross-presentation from lymph node LECs [26▪]. Under steady-state conditions, LEC-educated but not dendritic cell-educated $CD8^+$ cells developed into stem cell like central memory cells. However, these cells were not solely quiescent and under specific restimulation conditions could become functional, engage in cytotoxicity and were capable of elucidating multiple inflammatory cytokines. Consistent with this idea that LECs promote immunity, the same group demonstrated vaccination combined with VEGFC induced lymphangiogenesis leads to stronger T cell immunity against cancer antigens and increased survival and efficacy of immunotherapy in mice [27▪]. These studies together suggest that lymphatics can have different effects on the adaptive immune system in different contexts. It would be interesting to understand if there are roles for lymphatics in the phenotype of $CD8^+$ T-cells found in affected tissues in autoimmune diseases [28,29].

LECs also are capable of presenting antigen on MHCII. Deletion of MHCII in LECs leads to autoimmunity in mice [30]. Decreased macro-autophagy in LECs results in less MHCII expression and also resulted in autoimmunity [31▪▪]. MHCII on LECs acts predominantly on T-regs, increasing their suppressive functions. As mentioned previously,

regulatory T-cells are dysfunctional in many autoimmune diseases and manipulation of MHCII presentation by LECs could be a strategy to abrogate dysfunction. In a dust-mite allergy model, VEGFR3 antagonism exacerbated the allergic Th2 memory response in the lungs [32▪]. This was attributed to increased accumulation of naive T cells and decreased regulatory T cells in the draining lymph node, possibly due to lower lung tissue CCL21 without concomitant decreased CCL21 in the draining lymph node. These demonstrate a regulatory role for LECs on effector CD4 T cell and regulatory T cells.

Sphingosine-1-phosphate (S1P) expressed by LECs mediates T cell egress from lymph nodes and eventually into the blood circulation, from where the T cells can home into peripheral tissues [3]. Trapping of proinflammatory effector T cells within lymph nodes would prevent these T cells from incurring tissue damage, and this idea has been leveraged into the development of S1P-targeting therapeutics. FDA-approved Fingolimod (FYT720) acts in part to downregulate S1P receptor 1 (S1PR1) on T cells and inhibit egress of T cells out of the lymph node, preventing them from homing to peripheral tissue to induce inflammation. Fingolimod has been effective in multiple sclerosis but has a variety of side effects, potentially due to inhibitory effects on multiple S1PRs (S1PR1,3,4,5) and pleiotropic effects of S1P on multiple processes, including vascular permeability. However, nonselective blockade of S1PR can have off-target effects, including altering T cell egress from tissue to lymph node. For example, T cell S1PR1 and S1PR4 work together with LEC S1PR2 to promote migration into afferent lymph. This mechanism was separate from constitutive CCR7-mediated migration, making it more likely to be critical in inflammatory states [33▪]. There are several promising new selective S1PR agonists. Cenerimod, a selective S1PR1 inhibitor, was well tolerated and efficacious in a phase 1 SLE trial and has preclinical efficacy in scleroderma murine models [34,35]. Ozanimod, a selective S1PR1 and S1PR5, has been shown efficacious and well tolerated for induction and maintenance treatment in ulcerative colitis [36▪]. This synergy between basic science findings and the drug development pipeline is also driven in part by the importance of S1P to vascular function and many inflammatory disease processes, and this synergy holds promise for both better understanding of disease pathophysiology and development of new therapeutics.

TOOLS FOR INNOVATION

One of the difficulties in studying lymphatic function is the relative difficulty in manipulating lymphatics in vivo. Recent articles have delineated new tools that will allow further studies of lymphatic function. Two recent papers described targeted local delivery of pro-lymphangiogenic VEGFC by nucleoside-modified mRNA encapsulated lipid nanoparticles [37▪] and antibody conjugation [38], which should circumvent the inflammation and vascular permeability that can accompany delivery of systemic VEGFC. In addition, Kataru *et al.* [39▪▪] have generated a novel murine model that deletes PTEN, the negative regulator of VEGFR3 signalling, specifically in LECs. This model develops increased number of functional, nonleaky lymphatic vessels, allowing for studies to ask about the effects of having more lymphatics. These tools may be useful for the study of lymphatic function in autoimmune diseases.

CONCLUSION

The lymphatic system is a crucial part of the immune system which in turn likely play important roles in autoimmune diseases. However, to date they have been underexplored in the realm of rheumatology. Further investigation of the role of LECs in rheumatologic diseases will likely gain new insights into disease pathogenesis and novel therapeutic options.

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Figure and legend created with BioRender.com.

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Conflicts of interest

There are no conflicts of interest.

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Diagnostic, predictive and prognostic biomarkers in systemic lupus erythematosus: current insights

Julius Lindblom[a], *Chandra Mohan*[b], *and Ioannis Parodis*[a,c]

Purpose of review
Biomarkers for diagnosis, monitoring and prognosis still constitute an unmet need for systemic lupus erythematosus (SLE). Focusing on recent findings, this review summarises the current landscape of biomarkers in lupus.

Recent findings
Urine activated leukocyte cell adhesion molecule (ALCAM) exhibited good diagnostic ability in SLE and lupus nephritis (LN) whereas cerebrospinal fluid neutrophil gelatinase-associated lipocalin (NGAL) showed promise in neuropsychiatric SLE. Urine ALCAM, CD163 and vascular cell adhesion molecule 1 (VCAM-1) may be useful in surveillance of LN. Urine monocyte chemoattractant protein 1 was found to predict treatment response in SLE, and urine CD163 and NGAL treatment response in LN. Serum complement component 3 (C3) and urinary VCAM-1 have been reported to portend long-term renal prognosis in LN.

Summary
NGAL holds promise as a versatile biomarker in SLE whereas urine ALCAM, CD163 and VCAM-1 displayed good performance as biomarkers in LN. The overall lack of concerted corroboration of leading candidates across multiple cohorts and diverse populations leaves the current biomarker landscape in SLE in an urgent need for further survey and systematic validation.

Keywords
biomarkers, diagnosis, monitoring, prognosis, systemic lupus erythematosus

INTRODUCTION

The clinical heterogeneity of systemic lupus erythematosus (SLE) poses diagnostic difficulties, which is underlined by the lack of generally accepted diagnostic criteria [1]. Nonetheless, early diagnosis and treatment initiation are important to prevent organ damage accrual [1]. Moreover, the chronic nature of the disease with its varying course prompts for regular monitoring [2]. The recent approvals of new targeted therapies for SLE [3,4] and the increasing awareness of the long-term adverse effects of glucocorticoids [1] have necessitated optimisation of surveillance and treatment evaluation. Biomarker studies in SLE have historically focused on serum biomarkers but sampling from other locations, such as urine and cerebrospinal fluid (CSF), has gained interest, particularly for the monitoring of certain manifestations [5]. Determination of reliable biomarkers in lupus remains an unmet need. The purpose of this review is to summarise recent insights in biomarkers of diagnosis, monitoring, and prognosis of SLE, including lupus nephritis (LN) and neuropsychiatric SLE (NPSLE).

SELECTION OF ARTICLES

An initial systematic search to support the purpose of this review is described in the online supplementary material (Supplementary Fig. 1, http://links.lww.com/COR/A52) and includes a Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 flow diagram [6]. In short, a search of Medline for biomarker studies in adult patients with SLE from January 1, 2019 to November 1, 2021 was conducted to identify the most cited biomarkers. For diagnostic biomarkers and biomarkers of disease activity, only biomarkers reported in multiple

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KEY POINTS

- CSF NGAL exhibits a good diagnostic ability in neuropsychiatric systemic lupus erythematosus.
- Urine ALCAM, CD163 and VCAM-1 may prove useful in monitoring of lupus nephritis.
- MCP-1 portends treatment response in SLE, and urine NGAL and CD163 portend treatment response in lupus nephritis.
- Serum levels of C3 and urinary levels of VCAM-1 have shown promise in prognostication of long-term renal outcome.
- Although the above biomarker leads are promising, independent validation across multiple cohorts and diverse ethnicities remains an urgent need.

studies or validated in independent cohorts were included.

DIAGNOSTIC BIOMARKERS IN SYSTEMIC LUPUS ERYTHEMATOSUS/LUPUS NEPHRITIS/NEUROPSYCHIATRIC LUPUS

A recent meta-analysis by Orme *et al.* [7] corroborated the high specificity (95%) of antidouble stranded(ds)DNA for SLE, in comparison with patients with other rheumatic diseases (Table 1) [7–12,13▪,14,15]. In contrast, the sensitivity (52%) of antidsDNA was rather poor [7]. B cell activating factor belonging to the tumour necrosis factor ligand superfamily (BAFF) was also reported to display a good ability to discriminate between SLE and healthy controls (area under the curve [AUC] = 0.91) [16], corroborating previous knowledge [17,18]. Cluster of differentiation 163 (CD163) and activated leukocyte cell adhesion molecule (ALCAM, also known as CD166) both constitute attractive urinary biomarkers to discriminate LN from healthy status with a reported AUC of 0.97 and 0.98, respectively [19,12,13▪]. Interestingly, neutrophil gelatinase-associated lipocalin (NGAL, also known as lipocalin-2) in CSF was recently reported to be a diagnostic biomarker of NPSLE, as it distinguished Chinese patients with NPSLE from healthy individuals with an AUC of 0.85 [15]. NGAL is an acute-phase glycoprotein that is secreted also by cells other than neutrophils, including epithelial cells in renal tubules and neurons, and its expression increases during cellular stress [20,21]. Other promising diagnostic CSF biomarkers in NPSLE include macrophage colony-stimulating factor (M-CSF) and immunoglobulin M (IgM), which both displayed ability to discriminate NPSLE from healthy individuals and/or patients with other neurological conditions in two ethnically diverse cohorts of Canadian and Chinese patients [14]. M-CSF expressing T helper (Th) cells have been found to be enriched in CSF from patients with multiple sclerosis (MS), whereas CSF IgG index was associated with inflammatory lesions in the brain in conventional magnetic resonance imaging (MRI) in patients with newly diagnosed MS [22,23].

BIOMARKERS OF DISEASE ACTIVITY AND ORGAN DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS/LUPUS NEPHRITIS

Table 2 summarises recent findings of biomarkers of disease activity and accumulated organ damage [8,12,13▪,16,24–28,29▪,30,31,32▪,33–45,46▪,47–52,53▪–56▪,57]. Low complement component 3 (C3) [28] and C4 [28], and interferon (IFN)α [25] recently exhibited good performance as serum biomarkers of disease activity measured with Lupus Low Disease Activity State (LLDAS) [58] or Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [59]. Type I IFNs are known to play a central role in SLE pathogenesis [60] and the antitype I IFN receptor monoclonal anifrolumab [61,62] was recently approved by the US Food and Drug Administration (FDA) for the treatment of SLE [3]. Furthermore, in a French cohort of 150 SLE patients, serum IFNα predicted flares (AUC = 0.73) defined according to the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-SLEDAI [63] Flare Index [64], outperforming the predictive ability of antidsDNA and C3 [40]. Thus, type I INFs constitute attractive biomarkers in SLE. However, the fact that not all SLE patients display an IFN signature [65] poses limitations for their use as biomarkers of activity or organ damage.

In a recent report, circulating levels of C3 ($\rho = -0.99$) and C4 ($\rho = -0.83$) exhibited outstanding inverse correlations with disease activity in LN patients [34]. Interestingly, urine CD163 correlated strongly with National Institutes of Health (NIH) renal histology activity index scores [66] in serial kidney biopsies in a limited Mexican LN cohort ($\rho = 0.83$) [54▪]. CD163 is a scavenger receptor that constitutes a marker of macrophage activation, and it has also been shown to have biomarker attributes for activity in renal vasculitis [67,68].

Serum IL-17 [42], urine ALCAM [32▪], CD163 [54▪], and vascular cell adhesion molecule 1 (VCAM-1, also known as CD106) [32▪], all were recently shown to have ability to identify active LN (AUC ≥ 0.85), distinguishing them from lupus patients with inactive disease. It is worth noting that urine VCAM-1 and ALCAM both showed good performance in two validation cohorts comprising

Table 1. Performance of selected diagnostic biomarkers in SLE/LN/NPSLE

Biomarker	Sample	Study group	Comparator	Metrics	References
Traditional					
AntidsDNA	Serum/plasma	SLE	HC, other rheumatic diseases	sens.: 52%; spec.: 95%; PLR: 9.9; NLR: 0.5	Orme *et al.*, 2021 [7]
		LN	Nonrenal SLE	sens.: 72–100%; spec.: 71–72%; PPV: 44%; NPV: 100; AUC: 0.72–0.89; HR: 1.1–2.7; OR: 2.9–4.6	Barnado *et al.*, 2019 [8]; Kwon *et al.*, 2020 [9]; Liu *et al.*, 2021 [10]
Emerging					
ALCAM	Urine	SLE	HC	AUC: 0.73–0.96	Chalmers *et al.*, 2022 [11]
		LN	HC	AUC: 0.62–0.98	Chalmers *et al.*, 2022 [11]; Ding *et al.*, 2020 [12]
CD163	Urine	LN	HC	AUC: 0.90–0.97	Zhang *et al.*, 2020 [13▪]
IgG	CSF	NPSLE	HC, other neurological diseases	sens.: 70–100%; spec.: 89–100%; PPV: 83–100%; NPV: 75–100%; AUC: 0.78–0.95	Vanarsa *et al.*, (under revision) [14]
M-CSF	CSF	NPSLE	HC, other neurological diseases	sens.: 47–80%; spec.: 94–100%; PPV: 87–100%; NPV: 62–90%; AUC: 0.71–0.91	Vanarsa *et al.*, (under revision) [14]
NGAL	CSF	NPSLE	HC, other neurological diseases	sens.: 76–94%; spec.: 80%; PPV: 63–84%; NPV: 88–92%; AUC: 0.82–0.85	Mike *et al.*, 2019 [15]; Vanarsa *et al.*, (under revision) [14]

ALCAM, activated leukocyte cell adhesion molecule; antidsDNA, antidouble-stranded DNA; AUC, area under the curve; BAFF, B cell activating factor belonging to the tumour necrosis factor ligand superfamily; CD163, cluster of differentiation 163; CSF, cerebrospinal fluid; HC, healthy controls; HR, hazard ratio; IgG, immunoglobulin G; LN, lupus nephritis; M-CSF, macrophage colony-stimulating factor; NGAL, neutrophil gelatinase-associated lipocalin; NLR, negative likelihood ratio; NPSLE, neuropsychiatric systemic lupus erythematosus; OR, odds ratio; PBMCs, peripheral blood mononuclear cells; PLR, positive likelihood ratio; PPV, positive predictive value; sens., sensitivity; SLE, systemic lupus erythematosus; spec., specificity.

patients of African American, Caucasian and Asian origin [32▪]. Furthermore, in a recent study by Ding *et al.* urinary levels of ALCAM outperformed traditional serum biomarkers (antidsDNA, C3 and C4) in discriminating class III/IV (proliferative) LN from class V (membranous) LN [12], classified according to the 2003 International Society of Nephrology/Renal Pathological Society (ISN/RPS) algorithm [69]. Cell adhesion molecules play an important role in the extravasation of leukocytes to sites of inflammation [70]; VCAM-1 is expressed in endothelial and glomerular parietal epithelial cells [71], whereas ALCAM is mainly expressed on antigen-presenting cells and has been shown to mediate T cell migration through the endothelium and blood-brain barrier [72–74].

Osteopontin was recently reported as a CSF biomarker of disease activity in a small Japanese cohort of NPSLE patients [75], which however needs to be validated in independent cohorts. Osteopontin is an extracellular matrix protein found in many tissues, including the brain, and facilitates recruitment of macrophages and T cells during inflammation [76].

Modest correlations between serum levels of IFNγ and organ damage assessed with the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) were reported [16,77]. Urine VCAM-1 and ALCAM have been shown to determine the stage of chronic kidney disease (CKD) [55▪], whereas urine VCAM-1 was also correlated with NIH renal histology chronicity index scores in patients with LN [66,46▪]. Lastly, the percentage of $CD163^{+}$ M2c-like macrophages in kidney biopsies also correlated with NIH chronicity index scores ($\rho = 0.41$) [56▪].

PREDICTIVE BIOMARKERS OF RESPONSE TO THERAPY

Circular RNAs (circRNAs) are noncoding RNAs that regulate gene expression and are more stable compared with most linear RNAs [78]. Accumulating evidence suggests a role of circRNAs in SLE disease

Table 2. Performance of selected biomarkers of disease activity and organ damage in SLE/LN

Biomarker	Sample	Study group	Comparator[a]	Definitions of disease activity	Metrics	References
Traditional						
AntidsDNA	Serum/plasma	SLE	Inactive SLE, SLE without flare	cSLEDAI, LLDAS, SLEDAI, SELENA-SLEDAI Flare Index	sens.: 53–69%; spec.: 63–67%; PPV: 67–71%; NPV: 60–68%; PLR: 1.4–2.1; NLR: 0.5–0.7; AUC: 0.62–0.70; HR: 1.6–1.8; $\rho = 0.23–0.35$	Kianmehr *et al.*, 2021 [24]; Mathian *et al.*, 2019 [25]; Petri *et al.*, 2013 [26]; Ruchakorn *et al.*, 2019 [27]; Salazar-Camarena *et al.*, 2020 [28]; Sohrabian *et al.*, 2019 [29▪]
		LN	Inactive SLE, inactive LN, SLE without renal flare	rSLEDAI, SLEDAI, renal flare[b]	sens.: 52–88%; spec.: 51–99%; PPV: 63–75%; NPV: 61–98%; AUC: 0.66–0.85; HR: 21.7; OR: 4.2	Fasano *et al.*, 2020 [30]; Kianmehr *et al.*, 2021 [24]; Stanley *et al.*, 2019 [31]; Stanley *et al.*, 2020 [32▪]
Low C3	Serum/plasma	SLE	Inactive SLE, SLE without flare	cSLEDAI, LLDAS, SELENA-SLEDAI Flare Index	sens.: 62–85%; spec.: 71–75%; PLR: 1.6–5.8; NLR: 0.6; AUC: 0.65–0.91; HR: 1.5–3.7; $\rho = -0.41$	Cambron *et al.*, 2020 [33]; Petri *et al.*, 2013 [26]; Ruchakorn *et al.*, 2019 [27]; Salazar-Camarena *et al.*, 2020 [28]
		LN	SLE without flare	SLEDAI, renal flare[b]	sens.: 100%; spec.: 51%; AUC: 0.76; HR: 6.0; $\rho = -0.99$	Fasano *et al.*, 2020 [30]; Selvaraja *et al.*, 2019 [34]
Low C4	Serum/plasma	SLE	Inactive SLE, SLE without flare	cSLEDAI, LLDAS, SELENA-SLEDAI Flare Index	sens.: 47–83%; spec.: 63–88%; PLR: 1.5–6.8; NLR: 0.7; AUC: 0.61–0.93	Cambron *et al.*, 2020 [33]; Ruchakorn *et al.*, 2019 [27]; Salazar-Camarena *et al.*, 2020 [28]
		LN	SLE without flare	SLEDAI, renal flare[b]	sens.: 100%; spec.: 62%; AUC: 0.82; HR: 5.5; $\rho = -0.83$	Fasano *et al.*, 2020 [30]; Selvaraja *et al.*, 2019 [34]
Emerging						
PD-L1	Blood cells/PBMC, serum/plasma	SLE	N/A	SLEDAI	$\rho = -0.57–0.47$	Du *et al.*, 2020 [35]; Hirahara *et al.*, 2020 [36]; Jia *et al.*, 2019 [37]; Zhao *et al.*, 2020 [38]
BAFF	Serum/plasma	SLE	Inactive SLE, SLE without renal flare	LLDAS, Mex-SLEDAI, SELENA-SLEDAI Flare Index	sens.: 63%; spec.: 61%; PLR: 1.6; AUC: 0.59; $\rho = 0.32–0.62$; HR: 1.5–1.9	Petri *et al.*, 2013 [25]; Salazar-Camarena *et al.*, 2019 [12]; Salazar-Camarena *et al.*, 2020 [28]
IFNα	Serum/plasma	SLE	Inactive SLE, SLE without flare	cSLEDAI, SLEDAI, SELENA-SLEDAI Flare Index	sens.: 51–73%; spec.: 60–94%; PLR: 1.7–10.5; NLR: 0.37–0.70; PPV: 85–93; NPV: 67–76; AUC: 0.62–0.84; HR: 4.0–5.5; $\rho = 0.20–0.37$	Enocsson *et al.*, 2021 [39]; Mathian *et al.*, 2019 [25]; Mathian *et al.*, 2019 [40]; Ruchakorn *et al.*, 2019 [27]
IL-17	Serum/plasma, urine	SLE	Inactive SLE	BILAG, cSLEDAI, Mex-SLEDAI	AUC: 0.67–0.77; $\rho = 0.31–0.53$	Nordin *et al.*, 2019 [41]; Salazar-Camarena *et al.*, 2019 [16]
		LN	Inactive LN	AI, BILAG renal score, SLEDAI	AUC: 0.81–0.91; $\rho = 0.23–0.63$	Dedong *et al.*, 2019 [42]; Nordin *et al.*, 2019 [41]

Table 2 (*Continued*)

Biomarker	Sample	Study group	Comparator[a]	Definitions of disease activity	Metrics	References
MCP-1	Serum/plasma, urine	SLE	Inactive SLE	cSLEDAI, SLEDAI	sens.: 67%; spec.: 67%; PLR: 2.0; NLR: 0.5; AUC: 0.71; $\rho = 0.23–0.41$	Mirioglu *et al.*, 2020 [43]; Ruchakorn *et al.*, 2019 [27]; Smith *et al.*, 2019 [44]
		LN	Inactive SLE, inactive LN	Proteinuria >0.5g/24h, rSLEDAI, SLEDAI	sens.: 78–89%; spec.: 62–85%; PPV: 83%; NPV: 54%; PLR: 2.2; NLR: 0.2; AUC: 0.71–0.76; $\rho = 0.28–0.35$	Bona *et al.*, 2020 [45]; Liu *et al.*, 2020 [46▪]; Mirioglu *et al.*, 2020 [43]; Stanley *et al.*, 2020 [32▪]; Xia *et al.*, 2020 [47]
Neutrophil-lymphocyte ratio	Serum/plasma	SLE	Inactive SLE	SLEDAI	sens.: 61–83%; spec.: 50–77%; PPV: 72; NPV: 66; PLR: 2.6; NLR: 0.5; AUC: 0.68–0.69; $\rho = 0.24–0.32$	Firizal *et al.*, 2020 [48]; Peirovy *et al.*, 2020 [49]; Yu *et al.*, 2019 [50]
NGAL	Serum/plasma, urine, CSF	SLE	Inactive SLE	SLEDAI	sens.: 47–83%; spec.: 55–90%; AUC: 0.67–0.79; $\rho = 0.28–0.58$	Fasano *et al.*, 2020 [30]; Mirioglu *et al.*, 2020 [43]
		LN	Inactive SLE, SLE without flare	AI, proteinuria >0.5g/24h, rSLEDAI, SLEDAI, renal flare[b]	sens.: 72–80%; spec.: 67–71%; PLR: 2.4–2.5; NLR: 0.3–0.4; AUC: 0.74–0.77; $\rho = 0.31–0.43$	Fasano *et al.*, 2020 [30]; Liu *et al.*, 2020 [46▪]; Mirioglu *et al.*, 2020 [43]
PD-1	Serum/plasma	SLE	N/A	SLEDAI	$\rho = 0.20–0.38$	Du *et al.*, 2020 [35]; Hirahara *et al.*, 2020 [36]
TNF-α	Serum/plasma	SLE	N/A	Mex-SLEDAI, SLEDAI	$\rho = -0.31–0.41$	Salazar-Camarena *et al.*, 2019 [16]; Uzrail *et al.*, 2019 [51]
ALCAM	Urine	LN	Active nonrenal SLE, inactive SLE, inactive LN	rSLEDAI, SLEDAI, SLICC RAS	sens.: 52–90%; spec.: 91–92%; PPV: 77–91%; NPV: 78–90%; AUC: 0.64–0.96; $\rho = 0.15–0.58$	Chalmers *et al.*, 2022 [11]; Ding *et al.*, 2020 [12]; Stanley *et al.*, 2020 [32▪]
CD163	Urine	SLE	N/A	PGA, SLEDAI	$\rho = 0.30–0.67$	Gupta *et al.*, 2021 [52]; Zhang *et al.*, 2020 [13▪];
		LN	Active nonrenal SLE, inactive LN	AI, rSLEDAI, SLEDAI	sens.: 97%; spec.: 94%; AUC: 0.76–1.00; $\rho = 0.37–0.83$	Fava *et al.*, 2021 [53▪]; Gupta *et al.*, 2021 [52]; Mejia-Vilet *et al.*, 2020 [54▪]; Zhang *et al.*, 2020 [13▪]
IL-16	Urine	LN	N/A	AI	$\rho = 0.73$	Fava *et al.*, 2021 [53▪]
VCAM-1	Urine	LN	Inactive SLE, SLE without flare	AI, proteinuria >0.5g/24h, rSLEDAI, SLEDAI, renal flare[b]	sens.: 75–90%; spec.: 75–88%; PPV: 88%; NPV: 69–90%; AUC: 0.76–0.92; HR: 7.5; $\rho = 0.37$	Fasano *et al.*, 2020 [30]; Liu *et al.*, 2020 [46▪]; Stanley *et al.*, 2020 [32▪]

Table 2 (*Continued*)

Biomarker	Sample	Study group	Comparator[a]	Definitions of organ damage	Metrics	References
Traditional						
AntidsDNA	Serum/plasma	SLE	SLE without ESRD	ESRD	OR: 2.6	Barnado *et al.*, 2019 [8]
Emerging						
IFNγ	Serum/plasma	SLE	N/A	SDI	$\rho = 0.44$	Salazar-Camarena *et al.*, 2019 [16]
ALCAM	Urine	SLE	N/A	CKD stages	$\rho = 0.22–0.34$	Parodis *et al.*, 2019 [55▪]
	Kidney tissue	LN	N/A	CI	$\rho = 0.41$	Allam *et al.*, 2020 [56▪]
VCAM-1	Urine	SLE	N/A	CKD stages	$\rho = 0.32–0.40$	Parodis *et al.*, 2019 [55▪]
		LN	N/A	CI, CKD stages	$\rho = 0.39–0.50$	Liu *et al.*, 2020 [46▪]; Parodis *et al.*, 2019 [55▪]

AI, National Institutes of Health (NIH) renal histology activity index; ALCAM, activated leukocyte cell adhesion molecule; antidsDNA, antidouble-stranded DNA; AUC, area under the curve; BAFF, B cell activating factor belonging to the tumour necrosis factor ligand superfamily; BILAG, British Isles Lupus Assessment Group; C3, complement component 3; C4, complement component 4; CD163, cluster of differentiation 163; CI, National Institutes of Health (NIH) renal histology renal biopsy chronicity index; CKD, chronic kidney disease; cSLEDAI, clinical Systemic Lupus Erythematosus Disease Activity Index 2000; ESRD, end-stage renal disease; HR, hazard ratio; IFN, interferon; IL, interleukin; LLDAS, Lupus Low Disease Activity State; LLDAS, Lupus Low Disease Activity State; LN, lupus nephritis; MCP-1, monocyte chemoattractant protein 1; Mex-SLEDAI, the Mexican version of the SLEDAI; N/A, not applicable; NGAL, Neutrophil gelatinase-associated lipocalin; NLR, negative likelihood ratio; NPV, negative predictive value; OR, odds ratio; PBMCs, peripheral blood mononuclear cells; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PGA, physician global assessment; PLR, positive likelihood ratio; PPV, positive predictive value; rSLEDAI, renal domain scores of the SLEDAI; SDI, SLICC/American College of Rheumatology (ACR) Damage Index; SELENA, Safety of Estrogens in Lupus Erythematosus, National Assessment – SLEDAI; sens., sensitivity; SLE, systemic lupus erythematosus; SLICC RAS, Systemic Lupus International Collaborating Clinics renal activity score; spec., specificity; TNF-α, tumour necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1.
[a]If applicable.
[b]According to the American College of Rheumatology (ACR) criteria [57].

processes [79,80]. Peripheral blood mononuclear cell (PBMC) expression levels of circular RNAs, Hsa_circ_0000479 and hsa_circ_0082689 in particular [81], and serum programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) [36], and BAFF [28] showed merit as potential biomarkers of response to conventional immunosuppressive therapy in patients with SLE (Table 3) [28,29▪,36,46▪,53▪,54▪,82–86]. PD-1 is mainly expressed in activated T cells, and the interaction between PD-1 and PD-L1 results in inhibition of autoreactive T cells whereas promoting regulatory T cells [87]. The interplay between PD-1 and PD-L1 has also been reported to be important in the pathogenesis of other autoimmune diseases, including rheumatoid arthritis and MS [87]. In a Chinese cohort of patients with active LN, urine NGAL exhibited a sensitivity of 83% and a specificity of 81% in predicting response after six months of induction therapy [46▪]. Lastly, in a study by Mejia-Vilet *et al.* [54▪], urine CD163 outperformed circulating antidsDNA and C3 in predicting complete clinical renal response at 12 months in two separate cohorts of LN patients.

Introducing the concept of changes in levels rather than levels or positivity at one particular measurement, Cesaroni *et al.* [88] reported associations between reductions in serum levels of IFNγ from baseline through multiple follow-up visits and attainment of SLE Responder Index 4 (SRI-4) response [89] to ustekinumab, an interleukin (IL)-12 and IL-23 inhibitor, based on data from a phase II trial in SLE [90]. In the same fashion, another study found that an early decline in serum levels of IL-6 over the first three months of treatment was associated with sustained SRI-4 response to add-on belimumab and attainment of sustained clinical remission defined as SLEDAI-2K = 0 and prednisone ≤7.5 mg/day [85]. The same study found that anti-Smith (Sm) antibody positivity at the baseline assessment was associated with response to belimumab therapy [85]. Finally, another study reported associations of baseline urinary levels of monocyte chemoattractant protein 1 (MCP-1, also known as CCL2), a potent inducer of monocyte chemotaxis, and ceruloplasmin, an enzyme with copper-dependent oxidase activity, with response to rituximab therapy after 6–12 months from treatment commencement [86]. Finally, in a recent study of LN patients by Fava *et al.* [53▪], early decreases in urinary concentrations of IL-16, CD163 and transforming growth factor beta 1 (TGF-β1) were seen in complete and partial responders but not in nonresponders after 12 months of induction therapy.

PROGNOSTIC BIOMARKERS

Recent findings of prognostic biomarkers in SLE are summarised in Table 4 [54▪,55▪,83,91▪,92]. In a study from the large Hopkins Lupus Cohort by Petri *et al.*, the overall risk of long-term renal failure defined as a need for dialysis or renal transplant was estimated to be 4.8% within 10 years and

Table 3. Performance of selected biomarkers of response to therapy in SLE/LN

Biomarker	Sample	Study group	Main findings	References
Traditional				
AntidsDNA	Serum/plasma	SLE	OR 1.74 for clinical remission following belimumab therapy. Baseline antidsDNA in immune complexes was associated with response to belimumab.	Parodis *et al.*, 2019 [82]; Sohrabian *et al.*, 2019 [29▪]
		LN	Complete clinical renal response at 12 months: sens.: 66–83%; spec.: 45–56%; PPV: 54–67%; NPV: 59–74%; PLR: 1.3–1.6; NLR: 0.4–0.7	Mejia-Vilet *et al.*, 2020 [54▪]
C3	Serum/plasma	LN	Complete clinical renal response at 12 months: sens.: 65–76%; spec.: 55–72%; PPV: 61–75%; NPV: 62–75%; PLR: 1.7–2.4; NLR: 0.4–0.5	Mejia-Vilet *et al.*, 2020 [54▪]
Emerging				
circRNAs	Blood cells/PBMC	SLE	Expression levels of hsa_circ_0000479 and hsa_circ_0082689 decreased following conventional immunosuppressive treatment.	Luo *et al.*, 2020 [81]
Axl	Serum/plasma	LN	Levels decreased in clinical responders but not in nonresponders following induction therapy. High baseline levels yielded an adjusted OR 9.3 for histological response to induction therapy.	Parodis *et al.*, 2019 [83]
BAFF	Serum/plasma	SLE	Levels decreased in LLDAS achievers after 6 months of standard therapy. Levels at baseline predicted SLEDAI-2K response at 12 months.	Piantoni *et al.*, 2021 [84]; Salazar-Camarena *et al.*, 2020 [28]
IFN-γ	Serum/plasma	SLE	Reductions in serum levels from baseline through multiple follow-up visits were associated with attainment of SRI-4 response to ustekinumab.	Cesaroni *et al.*, 2021 [83]
IL-6	Serum/plasma	SLE	Decline in serum levels from baseline to month 3 was associated with attainment of sustained SRI-4 and clinical remission following belimumab therapy.	Parodis *et al.*, 2020 [85]
PD-1	Serum/plasma	SLE	Levels decreased in responders to immunosuppressive treatment.	Hirahara *et al.*, 2020 [36]
PD-L1	Serum/plasma	SLE	Levels decreased in responders to immunosuppressive treatment.	Hirahara *et al.*, 2020 [36]
CD163	Urine	LN	Early decline in concentrations in complete and partial responders but not in nonresponders following 12 months of induction therapy. Complete renal response at 12 months: sens.: 87–90%; spec.: 87–89%; PPV: 87–91%; NPV: 84–90%; PLR: 7.0–7.8; NLR: 0.1–0.2	Fava *et al.*, 2021 [53▪]; Mejia-Vilet *et al.*, 2020 [54▪]
Ceruloplasmin	Urine	SLE	Adjusted OR 0.6–0.7 for improvement with rituximab therapy at 12 months.	Davies *et al.*, 2021 [86]
IL-16	Urine	LN	Early decline in concentrations in complete and partial responders but not in nonresponders following 12 months of induction therapy.	Fava *et al.*, 2021 [53▪]
MCP-1	Urine	SLE	Adjusted OR 2.6 and 0.6 for major clinical response to rituximab at 6 and 12 months, respectively.	Davies *et al.*, 2021 [86]
NGAL	Urine	LN	Response after 6 months of induction therapy: sens.: 83%; spec.: 81%; PPV: 56%; NPV: 95%; AUC: 0.78	Liu *et al.*, 2020 [46▪]

Table 3 (*Continued*)

Biomarker	Sample	Study group	Main findings	References
TGF-β1	Urine	LN	Early decline in concentrations in complete and partial responders but not in nonresponders following 12 months of induction therapy.	Fava *et al.*, 2021 [53▪]

AUC, area under the curve; BAFF, B cell activating factor belonging to the tumour necrosis factor ligand superfamily; CD163, cluster of differentiation 163; circRNAs, circular RNAs; cSLEDAI-2K, clinical Systemic Lupus Erythematosus Disease Activity Index 2000; IFNγ, interferon gamma; IL, interleukin; LLDAS, lupus low disease activity state; LN, lupus nephritis; MCP-1, monocyte chemoattractant protein 1; NGAL, Neutrophil gelatinase-associated lipocalin; NLR, negative likelihood ratio; NPV, negative predictive value; OR, odds ratio; PBMCs, peripheral blood mononuclear cells; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PLR, positive likelihood ratio; PPV, positive predictive value; sens., sensitivity; SLE, systemic lupus erythematosus; spec., specificity; SRI-4, SLE responder index 4; TGF-β1, transforming growth factor beta 1.

Table 4. Performance of selected biomarkers of long-term outcome in SLE/LN

Biomarker	Sample	Study group	Main findings	References
Traditional				
AntidsDNA	Serum/plasma	SLE	6.0 and 10.0% risk of renal failure within 10 and 20 years from diagnosis, respectively.	Petri *et al.*, 2021 [91▪]
Low C3	Serum/plasma	SLE	7.0 and 11.0% risk of renal failure within 10 and 20 years from diagnosis, respectively. RR 2.0 (20-year risk).	Petri *et al.*, 2021 [91▪]
Low C4	Serum/plasma	SLE	6.7 and 10.8% risk of renal failure within 10 and 20 years from diagnosis, respectively.	Petri *et al.*, 2021 [91▪]
Emerging				
Axl	Serum/plasma	LN	Good renal outcome (creatinine concentrations ≤88.4 μmol/L) over 10 years: sens.: 42%, spec.: 91%, PPV: 80%, NPV: 65%, AUC: 0.71	Parodis *et al.*, 2019 [83]
ALCAM	Urine	LN	Persistently high levels at month 6 and 12 from a renal flare yielded a HR of 1.2 and 3.6, respectively, for doubling of serum creatinine over 28 months.	Mejia-Vilet *et al.*, 2020 [54▪]
NGAL	Urine	SLE	HR 1.0 for CKD at 54-month follow-up.	Li *et al.*, 2019 [92]
VCAM-1	Urine	SLE	Renal function deterioration over 10 years: sens.: 91%; spec.: 76%; PPV: 29%; NPV: 98%; AUC: 0.77; OR: 23	Parodis *et al.*, 2019 [55▪]

ALCAM, activated leukocyte cell adhesion molecule; antidsDNA, antidouble-stranded DNA; AUC, area under the curve; C3, complement component 3; C4, complement component 4; CKD, chronic kidney disease; HR, hazard ratio; NGAL, Neutrophil gelatinase-associated lipocalin; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RR, rate ratio; sens., sensitivity; SLE, systemic lupus erythematosus; spec., specificity; VCAM-1, vascular cell adhesion molecule 1.

8.4% within 20 years from SLE diagnosis whereas antidsDNA positivity, low C3 or low C4 at one or more assessments increased this risk to 6–7% and 10–11%, respectively [91▪]. Of those, low C3 was the best predictor of renal failure in patients followed for 20 years [91▪]. We recently showed that urine VCAM-1 exhibited a sensitivity of 91% and a specificity of 76% to predict renal function deterioration in patients with SLE within 10 years of follow-up [46▪]. Similarly, in patients with LN, low serum levels of the receptor tyrosine kinase Axl predicted a favourable renal outcome defined as creatinine concentrations ≤88.4 μmol/L, as previously commended [93], over 10 years from the diagnostic kidney biopsy (AUC = 0.71) [83]. Finally, persistently high urinary levels of CD163 at months 6 and 12 from a renal flare yielded a hazard ratio (HR) of 1.2 and 3.6, respectively, for doubling of serum creatinine over a median follow-up of 28 months in patients with LN [54▪].

CONCLUSION

Continuous technological advances have been empowering constantly evolving biomarker research within the field of SLE, which in turn contributes to a better understanding of its pathogenetic mechanisms and optimised diagnostic and prognostic tools. In different study settings, investigators have focused on diagnostic biomarkers, biomarkers reflecting global or organ-specific disease activity, baseline levels or early changes in levels of biomarkers in relation to response to treatment, predictors of flares, or predictors of long-term prognosis. Several recent studies corroborated the role of traditional serum biomarkers used in clinical practice such as antidsDNA and levels of complement components, which remain benchmarks when evaluating emerging biomarkers. Although selected molecules or a set of markers have emerged as promising biomarkers in selected cohorts in cross-sectional or single-centre settings, validations in diverse SLE populations have in general been scarce, necessitating critical appraisal of the literature and further survey specifically designed to develop novel biomarkers, using proper methodology and statistical analysis. The lack of a concerted effort to select the best candidate markers for validation studies in large cohorts of well-characterised patients is further underlined, possibly owing to the limited availability of and/or access to such cohorts. Among recently studied molecules, NGAL has shown promise as a versatile biomarker in SLE, and ALCAM and CD163 have merit in LN.

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Conflicts of interest

J.L. and C.M. declare that they have no conflicts of interest. I.P. has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia Pharmaceuticals, Elli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Novartis and F. Hoffmann-La Roche AG.

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