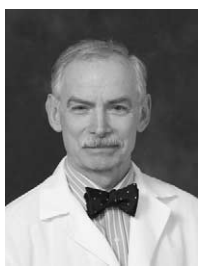
Editorial introduction

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 Editor for this issue.

SECTION EDITOR

W. Joseph McCune



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REVIEW

OPEN

Advances in the clinical use of hydroxychloroquine levels

Katherine Chakrabarti and W. Joseph McCune

Purpose of review
This review summarizes the recent literature exploring hydroxychloroquine levels and their relationship with disease activity and risk of toxicity.

Recent findings
There is no clear correlation between weight-based dosing of hydroxychloroquine and the resulting blood levels of the medication. Recent studies have shown that increased hydroxychloroquine levels are associated with lower lupus disease activity and likely also increased risk of medication toxicity.

Summary
Mounting evidence supports use of hydroxychloroquine levels in clinical practice to document adherence and ensure safety.

Keywords
drug level, hydroxychloroquine, lupus, treatment

INTRODUCTION

Studies correlating hydroxychloroquine levels with control of lupus activity suggest that the association of higher levels with a favorable outcome may be both causal – resulting from benefit of achieving high levels – and that lower levels may indicate noncompliance. Conversely, studies of the association of levels with toxicity take into account levels achieved regardless of compliance. Articles from Petri *et al.* suggest there is no clear correlation between prescribed weight-based dosing of hydroxychloroquine and the resulting blood level in an individual (Fig. 1) emphasizing the potential utility of following blood levels of hydroxychloroquine (HCQ) rather than relying on administrating a calculated dose. This review summarizes new literature published since an earlier review published in this journal in 2018 [1]. The data available to date support the use of hydroxychloroquine levels in clinical practice both to help achieve therapeutic levels and reduce risk of toxicity.

MEASUREMENT OF HYDROXYCHLOROQUINE LEVELS

Hydroxychloroquine levels are measured by liquid chromatography or tandem mass spectrometry in isolation or in combination [2,3]. Levels can be measured in whole blood, serum or plasma, although whole blood is the preferred sample [4,5]. In a study of 26 lupus patients, whole blood had a concentration twice as high as serum or plasma (mean level 813 vs. 436 ng/ml for serum and 362 ng/ml for plasma) [4]. A strong correlation was noted between serum levels of hydroxychloroquine and whole blood levels ($R^2 = 0.82$) but a poor correlation between plasma levels and whole blood levels ($R^2 = 0.46$) suggesting that plasma levels should be avoided [4] as documented in the figure from Carlsson *et al.*, which also corroborates the lack of a correlation between hydroxychloroquine dose and level, further strengthening the role of measuring hydroxychloroquine levels (Fig. 2). In this review, blood levels refer to whole blood levels as the default measure except when otherwise specified.

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KEY POINTS

- There is poor correlation between weight-based dosing of hydroxychloroquine and the resulting blood levels.
- Higher hydroxychloroquine levels are associated with lower lupus disease activity but the utility of upward dose adjustment based on low levels to achieve better disease control is less well established.

APPROPRIATE TIMING OF HYDROXYCHLOROQUINE LEVELS

Because of the long half-life of hydroxychloroquine, it was initially thought that measurement of the level at any point after several months of use was valid. Al-Rawi *et al.* (2018), however, demonstrated that even after 6 months, whole blood levels of hydroxychloroquine measured at seven timepoints over a 12-h period varied for the same patient by 27%. Maximum levels occurred 2–6 h after administration. Knowing the time since the preceding hydroxychloroquine dose is important to properly interpret hydroxychloroquine levels, particularly when values are at the extremes of expected values [6]. Alternating daily doses, for example, alternating 400 mg with 200 mg every other day to achieve a mean daily dose of 300 mg, reduces accuracy of assessment.

MEASURING HYDROXYCHLOROQUINE LEVELS HELPS TO IDENTIFY NONADHERENCE

Nonadherence with hydroxychloroquine is a common problem [5,7–10] of which most rheumatologists are unaware [11▪▪,12▪]. In the US Medicaid

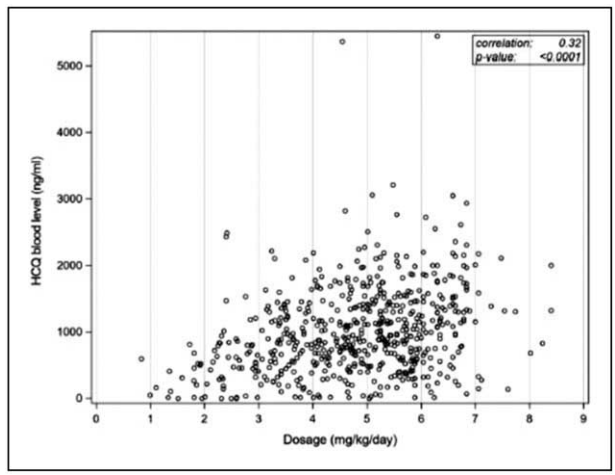

FIGURE 1. There is no strong correlation between a weight-based dose of hydroxychloroquine and the resultant hydroxychloroquine blood level. Reproduced with permission from Petri *et al.* [23▪].

population followed for 1 year after initiation of hydroxychloroquine, 36% of patients were persistently and 47% of were partially nonadherent (hydroxychloroquine use <80% days/month). Adherence declined over the course of a year [7].

Although there is no established threshold level to define nonadherence, less than 200 ng/ml has been most frequently utilized in the literature [5,12▪]. This value is affected by the use of different assays and may not be the appropriate cutoff for all laboratories. Blanchet *et al.* [5] suggested a serum hydroxychloroquine level of 106 ng/ml. Because of individual differences in metabolism, extremely low levels are most reliable indicators of nonadherence. Several studies have found that use of hydroxychloroquine levels to identify nonadherence and

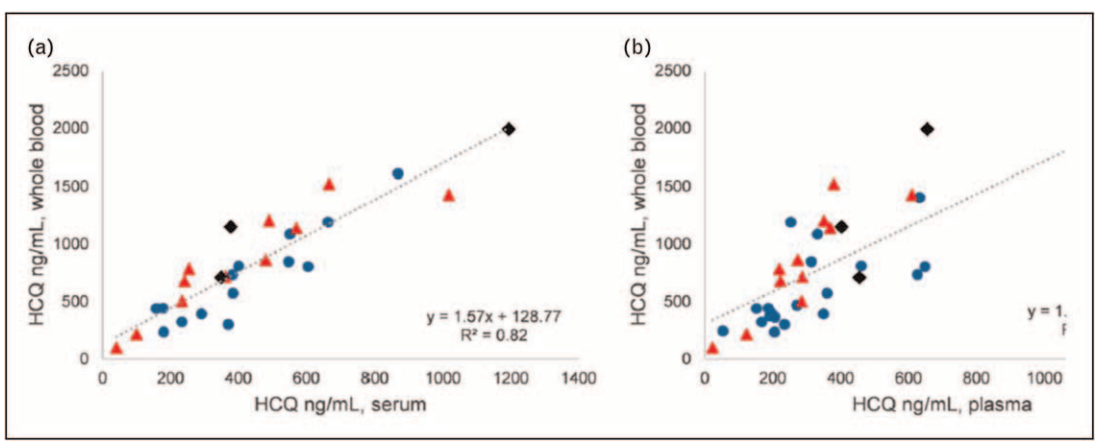

FIGURE 2. A strong correlation exists between hydroxychloroquine serum and whole blood levels while the correlation between plasma and whole blood is weaker and plasma measurements were less reproducible. (a) Graph of HCQ serum vs. HCQ whole blood levels. (b) Graph of HCQ plasma vs. HCQ whole blood levels. Various doses of HCQ are indicated as follows: circle = 1400 mg/week, triangle = 2000 mg/week, diamond 2800 mg/week. Adapted with permission from Carlsson *et al.* [4]. HCQ, hydroxychloroquine.

resulting physician–patient discussions improved patient adherence [12▪,13–15]. Additionally, questionnaires to assess for noncompliance have poorly correlated with blood levels [9]. In one study, 43% of the patients who were nonadherent when detected by drug levels would have qualified as being adherent based on the questionnaire [11▪▪].

WHAT HYDROXYCHLOROQUINE LEVEL DO WE TARGET?

A target therapeutic hydroxychloroquine level is not established in part as there is also no current standardization of hydroxychloroquine levels across various labs. Numerous studies have suggested levels of 500–1000 ng/ml as a therapeutic target [12▪].

In particular, several studies have focused levels needed for the prevention of lupus flares. In the PLUS study, a randomized control trial to evaluate the effects of targeting a hydroxychloroquine level at least 1000 ng/ml on the incidence of systemic lupus erythematosus (SLE) flares, increasing the dose of hydroxychloroquine to achieve levels at least 1000 ng/ml did not decrease the number of SLE flares over 7 months of follow-up. However, adherence increased in the control group and only 39% of the treatment group stayed above the 1000 ng/ml goal threshold [16]. Conversely, in two retrospective observational studies, Cunha *et al.* [17] reported that a hydroxychloroquine level greater than 600 ng/ml was associated with decreased likelihood of renal flares in patients with lupus nephritis, and Pedrosa *et al.* [18] reported that persistently low hydroxychloroquine levels less than 613.5 ng/ml best predicted risk of flares in 82 patients with lupus nephritis.

HYDROXYCHLOROQUINE LEVELS AND DISEASE ACTIVITY

Multiple studies have correlated higher disease activity with lower hydroxychloroquine levels [10,13,14,16–19]. This data is well synthesized in the excellent meta-analysis by Garg *et al.* Hydroxychloroquine levels reported varied widely with no consensus on appropriate level adequate for treatment. Hydroxychloroquine levels of at least 750 ng/ml predicted a 58% lower risk of active lupus [12▪].

Blanchet *et al.* [5] in 2020 reported that whole blood levels were higher in patients with low disease activity (SLEDAI $\leq$4) vs. high disease activity (SLEDAI $>$ 4) (940.8 ± 448 vs. 765.9 ± 426 ng/ml, $P = 0.001$). Geraldino-Paradilla *et al.* (2019) evaluated 108 patients with SLE and found that patients who were nonadherent by their definition (defined as a hydroxychloroquine level $\leq$500 ng/ml) had a higher SLEDAI-2K score compared with those who were adherent (5.7 vs. 3.2) [10]. Iudici *et al.* in 2018 reported that the 5 of 83 lupus patients who flared during a 6 month follow-up period had a lower median hydroxychloroquine level at baseline compared with those who did not experience a flare (284 vs. 435 ng/ml) [20].

Two recent studies of lupus nephritis reported that persistent values above a target hydroxychloroquine level were correlated with lower likelihood of lupus nephritis flare. In the first study of 171 patients with class III, IV, or V lupus nephritis not on renal replacement therapy, no correlation between hydroxychloroquine levels and lupus nephritis flares was identified [17]. In patients with active nephritis at baseline the hydroxychloroquine levels of patients who went into remission were similar to those who continued to have active disease ($P = 0.23$). In patients with partial or complete remission at inclusion, the hydroxychloroquine levels were lower in those who experienced a renal flare during the follow-up period (0.59 vs. 0.81 mg/l, $P = 0.005$). The data suggested that a target hydroxychloroquine level of greater than 600 ng/ml reduces the likelihood of lupus nephritis flares [17]. Pedrosa *et al.* [18] reported that persistently low hydroxychloroquine levels were associated with higher risk of lupus nephritis flares in a study of 82 patients. A hydroxychloroquine level less than 613.5 ng/ml best predicted risk of flare in a study of 82 patients with lupus nephritis [18]. Table 1 summarizes recent study conclusions.

In assessments of dermatologic disease with use of the CLASI, arguably the most objective lupus disease activity measurement, Chasset *et al.* [21] reported that increased HCQ dose and HCQ levels were associated with a statistically significant decrease in both CLASI and RCLASI score (P values <0.001 for both). Frances *et al.* [22] did not report a CLASI score but concluded that hydroxychloroquine levels correlated with cutaneous disease remission in both univariate and multivariate analyses.

SHOULD HYDROXYCHLOROQUINE LEVELS BE UTILIZED TO GUIDE AN INCREASE IN THE DOSE OF MEDICATION?

Aside from identifying patients at risk for toxicities, hydroxychloroquine levels can also be utilized to guide the need for increasing the dose of the medication. A study published in 2016 in *Journal of American Academy of Dermatology* included 34 patients with active cutaneous lupus (defined by CLASI or Revised CLASI score) and hydroxychloroquine level 750 ng/ml or less. The dose of hydroxychloroquine was increased by 200 mg per day and

Table 1. Summary and conclusions of recent studies evaluating hydroxychloroquine levels in SLE patients

Author (year)	Study population	Comparator groups	Conclusion
Blanchet *et al.* (2020)	SLE patients on hydroxychloroquine for ≥6 months without dose modification in ≥2 months	Low disease activity: SLEDAI ≤4 High disease activity: SLEDAI >4	Whole blood levels were higher in patients with low disease activity (940.8 ± 448 vs. 765.9 ± 426 ng/ml, $P = 0.001$)
Geraldino-Paradilla *et al.* (2019)	SLE patients on hydroxychloroquine for ≥6 months who reported medication adherence	Hydroxychloroquine level ≤500 ng/ml vs. hydroxychloroquine level >500 ng/ml	SLEDAI-2K score higher in those who had level ≤500 ng/ml compared with adherent to hydroxychloroquine (5.7 vs. 3.2)
Iudici *et al.* (2018)	SLE patients in remission for >1 year and taking stable dose of hydroxychloroquine	Patients with flare vs. no flare over 6-month period based on SELENA-SLEDAI score	Median baseline hydroxychloroquine level lower in patients who experienced a flare over a 6 month period (284 vs. 435 ng/ml, $P = 0.225$)
Cunha *et al.* (2018)	Biopsy-proven class III, IV or V lupus nephritis on hydroxychloroquine for ≥3 months	Patients with flare vs. patients with no flare	In patients with active nephritis at baseline the hydroxychloroquine levels of those who received remission was similar to those who continued to have active disease. In patients in complete or partial remission at baseline, patients who experienced a renal flare had lower average hydroxychloroquine levels
Pedrosa *et al.* (2020)	Lupus nephritis patients	Patients with flare vs. patients with no flare	Flares were found to be more frequent in patients with hydroxychloroquine level <613.5 ng/ml (28 vs. 5%, $P = 0.023$)

SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

hydroxychloroquine levels were reassessed at 3 months. For those with persistently low levels, the dose was again increased by 200 mg with repeat level in 3 months. It should be noted that doses utilized in the trial exceeded those recommended by recent AAO guidelines with maximum daily dose of 800 mg/day in some study patients. With the increased hydroxychloroquine level, however, the investigators found a statistically significant decrease in both CLASI and RCLASI score (P values <0.001 for both). The hydroxychloroquine levels increased from 638 ng/ml at baseline to 1187 ng/ml [21]. This study supports the notion that an increased hydroxychloroquine level improves disease activity. Although such high doses of hydroxychloroquine are not currently recommended in clinical practice.

RETINOPATHY

Retinopathy is a feared complication of hydroxychloroquine use and the ability to identify patients at high risk for retinopathy is highly sought after by rheumatologists.

In a sentinel article, Petri *et al.* [23▪] in 2020 reported that blood levels of hydroxychloroquine helped predict retinal toxicity and should be used in clinical practice to guide dosing of hydroxychloroquine going forward. The study included 537 patients with SLE, 23 of whom (4.3%) developed retinal toxicity. Retinopathy was more common with higher hydroxychloroquine blood levels and usually occurred in patients treated for a duration greater than 5 years. The authors concluded that hydroxychloroquine levels should guide decreasing the dose of hydroxychloroquine to minimize toxicities [23▪].

Interestingly, an article by Lenfant *et al.* [24▪▪] did not find a similar significant relationship between hydroxychloroquine levels and risk for toxicity. The study included 23 patients on hydroxychloroquine with retinal toxicity and 547 healthy controls on hydroxychloroquine for more than 6 months. The study did, however, identify a relationship between cumulative dose of hydroxychloroquine and longer duration of medication use and risk for retinopathy [25]. The author hypothesized that differences in control populations may have contributed to discordant findings between studies.

OBESITY

In the past decade, guidelines for appropriate dosing of hydroxychloroquine in the setting of obesity

have fluctuated. The 2011 American Academy of Ophthalmology (AAO) Guidelines recommended the maximum dosage of hydroxychloroquine as 6.5 mg/kg/day (maximum dose of 400 mg), but in the setting of obesity, ideal body weight rather that real body weight should be utilized [26]. In 2016, the AAO changed the dosing recommendations to a maximum of 5.0 mg/kg of real body (maximum dose 400 mg daily) without changes in the setting of obesity [27].

Melles *et al.* (2014) concluded that real body weight is a better predictor of retinal toxicity. Their data suggested that with utilization of either 5 mg/kg/day real body weight and 6.5 mg/kg/day ideal body weight, the predicted rate of hydroxychloroquine retinopathy decreased with an increase in BMI [28].

Conversely, in a 2019 study of 537 lupus patients on hydroxychloroquine, Petri *et al.* [23▪] found that a higher BMI was associated with a higher risk of medication toxicity ($P = 0.0160$). Two percentage of patients with BMI less than 20 km/m^2 experienced toxicity from hydroxychloroquine compared with 9.4% of patients with BMI greater than 35 kg/m^2 [23▪]. In a 2021 study of 108 lupus nephritis patients, Pedrosa *et al.* determined that obese patients were prescribed a lower daily dose of hydroxychloroquine based upon real body weight (4.4 vs. 4.9 mg/kg/day) but interestingly, the median hydroxychloroquine blood level was higher in the obese patients (BMI $\geq$30 kg/m^2) ($P = 0.002$). Although they did not collect data on toxicity, the authors hypothesize that obese patients are, therefore, at an increased risk and posit that dosing based on ideal body weight should be considered [29].

This issue was addressed in the 2016 American Academy of Ophthalmology Hydroxychloroquine Guidelines for Short, Obese patients [30]. The authors identified 64 cases of hydroxychloroquine retinopathy in obese patients, 27% of whom had been treated with hydroxychloroquine with well tolerated doses per the 2016 AAO guidelines but still developed toxicity. The authors noted overdosing in women particularly is not uncommon. They recommended use of hydroxychloroquine to maximum of 6.5 mg/kg of ideal body weight rather than the widely utilized 5 mg/kg of real body weight [30]. These conflicting results raise the question: perhaps toxicity could be avoided if the dose utilized satisfied both of the recommendations (i.e. the dose was lower than upper limit recommended in both situations)?

We do not have full understanding of why hydroxychloroquine levels may be higher in obesity. It has been hypothesized that hydroxychloroquine does not deposit in adipose tissue but rather other connective tissues [31,32]. More recent literature, however, has suggested this may not be true although an alternative feasible hypothesis has not been confirmed to our knowledge [26,33].

In conclusion, while consensus on dosing hydroxychloroquine in the setting of obesity does not exist, the presence of obesity should prompt a provider to exercise caution when choosing dose of hydroxychloroquine and consider obtaining a hydroxychloroquine level.

THROMBOSIS

Higher hydroxychloroquine blood levels may convey a protective effect against the risk of thrombosis —a feared complication of SLE. A 2021 study by Petri *et al.* reported a correlation between a lower mean hydroxychloroquine whole blood level and thrombotic events (720 vs. 935 ng/ml, $P = 0.0247$). The study included 739 patients enrolled in the Hopkins Lupus cohort, with an overall incident thrombosis rate of 5.1% (38 patients). Levels found to be protective against thrombosis in their cohort included: a mean whole blood level of at least 1068 ng/ml and a most recent whole blood level of at least 1192 ng/ml [34▪].

A letter to the editor in *Arthritis and Rheumatology* by Kao *et al.* pointed out that although high whole blood levels of hydroxychloroquine may be protective against thrombosis, this increases the risk of retinopathy [35]. Petri *et al.* [23▪] in 2020 reported that by dividing hydroxychloroquine levels into tertiles, most toxicity occurred with blood levels of 1177–3513 ng/ml. If the level required to mitigate risk of thrombosis is 1068 ng/ml, this leaves only a very narrow therapeutic window between treatment and toxicity.

HYDROXYCHLOROQUINE IN PREGNANCY

The guidelines for the treatment of SLE in pregnancy recommend hydroxychloroquine as first-line treatment. It is highly likely that the use of hydroxychloroquine in lupus pregnancies has contributed to lower rates of preterm delivery [36], intra-uterine grown restriction [36,37], preeclampsia [37], and lupus flares [36,38]. Additionally, lupus flares are predicted by hydroxychloroquine discontinuation during pregnancy [39].

In addition to controlling disease activity and decreasing flares, hydroxychloroquine has the potential benefit of decreasing the risk of congenital heart block based on observational data from the PATCH study in which +Ro/SSA mothers with a prior pregnancy complicated by complete heart block were treated with hydroxychloroquine

400 mg daily [40]. Hydroxychloroquine is also recommended for use with any history of obstetric or thrombotic APS to decrease the risk of thrombosis [41].

A recent observational analysis of 50 patients with rheumatic diseases enrolled in the Duke Autoimmunity in Pregnancy registry evaluated the association between hydroxychloroquine levels and premature delivery. Fifty-six percent of the patients included had underlying lupus. Of the patients with SLE, premature deliveries occurred with both hydroxychloroquine levels less than 100 ng/ml and greater than 500 ng/ml although the frequency of premature birth was much greater in the group with the lower hydroxychloroquine level (83 vs. 21%) [42]. In an ACR abstract published around this time by the same research group, the authors hypothesize that hydroxychloroquine levels of 101–500 ng/ml by their assay is ideal. They did also note that hydroxychloroquine levels decline as pregnancy progresses, with a nadir in the third trimester [43]. Given the wide variety of levels reported in the literature, further work is needed to investigate this issue.

Another article from the Duke Autoimmunity in Pregnancy registry data sought to understand the complex physiology of hydroxychloroquine levels during pregnancy including 50% increase in blood volume, increased adipose tissue, and changes in glomerular filtration, which can have marked effects on drug metabolism. The authors concluded that although the volume of distribution of hydroxychloroquine increased with the changes of progression through pregnancy, the total drug exposure did not change when compared with the same group postpartum [44].

CONCLUSION

The use of hydroxychloroquine levels can help to advance our clinical use of a medication that has been the cornerstone of lupus treatment for decades. Although the ultimate therapeutic target for hydroxychloroquine levels remains unclear, we believe that there is utility in routinely obtaining levels on at least one occasion in lupus patients. The results must be interpreted in the context of the local clinical laboratory and therapy adjusted according to the risk for undertreatment or toxicity. Additionally, the identification of nonadherent patients and attempting to improve adherence with counseling and subsequent monitoring of hydroxychloroquine levels can lead to better care of lupus patients.

On the basis of the literature available, we believe that prospectively following hydroxychloroquine levels might help avoid medication toxicity. Toxicity of hydroxychloroquine increases over time and following levels may enable appropriate surveillance and decreasing of medication dose in an effort to avoid long-term toxicity particularly after 5–10 years of exposure.

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Conflicts of interest

There are no conflicts of interest.

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Therapeutic advances in eosinophilic granulomatosis with polyangiitis

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Purpose of review
In recent years, therapeutic advances in eosinophilic granulomatosis with polyangiitis (EGPA) have changed our treatment paradigm. This review will summarize and discuss updates in management of EGPA, with a particular focus on biologic therapies.

Recent findings
The anti-interleukin (IL)-5 agent mepolizumab (the first FDA-approved drug specifically for EGPA) is effective in induction and maintenance of remission particularly in patients with predominantly asthma and allergic manifestations, though efficacy in ANCA-positive, vasculitic disease is unclear; additional anti-IL-5 agents are under study. Rituximab is currently recommended for remission induction in severe disease, particularly in ANCA-positive patients with vasculitic manifestations, though the supportive evidence is mostly observational. Evidence supporting use of traditional DMARDs and other biologic agents such as omalizumab remains limited and observational.

Summary
Although management of this heterogeneous disease remains challenging and unanswered questions remain, advances in biologics (particularly anti-IL-5 agents and an evolving interest in rituximab) have expanded our treatment armamentarium in EGPA.

Keywords
biologics, eosinophilic granulomatosis with polyangiitis, vasculitis

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a small and medium-vessel vasculitis with an estimated prevalence of 18 per million in the United States [1]. EGPA is characterized histologically by eosinophilic infiltration as well as by vasculitis. Its clinical presentation is wide ranging and can present with both vasculitic (e.g. purpura, glomerulonephritis, mononeuritis multiplex) and/or eosinophilic, nonvasculitic manifestations (asthma, rhinosinusitis, peripheral and tissue eosinophilia, cardiomyopathy). Along with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), EGPA is considered an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV); however, EGPA stands apart clinically and therapeutically such that the recently published American College of Rheumatology/Vasculitis Foundation (ACR/VF) Guidelines for the Management of AAV provide separate recommendations for GPA/MPA and EGPA [2▪▪]. ANCA-positivity is present in only about 40% of EGPA patients and is associated with the presence of vasculitic manifestations, while ANCA-negative patients are more likely to present with cardiomyopathy [3].

Like in GPA and MPA, treatment of EGPA follows a two-staged approach with induction of remission followed by a maintenance of remission phase. Patients are stratified by disease severity as measured by the Five Factor Score (FFS) and major organ damage [4]. Historically, gold standard regimens have included cyclophosphamide and glucocorticoids for severe disease [4] and glucocorticoid-monotherapy for nonsevere disease [5]. The role of traditional disease-modifying antirheumatic drugs (DMARDs) such as azathioprine, methotrexate and mycophenolate mofetil has been less clear with limited evidence suggesting a potential benefit

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KEY POINTS

- EGPA is a small and medium-vessel vasculitis with a wide-ranging and heterogeneous clinical spectrum of disease, ranging from primarily eosinophilic/allergic manifestations (asthma, sinonasal disease) to more classic vasculitic manifestations.
- Anti-IL-5 agents such as mepolizumab are an attractive option for induction and maintenance of remission along with glucocorticoids in patients with nonsevere EPGA, particularly those with predominantly asthma and sinonasal disease, though efficacy in vasculitic manifestations and ANCA-positive disease remains unclear.
- Rituximab may be considered for remission induction in severe forms of EGPA, particularly among ANCA-positive patients with predominantly vasculitic manifestations.
- Despite recent therapeutic advances, many patients are unable to achieve remission and require long-term glucocorticoids, particularly due to refractory asthma/allergic disease.

for use in induction of remission in nonsevere disease [5].

Long-term glucocorticoid dependence is unfortunately common in EGPA, largely driven by refractory asthma and allergic disease [6]. With the introduction of biologic agents, the EGPA therapeutic landscape is changing. In 2017, the landmark MIRRA trial led to the antiinterleukin 5 agent mepolizumab (MEPO) becoming the first FDA-approved drug for EGPA [7]. There has also been increasing interest in other biologic agents, including rituximab (RTX) in EGPA. In this review, we will summarize and discuss recent advances in EGPA therapeutics, with a particular focus on biologic therapies.

ANTI-INTERLEUKIN-5 AGENTS

Interleukin 5 (IL-5) is a critical cytokine in the growth, maturity and differentiation of eosinophils, making it an attractive target in EGPA [8]. Several agents targeting IL-5 and its receptor have been investigated for use in EGPA.

Mepolizumab (MEPO), a humanized mAb to the IL-5 alpha subunit, disrupts binding of IL-5 to its receptor (IL-5R). In 2017, after the landmark MIRRA trial, MEPO became the first FDA-approved drug for EGPA [7]. This placebo-controlled, double-blinded trial randomized 136 patients with relapsing or refractory EGPA to receive either (MEPO) 300 mg subcutaneous every 4 weeks or placebo on background standard-of-care therapies (glucocorticoid with or without immunosuppressive therapy). More patients achieved the primary endpoint of at least 24 weeks of accrued remission (defined as a Birmingham Vasculitis Scale of 0 and prednisone dose <5 mg daily) over the 52-week study period with MEPO (28%) than with placebo (3%). In addition, MEPO reduced relapse rates by half and had a significant steroid-sparing effect. Although these findings were exciting, the MIRRA trial only included patient with mild disease, as patients with organ/life-threatening disease were excluded, and ANCA positivity (about 10%) and biopsy-proven vasculitis (<40%) were rare in the cohort, limiting generalizability of results to ANCA-positive patients with vasculitic manifestations. It is also important to note that 47% of patients in the treatment group did not achieve remission at 52 weeks. Some have suggested the remission criteria were too stringent. A subsequent post hoc analysis by the authors showed 'clinical benefit' (as defined by lack of flares, reduction in glucocorticoid, or remission at any time using a more relaxed definition of BVAS 0 and prednisone <7.5 mg/day) was achieved in 87% of patients in MEPO group compared with 53% in placebo group, $P < 0.001$ [9▪]. These findings have led to the ACR/VF guidelines to recommend MEPO + glucocorticoid as first-line therapy for active, nonsevere forms of EGPA [2▪▪]. MEPO might be a particularly appropriate choice for patients with asthma and allergic manifestations, and perhaps those with higher baseline serum eosinophilia [7,10]. However, its use in ANCA-positive, primarily vasculitic disease is undefined.

Several subsequent real-world retrospective studies have also demonstrated efficacy of MEPO [11,12,13▪▪], both at the approved 300 mg monthly dose and reduced dose 100 mg monthly used in eosinophilic asthma [12,13▪▪,14]. A controlled trial comparing both dosages would be welcomed.

Two additional anti-IL-5 agents currently approved for asthma are under study in EGPA. Reslizumab, a mAb directed against the IL-5 alpha chain, showed promising results in reducing glucocorticoid use in an open-label, pilot study of 10 EGPA patients [15▪]. Benralizumab, a mAb directed against IL-5R, demonstrated efficacy in another open-label, pilot study of 10 EGPA patients, with half tapering off glucocorticoid at the end of the study [16▪]. The ongoing MANDARA trial will compare benralizumab to MEPO in relapsing or refractory EGPA, and will be the first RCT in EGPA to compare two biologics head-to-head (ClinicalTrials.gov Identifier: NCT04157348).

RITUXIMAB

Subsequent to its FDA approval for GPA and MPA in 2011, rituximab (RTX), a mAb targeting the CD20 antigen on the surface of B cells, has become a first-line agent for the treatment of AAV for both induction and maintenance; however, patients with EGPA were not included in the pivotal randomized controlled trials leading to the drug's approval [17–19]. Given the potential for B cell involvement in the pathogenesis of the disease, there has been increasing interest in the role of RTX in EGPA. Data from case series and cohort studies have suggested that RTX might have a role in severe, refractory or relapsing EGPA, especially in patients with ANCA-positivity [20–23]. Results from two recent systematic reviews support the conclusions of the observational studies [24▪▪,25▪]. In their analysis of 368 EGPA patients treated with RTX, Menditto *et al.* [24▪▪] demonstrated an 80% remission rate (partial or complete) with a trend towards higher rate of response in the ANCA-positive subset. However, the authors questioned the legitimacy of their results given the prevalence of missing data as well as the heterogeneity in disease classification and outcome definitions amongst the studies included into the systematic review; in fact, only one-third of the patients in their study met ACR criteria for diagnosis of EGPA. Furthermore, ANCA-positivity was used as an inclusion criterion in most of the studies they reviewed, making the results less generalizable to the broader EGPA population. Similar response rates (73% remission or partial response) were found among 63 EGPA patients treated with RTX in the European Collaborative Study, a retrospective review of biologic use in EGPA for refractory and/or relapsing disease [13▪▪]. It was noted that in the large majority of patients, RTX was initiated for vasculitic manifestations and that RTX seemed to have a significant but not complete steroid-sparing effect due to relapses of asthma and ENT flares.

Clouding the picture, data from the REOVAS trial, the only randomized, double-blind, controlled trial of RTX in EGPA (presented in abstract form at the ACR 2021 Convergence meeting) show conflicting results [26▪▪]. Of the 105 participants, 64 with FFS = 0 were randomized to RTX+ GC versus glucocorticoid alone, and 42 with FFS at least 1 were randomized to RTX+ glucocorticoid versus CYC (given at a dose of 600 mg/m^2 every 14 days for three doses followed by a fixed dose of 500 mg every 21 days to complete 6 months) and glucocorticoid. Rituximab was not found to be superior to conventional therapy in either subgroup of disease severity. As had previously been shown in observational studies, in patients with FFS = 0, RTX had no benefit over steroids alone and was not steroid sparing. Surprisingly, subgroup analysis did not show that ANCA-positive patients did better with Rituxan than ANCA-negative patients, which had previously been reported in other studies [20–23]. This study was powered for superiority and not for equivalence, and thus, there may still be a role for RTX in patients with severe disease, particularly those at risk of CYC toxicity.

The aforementioned 2021 ACR/VF guidelines, published prior to the release of the REVOAS data, recommend consideration of RTX for induction of severe new-onset or relapsing EGPA particularly in patients with ANCA-positivity, active glomerulonephritis or those at high risk of CYC toxicity [2▪▪]. In patients with cardiac involvement, CYC is preferred over RTX. The authors based this recommendation on low-quality evidence and expert opinions. Furthermore, they recommend treatment with a traditional DMARD over RTX for remission maintenance in patients who achieved remission after CYC induction due to the lack of data with RTX as maintenance therapy, though this question will be examined in the ongoing MAINRITSEG trial, and we look forward to the results (ClinicalTrials.gov Identifier: NCT03164473). The safety profile of RTX in EGPA has consistently been similar to those from the AAV RCTs with infusion reactions, infections and hypogammaglobulinemia being the most common adverse events [13▪▪,20–23,24▪▪,25▪].

Although it is exciting to have another agent in our armamentarium, in patients with mild disease who have primarily asthma or ENT manifestations, and perhaps also in those who are ANCA negative, the utility of RTX seems limited. More data from prospective studies and RCTs are needed to better define the role of RTX in this disease.

TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Literature exploring the efficacy of traditional DMARDs in EGPA is quite limited. CYC in combination with glucocorticoid is standard-of-care for induction of remission in severe disease [4]; similar to the paradigm for GPA/MPA, once remission is achieved, less toxic DMARDs are used for the maintenance of remission, though their use in this capacity has not been formally studied. For nonsevere disease, induction of remission can usually be achieved with glucocorticoid monotherapy [5], and whether addition of a traditional DMARD provides further benefit beyond glucocorticoid in this setting is unclear. In fact, the 2017 CHUSPAN II trial comparing AZA and glucocorticoid to glucocorticoid alone for remission induction in nonsevere EGPA, MPA and polyarteritis nodosa was negative,

including subgroup analyses according to vasculitis type [27]. Despite paucity of data, MTX, MMF and AZA are still often employed clinically in addition to glucocorticoid in nonsevere disease in both induction and remission phases in the spirit of steroid-sparing, and these traditional DMARDs and glucocorticoid are favoured over glucocorticoid monotherapy in the recent 2021 ACR/VF guidelines [2▪▪]. Two recent small retrospective studies of traditional DMARD use for remission induction in EGPA have shown favourable results [28▪,29▪], including a study of MMF in 15 newly diagnosed EGPA patients in which two-third achieved remission at 6 months with median prednisone dose 7.5 mg/day [29▪]. Larger, controlled trials are certainly needed.

MISCELLANEOUS THERAPIES

Other biologics and immunotherapies are considered for the allergic manifestations of EGPA, though with limited data to their efficacy.

Omalizumab

Omalizumab (OMA) is a humanized mAb targeting the Fc fragment of free circulating IgE, preventing interaction of IgE with receptors on basophils and mast cells thereby blocking the allergic cascade [30▪]. Currently, FDA approved for use in moderate to severe persistent asthma, chronic idiopathic urticaria, and nasal polyps, the limited data on OMA in EGPA suggest a possible steroid-sparing benefit specifically for asthma and sinonasal manifestations [31,32,33▪]. The previously discussed retrospective European collaborative study of biologic use in EGPA included 33 patients who received OMA, namely for glucocorticoid-dependent asthma, and with very low rates of ANCA positivity or vasculitic manifestations [13▪▪]. Frequency of remission or partial response was 15 and 33%, respectively, in patients who received OMA, which underperformed compared with MEPO (78 and 10%). With respect to safety, 15% of patients in OMA group developed vasculitis flare during treatment. Although this is probably attributed to steroid-tapering 'unmasking' underlying EGPA in asthma patients, a paradoxical response to OMA in EGPA causing worsening disease is theoretically possible. These data suggest that, particularly compared with MEPO, OMA has limited efficacy profile in EGPA.

Reflecting the lack of clinical trial data, the 2021 ACR/VF guidelines conditionally recommend adding MEPO over OMA for EGPA patients who experience relapse with asthma and/or sinonasal manifestations, even if serum IgE level is high [2▪▪]. The 2020 French Vasculitis Study Group recommendations consider OMA as maintenance therapy only in patients who fail conventional treatment and MEPO, after multidisciplinary discussion [34▪]. In our experience, since the advent of anti-IL-5 agents in EGPA, we are using OMA less and less for this indication in our patients with EGPA, and only with collaboration with allergy and/or pulmonology.

Dupilumab

Dupilumab is a mAb that binds to the IL-4Rα subunit, inhibiting IL-4 and IL-13 signalling upstream of IL-5 and decreasing IgE production. Its use in EGPA is currently experimental and evidence is limited to case reports describing successful use for refractory asthma in ANCA-negative EGPA [35–37]. However, as eosinophilia has been observed in up to 14% of patients treated with dupilumab in clinical trials (possibly related to reduced chemotaxis of eosinophils into tissues), there are theoretical concerns about its potential to worsen EGPA [37]. For this reason and given the current paucity of data, we do not currently recommend use of dupilumab in EGPA.

Intravenous immunoglobulin

Evidence demonstrating utility of intravenous immunoglobulin (IVIG) in EGPA is mostly limited to case reports and small case series, including successful use in mononeuritis multiplex and cardiomyopathy [38–40]. A recent case series of two patients with EGPA manifesting as mononeuritis multiplex reported successful combination therapy of IVIG with MEPO [41]. Prospective studies are needed to further explore what would likely be a niche use of IVIG in EGPA.

CONCLUSION

Over several years, we have seen impressive advances in the management of EGPA, particularly the introduction of biologics into our treatment paradigm (Table 1). Despite these developments, the management of EGPA remains challenging and there continue to be unmet needs.

MEPO (in combination with glucocorticoid) has emerged as a first-line agent in the treatment of nonsevere disease, and its efficacy and safety profile make it an attractive choice for asthma and allergic manifestations. Optimal dosing and duration of MEPO remain undefined; alternative anti-IL-5 agents benralizumab and reslizumab remain under study and will hopefully further expand the

Table 1. Summary of therapeutic agents in eosinophilic granulomatosis with polyangiitis

	Therapeutic agent	Dosing	Level of evidence in EGPA	Considerations for use
IL-5	Mepolizumab	300 mg SC every 4 weeks	RCT (MIRAA) Retrospective and prospective case series	Consider use in asthma and allergic manifestations ACR/VF guidelines recommend as a first line agent along with steroids for nonsevere forms of EGPA MEPO's benefit in patients with vasculitic manifestations remains unclear
	Benralizumab	30 mg SC every 4 weeks	Open-label pilot study Case reports	Consider as an alternative for MEPO in patients who do not tolerate MEPO or who have failed MEPO due to asthma/allergic symptoms
	Reslizumab	3 mg/kg IV every 4 weeks	Pilot study	Too early to determine its use in EGPA
B-cells	Rituximab	1 g once x 2 doses given 2 weeks apart	RCT (REOVAS) released in abstract form Two systematic reviews Retrospective case series	Consider for induction of remission in severe disease For use in patients with vasculitic manifestations May have increased efficacy in ANCA positive patients No current data on maintenance of disease remission
IgE	Omalizumab	150–600 mg SC every 4 weeks	RCTs in asthma, nasal polyposis, none in EGPA Retrospective systematic review	Approved for asthma Consider for patients with refractory asthma/allergic disease who have failed MEPO Theoretical concern about 'unmasking' EGPA
IL-4	Dupilumab	600 mg SC loading dose followed by 300 mg SC every 2 weeks	Case reports/series	Approved for asthma On the basis of the current paucity of data, and the concerns for potential worsening of EGPA, we do not recommend the use of this agent in EGPA
Ig	IVIG	2 g/kg IV over 2–5 days every 4 weeks	Case reports/series	IVIG has mainly been used with benefits in EGPA patients with neuropathy, and cardiomyopathy

Ig, immunoglobulin; IL, interleukin; SC, subcutaneous.

treatment armamentarium. Anti-IL-5 agents are not, unfortunately, an alternative to steroids in most patients as a substantial proportion remain glucocorticoid-dependent due to refractory asthma. Some have suggested that refractory asthma in EGPA represents airway remodelling rather than active eosinophilic disease [36]; perhaps novel approaches in the asthma world, such as bronchial thermoplasty, could provide insight [42].

In severe disease, there has been some promising observational data on RTX as an alternative to CYC for induction of remission, and the recent ACR/VF guidelines support the consideration of RTX in this scenario, particularly in ANCA-positive patients. However, more recent unpublished data from our only RCT [26▪▪] present conflicting findings on its efficacy over standard-of-care therapy. Although more data are needed to better define the role of RTX in our treatment algorithm, it presents another option for a subset of patients.

This heterogeneous and complex disease demands that the research community continue to think outside of the box with creative approaches to the use of our currently available therapies. Combination therapy with traditional DMARDs and the efficacy of switching between various anti-IL-5 agents has yet to be explored. Interestingly, case reports suggest a role for multitargeted regimens combining anti-IL5 with either B cell depleting agents [43▪,44] or IVIG [41] and this too should be examined in larger studies and RCTs.

Although there remains more to learn, there is no doubt that the recent breakthroughs in EGPA therapeutics have revolutionized treatment in this rare disease.

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Conflicts of interest

There are no conflicts of interest.

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Persistent hand pain despite adequate immunosuppression? The distinct value of occupational therapy in the era of biologics

Deeba Minhas[a], *Patricia Cagnoli*[a], *and Carole Dodge*[b]

Purpose of review
Despite the tremendous advancement in the use of biologics, many patients with inflammatory arthritis do not achieve remission, and the risk of joint damage remains high. A multidimensional approach to treatment is essential. Joint disease in the hands and wrists may prevent patients from performing daily and valued life activities. This review will discuss the role of occupational therapists in inflammatory arthritis, recent updates on joint protection and assistive devices, as well as highlighting adjunctive treatment options for rheumatologists to help patients manage their symptoms.

Recent findings
This article describes the meaningful role of occupational therapy and assistive devices in improving the outcomes for patients with inflammatory arthritis. We describe orthoses, assistive devices and adjunctive therapies utilized in inflammatory arthritis. We provide evidence supporting joint protection and occupational therapy as ways to help with these diseases. A multidisciplinary approach including the entire healthcare provider team, including occupational therapists, is essential to providing individualized treatment focusing on maximizing mobility in each patient's daily routine.

Summary
Although larger studies are needed, assessment by hand-certified occupational therapists for instruction in joint protection techniques, assistive devices and customized orthoses and devices are important adjuncts to pharmacologic management in inflammatory arthritis.

Keywords
assistive devices, inflammatory arthritis, occupational therapy, orthoses

INTRODUCTION

Disease-modifying agents (DMARDs) and biologics have altered the rheumatology landscape and have substantially improved outcomes in patients with inflammatory arthritis; still, a large percentage of patients do not achieve remission or avoid joint damage.

Some patients may not have access to medications either for socioeconomic reasons or lack of access to rheumatologists. In other cases, the medication may just be given too late to be effective.

Many patients need to try more than one agent before they achieve an optimal treatment response. Patients may also not approve the drug of choice specified by the rheumatologist. Many have medication adherence issues, side effects, comorbidities that limit treatment options, or may be trying to stretch their medications.

In a recent systemic review, patients with inflammatory arthritis reported that pain and stiffness were the primary factors leading to functional limitations. Patients felt anxious, frustrated or 'like a failure', especially when they were unable to do their activities of daily living (ADLs) and needed assistance from their children [1▪]. Participants expressed a desire for assistive devices to make ADLs easier in the home, in the workplace and outdoors in order to feel more 'normal' [1▪].

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KEY POINTS

- Despite the prevalent use of biologics in the treatment of inflammatory arthritis, many patients do not achieve remission and/or continue to complain of persistent hand pain.
- Evaluation by hand occupational therapy for instruction in joint protection techniques, assistive devices and customized orthoses and devices are important adjuncts to pharmacologic management in inflammatory arthritis.

Discordance has been reported between physician priorities, focused on clinical examination and validated outcome measures, and patient priorities. A recent multinational survey reported that patients want to set personal, social, functional treatment goals and often feel in their clinic visits that they are unable to adequately express their disease burden and the functional treatment goals critically important to them [2].

A multidisciplinary approach is needed, and occupational therapists play a key role in improving patient outcomes. In addition to conducting a physical assessment, occupational therapists take a detailed psychosocial history focusing on ADLS, what activities are easy, difficult, painful and which patients avoid all together. They incorporate assessment of the patient's occupation, interests and hobbies to assist in navigating how inflammatory arthritis affects their functioning and needs. Their goal is not to limit activities but to teach ways to protect joints and how to pace activities so that individuals can continue to do all the things they need and want to do.

ASSISTIVE DEVICE

In their clinics, occupational therapists have many devices and types of equipment that are designed to limit stress to joints and allow patients to do tasks that they may otherwise be unable to do.

Patients can work with the occupational therapist to try devices that assist the individual patient with the specific task they are having difficulty with, and all of them are easily bought either in the community or using online resources

Using lever arms that extend handles – such as a broad key holder, buttoning and zipping aids, or a sock aid (Fig. 1) – will decrease the torque required for an activity and allow for use of bigger muscles and core stability, rather than the small muscles of the hand [3].

Assistive devices with built-up handles – such as an easy-to-hold utensils (Fig. 1) – and other modifications to avoid tight grasping, for example electric jar openers, medication bottle openers have been designed to decrease effort and dexterity demands [3].

FIGURE 1. Broad key holder, buttoning and zipping aids, easy-to-hold utensils, electric jar opener, medication bottle opener.

ORTHOSES

Orthoses align, position, immobilize, prevent or correct deformity, assist weak muscles or improve function.

RING ORTHOSES

Common deformities in rheumatoid arthritis (RA) include swan neck deformities and boutonniere deformities resulting from persistent synovitis and subluxation or the lateral bands. Systemic lupus erythematosus may present with Jaccoud's arthropathy and Z-type thumb deformities resulting from recurrent synovitis and inflammation. Many patients with inflammatory arthritis may also have extreme ligamentous laxity of the joint capsules from coincident hypermobility-related syndromes, allowing for a tendency for hyperextension at proximal interphalangeal joints (PIPs) that can cause functional deficits and eventually lead to contractures.

Ring orthoses can correct swan neck deformities which are characterized by PIP hyperextension and DIP flexion resulting from MCP or PIP disease, by positioning the PIP in slight flexion thus limiting full PIP joint extension, while allowing for full PIP flexion and full DIP range of motion.

Ring orthoses can also correct instability at MCP, PIP, DIP and realign the joint, while allowing some flexion and extension to avoid limiting motion. The improved biomechanics allow patient to better grasp objects without feeling that the joint is going to give out (Fig. 2).

Silver ring splints (SRS) are a more expensive but popular choice for long-term use, as they are made of high-quality sterling silver, strong, rigid, easy to clean, hypoallergenic and can look like jewellery.

In a study by Van Der Giesen *et al.* [4] in RA patients with mobile swan-neck deformities, SRS and commercial prefabricated thermoplastic orthosis were equally preferred and improved dexterity after four weeks of wear. Zijlstra *et al.* [5] noted that RA patients had similar dexterity results with SRS. They are best applied during the earlier stages of deformity, when correction is still relatively easy and patients with more advanced deformities required larger forces from ring splints to correct them, causing skin damage, pain and paresthesia [5].

WRIST ORTHOSES

The wrist is commonly affected in inflammatory arthritis; wrist instability can weaken grip strength and reduce dexterity.

Studies, including a mixed methods systematic review, found that patients with RA wrist orthoses generally decrease pain [6–8], moderately improve grip [9], have an inconclusive effect on function [10], but in some cases can decrease dexterity [9].

Occupational therapist frequently fabricate rigid thermoplastic resting orthoses to hold the joints in slight anatomical flexion position used at night to rest the joint while the patient sleeps. They can reduce swelling and hand pain and prevent deformity (Fig. 3) [7,11].

Softer type orthotics are recommended for use during the day, because the hand and forearm muscles can fight the rigid splint during activities [12] potentially contributing to more pain. Materials such a neoprene provide support yet allow more range of motion. Studies have found that soft wrist extension splints during certain functional tasks significantly relieve wrist pain and after 1 month and do not compromise dexterity and grip strength. An evidence-informed approach in which occupational therapists use their clinical experience while integrating all available levels of evidence to meet the patients' needs and goals is recommended.

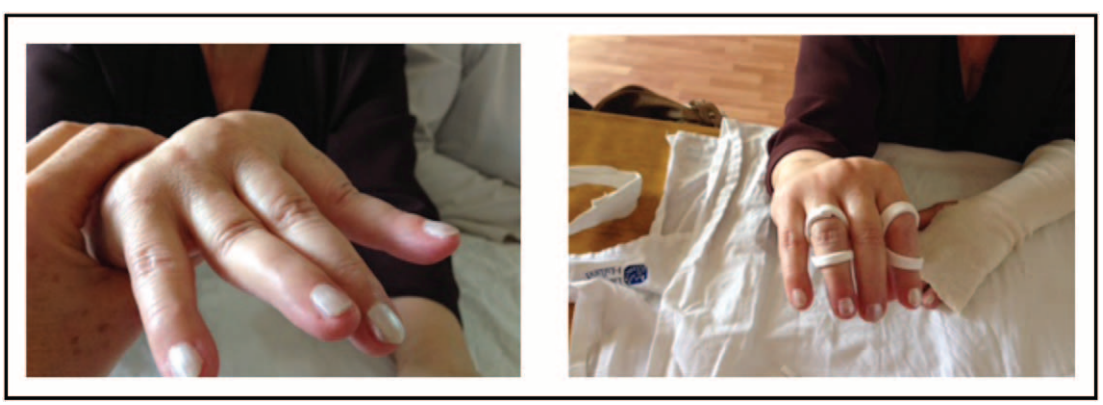

FIGURE 2. MCP subluxation and swan neck deformity, which caused patient's digit to lock when extended. With fabricated orthosis, her PIP joints were placed into a neutral position, so she could extend her digit without locking and could close for normal grasp release, which enhanced her function.

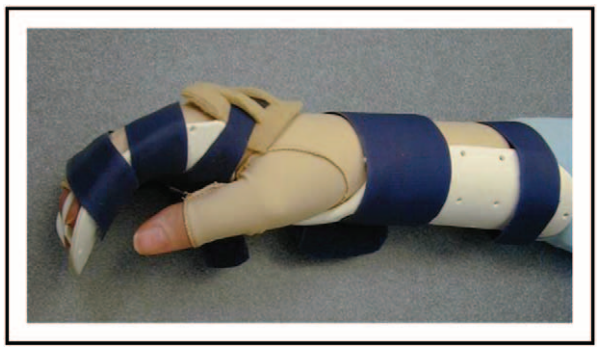

FIGURE 3. Resting hand splint.

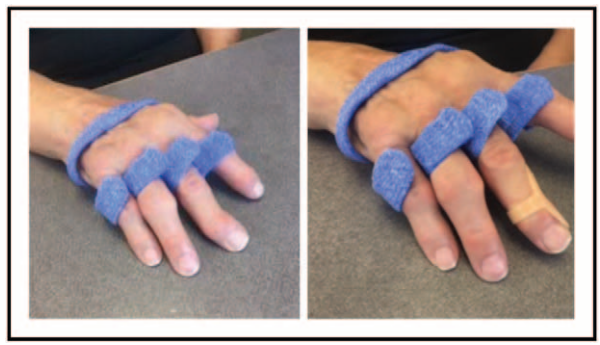

FIGURE 4. Ulnar deviation orthosis.

ULNAR DEVIATION SPLINTS

One of the most common deformities in RA is subluxation of the MCPs and ulnar deviation. This instability has a profound effect on grip and pinch and impairs the ability to open the hand to grasp large objects, leading to difficulty performing ADLs. Figure 4 shows a low temperature fabricated hand based Orficast orthosis, which allows supportive use of the hands during the day. By supporting and positioning the MCP joints, alignment is improved to protect against the stressors that push the joints into ulnar deviation.

Several materials are available; a recent study reported leather ulnar deviation orthosis led to significant improvements in pain reduction, upper limb function and grip strength of all patients after 4 weeks of use without restricting [13▪].

THUMB ORTHOSIS

Thumb spica splints can be fabricated to support the joints of the thumb. They can be forearm-based, supporting the wrist and thumb, or hand-based just supporting the thumb, allowing greater range of motion of the hand (Fig. 5). In addition, softer fabrics such as neoprene will provide less limited in physical activity.

For people with boutonniere-deformity of the thumb secondary to RA, use of a custom-made thermoplastic thumb orthosis during functional activities resulted in a significant reduction in pain compared with no orthosis but did not affect general hand function, grip strength and dexterity. At the end of the study, patients in the orthosis group reported a 75% improvement in hand function with the orthosis [14].

COMPLIANCE

A recent literature review found rates of compliance with orthotic use ranged from 25 to 65% [15▪]. Patients were more likely to use orthoses fabricated to help perform activities regularly (57%) vs. resting immobilization orthoses (17%). Half of the patients cited discomfort as the reason for nonuse [15▪].

If the fit of orthoses is poor, patients are not counselled on the correct method to don and doff them correctly, or what the proper wear schedule is, the orthosis could put more pressure on the joint promoting more pain. Seeing an occupational therapist to ensure the proper fit is essential to improve compliance.

KINESIOTAPING

In the recently published management of osteoarthritis guidelines from the American College of Rheumatology, Kinesiotaping is conditionally

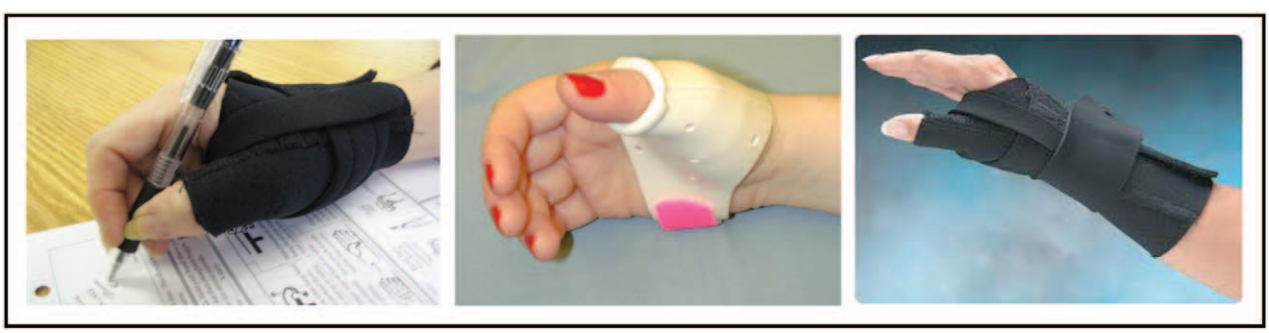

FIGURE 5. Thumb spica splints – neoprene, rigid thermoplastic, forearm based.

recommended for CMC joint osteoarthritis. When used to correct ulnar positioning of the hand in combination with physiotherapy in patients with RA, muscle strength and speed significantly increased ($P < 0.05$) compared with standard physiotherapy group [16]. Kinesiotaping of the MCPs has also been reported to significantly decrease pain ($P = 0.001$) and improve range of motion ($P = 0.001$ bilaterally) [17].

Unlike regular athletic tape or braces, kinesiotape helps to support the muscle and soft tissue by providing light stabilization and additional sensory feedback for neuromuscular retraining. It is less restricting and allows normalization of hand patterns with ADLs. Kinesiology tape could also be used on the ulnar styloid for light support. It should be avoided on fragile or broken skin, which is frequently seen in a patient with inflammatory arthritis on long-term steroids, or those with allergy to tape or adhesive.

Reports of the effectiveness of kinesiology taping in inflammatory arthritis are often anecdotal in nature, and therapists often use their clinical acumen. The utility of hand positioning correction to improve in biomechanical conditions for hand muscle work needs to be assessed in a larger group of patients.

COMPRESSION GLOVES

Compression gloves and heated mitts are commonly used by patients' day or night. Heated mitts can reduce stiffness of the joints effective prior to exercising or utilized to help end of the day pain in the evenings. Compression gloves do not lessen inflammation in inflammatory arthritis, which is related to synovitis, as their function is to provide comfort. This was demonstrated in A-GLOVES, a recent parallel randomized control trial in 206 patients with RA or UIA. Hammond *et al.* [18▪] found that arthritis gloves provide compression and warmth and loose-fitting placebo gloves just provide warmth, and had only slight improvement on hand pain, stiffness and function with no differences between glove types. Due to the lack of efficacy, lack of cost benefit and discomfort, the authors recommended against arthritis gloves in routine clinical practice [18▪].

ON THE HORIZON

Three-dimensional (3D) prototyping is a rapidly emerging technology, allowing the creation of individual cost-effective, 3D objects with almost any material. This has been applied to 3D arthritic joint models localizing and measuring bone loss and erosions [19] and creating orthoses protype [20]. A recent case series found that patients using custom-designed 3D-printed finger orthoses rated the fit as excellent, wore them regularly, planned to continue use and noted less joint stiffness and increased comfort with performing tasks [21]. As these newer technologies increasingly become available, therapists can assist in integrating them into clinical care.

Sensory gloves have also recently been in development that have the capability of remotely monitoring morning stiffness and the assessment of hand function, which could aid diagnostically and clinically so that patients can be assessed when they are the most symptomatic [22]. This may allow earlier detection of inflammatory arthritis even at the preclinical stage, when the disease is more malleable, amenable to treatment preventing joint damage and allowing for a quicker disease remission.

CONCLUSION

At a time when drug development continues to allow more effective control of disease activity and synovitis, many patients continue to have issues with hand pain affecting their ability to perform ADLs and valued life activities.

Assessment by a certified hand occupational therapist is essential to help patients get optimal assistive devices and to determine the daily wear pattern that maximizes benefit taking into consideration the type of orthotic prescribed. Patients with nearly the same functional state may differ tremendously in their need for assistive devices according to their interests and tasks in private and professional life.

Achieving optimal orthotic fit and comfort is important in achieving pain reduction and functional improvement. More rigorous, adequately powered studies examining the different types of assistive devices and orthoses should help to determine the short and long-term effectiveness in treating inflammatory arthritis.

Acknowledgements

Resource for clinicians: Patients can find a local certified hand occupational therapist in their zip code at www.htcc.org.

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None.

Conflicts of interest

There are no conflicts of interest.

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Healthcare disparities in telemedicine for rheumatology care

Lesley E. Jackson and Maria I. Danila

Purpose of review
We summarize the recent literature published in the last 2 years on healthcare disparities observed in the delivery of rheumatology care by telemedicine. We highlight recent research dissecting the underpinnings of healthcare disparities and identify potentially modifiable contributing factors.

Recent findings
The COVID-19 pandemic has had major impacts on care delivery and has led to a pronounced increase in telemedicine use in rheumatology practice. Telemedicine services are disproportionately underutilized by racial/ethnic minority groups and among patients with lower socioeconomic status. Disparities in telemedicine access and use among vulnerable populations threatens to exacerbate existing outcome inequalities affecting people with rheumatic disease.

Summary
Telemedicine has the potential to expand rheumatology services by reaching traditionally underserved communities. However, some areas lack the infrastructure and technology to engage in telemedicine. Addressing health equity and the digital divide may help foster more inclusive telemedicine care.

Keywords
health disparities, rheumatology, telemedicine

INTRODUCTION

Inadequate access to rheumatology care represents a major problem for many patients with autoimmune and inflammatory rheumatic diseases in whom early diagnosis and access to drug therapy are critical to achieving remission [1–4]. Disparities in access to care disproportionally affect rural populations, individuals of lower socioeconomic status, and the uninsured [1,5]. Telehealth is the use of communication and information technology in place of traditional in-person healthcare delivery models and may include applications involving video or telephone visits (i.e. telemedicine) [6]. Telemedicine was rapidly adopted as a potential solution to provide care to rheumatology patients in the setting of the coronavirus disease 2019 (COVID-19) pandemic [7▪,8,9▪▪], and several models have been suggested to address access, health equity, and quality of care barriers [10,11]. Within rheumatology, telemedicine provides an opportunity to address several barriers to adequate care including workforce shortages [12], reaching patients in rural or medically underserved areas [13] or those reluctant to present for in-person care because of the risks of contracting COVID-19 [14].

Despite its potential for expanding rheumatology services, use of telemedicine may inadvertently exacerbate existing disparities in care through the 'digital divide' [15–17]. This refers to disparities in access and utilization of telemedicine related to social, language, financial, and other barriers among diverse communities by race/ethnicity and socioeconomic characteristics [15,18▪]. A major contributing factor to disparities in care delivery by telemedicine relate to inequities in access to virtual visits (e.g. broadband internet, adequate technology) and variable digital literacy [7▪,19,20].

Given the sudden but persistent changes in the healthcare environment since the onset of the COVID-19 pandemic [21,22] in conjunction with the racial and ethnic disparities observed related to

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KEY POINTS

- Telemedicine has the potential to expand rheumatology services by reaching underserved or vulnerable populations.
- Key strategies include facilitator-assisted telemedicine programs, care support teams to assist with technology set up, and integration of electronic patient-reported outcomes for telemedicine visits.
- Further research is needed to determine the best mechanism to integrate telemedicine into rheumatology care with particular consideration in addressing health equity.

COVID-19 morbidity and mortality [23–25], it is crucial to understand the contribution of telemedicine in augmenting or mitigating health disparities. We reviewed the recent literature on telemedicine focusing on health disparities in rheumatology care delivery and outline innovative approaches which may promote equity in virtual rheumatology care.

TELEMEDICINE HIGHLIGHTS HEALTH INEQUITIES DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

Health disparities contribute to the widening gap in care for some vulnerable populations at highest risk of adverse outcomes because of their rheumatologic disease. Among rheumatic disease patients, there is higher morbidity and mortality rates in racial/ ethnic minorities and individuals of lower socioeconomic status [26–28]. Importantly, social determinants of health affect quality of care and access that ultimately define health outcomes in this population [29,30]. This finding is of particular concern as appropriate monitoring and reliable use of immune suppressive medications for systemic lupus erythematosus (SLE) can reduce risk of end-stage renal disease and premature coronary artery disease [4,31,32]. Among patients with rheumatoid arthritis (RA), early diagnosis and access to disease-modifying antirheumatic drugs (DMARDs) can dramatically change the course of the disease [33] but high costs of highly effective therapies (e.g. biologies, targeted synthetic DMARDs) disadvantages vulnerable populations with inadequate health insurance coverage [34,35]. As a result of disparate access to timely care and appropriate medications, vulnerable populations may be at higher risk of delayed diagnosis, inconsistent monitoring, and consequently worse outcomes [2,29].

Throughout the COVID-19 era, telemedicine has been an important part of rheumatology practice but disparities in access to care have persisted for certain vulnerable groups [7▪,20,36]. Furthermore, lower telemedicine use in vulnerable populations have threatened to intensify prevailing disparities in the care of people with rheumatic disease [7▪]. Telemedicine services have been disproportionately underutilized by racial/ethnic minorities, patients with lower socioeconomic status, and older patients [7▪,20,36,37].

Nonmodifiable factors such as generational trends involving limited access and familiarity with technology among older individuals represent a major challenge to implementation efforts in this group [38▪,39]. Differences in digital literacy, a modifiable factor, may leave some patients without the ability to attend video visits [38▪,39]. Technical challenges include discrepancies in access to broadband or cellular network access in rural areas [36]. In addition, many new telemedicine applications require costly smartphone devices and monthly data plans, which may present financial difficulties. Identifying modifiable factors that contribute to disparities in telemedicine use will allow the development of strategies to overcome challenges in care delivery and improve outcomes for all patients with rheumatic diseases.

Disparities in use of telemedicine have been observed in a few recent studies of people with rheumatic disease. A large, multistate, community rheumatology practice found that older age, lower socioeconomic status, and rural residence were associated with lower use of telemedicine [7▪]. Additionally, cancellations for outpatient follow-up visits occurred more often in people who were older, of black race or Hispanic, of lower socioeconomic status, and living in rural areas [7▪]. These factors were also associated with a lower likelihood of engaging in telemedicine compared with in-person clinic visits [7▪].

Age was found to be the largest contributing factor in ability and willingness to use telemedicine services in a cross-sectional study of United States rheumatology patients [38▪]. A recent study found that older patients were less likely to feel that a visit could have been possible via phone call or video conferencing, that their needs could have been met with telemedicine, and that telemedicine was an appropriate alternative mode of healthcare delivery [38▪]. In addition, younger patients were more likely to have access to front-facing camera, telephone, and stable internet connection [38▪]. An observational study in the United Kingdom found that access to video calls decreased with increasing age and less than half of people older than 65 years had the ability to conduct video telemedicine calls [39]. In addition, older individuals were more likely to

report dissatisfaction with telephone telemedicine visits, while reporting a preference for telephone vs. video contact and face-to-face appointments vs. telemedicine [39].

In response to the COVID-19 pandemic, the Centers for Medicare and Medicaid Services offered temporary payment parity for video and telephone visits. For many rheumatology practices, telephone visits were instrumental in maintaining access to healthcare services during the pandemic [9▪▪,38▪,39,40▪]. In particular, patients who resided further away from their rheumatologist office were more willing to utilize telephone consultations over in-person visits [38▪]. The uncertain future of telephone-only visits in lieu of video-based methods may disadvantage some patients that are only able or willing to participate in telephone calls.

Disruptions in the care of rheumatic disease patients because of the COVID-19 pandemic were partially offset by the growth in telemedicine use; however, widespread uptake may be exacerbating health disparities. There is an urgent need to address telemedicine implementation challenges across a range of barriers including socioeconomic status, race/ethnicity, age, sex, geographic regions, and digital literacy.

TELEMEDICINE AND TELEHEALTH STRATEGIES TO IMPROVE CARE DELIVERY FOR VULNERABLE PATIENTS WITH RHEUMATIC DISEASES

Advancing telemedicine or telehealth programs without addressing existing disparities in access and infrastructure may exacerbate the 'digital divide'. Here we present several strategies to improving virtual care delivery for vulnerable patients (Table 1).

Facilitator-assisted telemedicine programs

The disparate access to rheumatology care in rural or underserved areas may be mitigated by utilizing local facilitators for telemedicine visits. Some patients participate in telemedicine videoconferencing by visiting a local clinic with the support of a facilitator (e.g. nurse, physical therapist, or general practitioner) who assists with an in-person physical examination, blood draws, or imaging [41▪,42▪▪,43▪].

An international study described remote care in which a United States-based rheumatologist saw more than 4800 patients remotely in Iran. They were aided by a general physician and a nurse at a local charity hospital [42▪▪]. In another application, a nurse-led, rheumatologist-assisted telemedicine intervention effectively addressed suboptimal management of urate-lowering therapy in gout patients. Patients underwent an initial in-person evaluation by a rheumatologist, and subsequently had virtual visits with nurses who performed patient education, monitored for adverse events, and directed of urate-lowering drug escalation. Partnerships with local primary healthcare providers enabled laboratory testing [43▪]. Such studies herald the way for virtual clinics with primary care or nurse-assisted remote care in areas without easily available rheumatology subspecialty care.

Care support team to assist with setting up and troubleshooting issues with telemedicine visits

Elderly patients in particular may struggle with smartphone technologies often necessary to engage in telemedicine visits. Care support teams may provide personalized and targeted assistance for patients with lower digital literacy [41▪,44▪]. This approach may address lack of access or technological knowledge in use of a smartphone, tablet, or computer.

At the onset of the COVID-19 pandemic, the Hospital for Special Surgery rapidly implemented telemedicine visits for rheumatology patients [41▪]. A communication technology team assisted patients with downloading the Zoom application and logging on before their scheduled visit. This support allowed rheumatologists to efficiently deliver care to patients when telemedicine use increased drastically during the pandemic [41▪].

Some patients rely on family or friends for access to smartphone devices necessary to participate in a virtual rheumatology visit [44▪]. In a study of teleconsultation services in which participants often enlisted relatives or friends for assistance with the videoconferencing procedure, three-quarters of respondents reported they would have otherwise stopped their medications or self-medicated without the service [44▪]. This highlights the importance of access to telemedicine care enabled by technical assistance.

Integration of electronic patient-reported outcomes for telemedicine visits

Patient-reported outcomes (PROs) are useful to track symptoms and assess disease activity, which are necessary components in the ongoing management of many rheumatic diseases [45▪]. Although standard care involves collection of PRO data points only during in-person visits, emerging digital telehealth technologies could enable patient-reported outcome collection between visits or during telemedicine visits [40▪]. PROs contribute to the

Table 1. Potential innovative solutions to reduce disparity in access and utilization of telemedicine

Focus	Related studies	Intervention	Potential impact on health disparities	Limitations
Facilitator-assisted telemedicine programs	Rezaian *et al.* [42▪▪] Phang *et al.* [43▪]	Nurses, physical therapists, general practitioners who facilitate virtual evaluation by a rheumatology specialist	Remote care may improve access to rheumatology services in rural/ underserved areas without access to local subspecialty care	Relies on a local support network for on-site facilitation Dependent on access to technology devices and high-speed broadband internet
Care support teams	Gkrouzman *et al.* [41▪] Shenoy *et al.* [44▪]	Assist with setting up and troubleshooting issues with telemedicine visits	Simple mechanism that may enable access to telemedicine services for patients with low digital literacy	Relies on presence of a technical support team Relies on access to a smartphone or other devices
Integration of electronic patient-reported outcomes	Nowell *et al.* [45▪] Chevallard *et al.* [40▪] Subash *et al.* [46▪] Glintborg *et al.* [47▪] Colis *et al.* [48▪] Richter *et al.* [49▪]	Track patient-reported outcomes and assess disease activity between in-person visits	Optimizes treat-to-target strategies Potential to engage vulnerable older adults in self-care	Reliant on individual health-literacy Dependent on access to a smartphone and broadband internet
eConsults	Patel *et al.* [50▪] Keely *et al.* [51▪]	Provider to provider electronic asynchronous communication	Reduces the need for in-person specialist evaluation Decreases wait times for in-person specialist visits Provides support for patients pending in-person consultation Addresses rheumatology workforce shortage	Increases workload for the provider requesting the eConsult Lack of insurance reimbursement
Telemedicine osteoporosis management program	Palcu *et al.* [56▪▪]	Telemedicine delivery of specialist osteoporosis care to improve access for underserved populations	Improves access to specialty bone health services for rural patients	Substantial proportion require bone mineral density measurement to complete the clinical assessment
Remote Fracture Liaison Service	English *et al.* [58▪▪]	Virtual clinic for people with low trauma fragility fracture to receive evaluation and management for osteoporosis	Ability to recommend pharmacotherapy and provide counseling for fracture risk reduction Addresses gaps in delivery of secondary fracture prevention, especially among vulnerable populations	Substantial proportion require bone mineral density measurement to complete the clinical assessment
Virtual or remote telementoring for osteoporosis management	Lewiecki *et al.* [60▪] Lewiecki *et al.* [59]	Learning model for primary care providers to develop skills to care for specialty patients through virtual specialist-to-provider connections	Enables rural and underserved patients to receive osteoporosis management by their primary care provider Greater convenience and lower cost than referral to a specialist	Relies on primary care provider and specialist continued engagement in videoconference activities
Appropriateness of telemedicine follow-up	Subash *et al.* [46▪] Piga *et al.* [61▪] Kavadichanda *et al.* [62▪]	Risk stratifies patients for in-person vs. telemedicine follow-up	May help predict a subset of patients who can safely be seen virtually, decreasing the burden on the patient	May not be suitable for all rheumatic diseases (e.g. systemic lupus erythematosus) or for those patients not in low disease activity

recommended treat-to-target approach in managing diseases like RA, which has been shown to improve outcomes. Regrettably, efforts to adhere to treat-to-target strategy have been especially hampered because of reduction of in-person evaluations in the setting of the COVID-19 pandemic [46▪,47▪].

The RISE LC (Rheumatology Informatics System for Effectiveness Learning Collaborative) shared best practices in PRO collection and use [46▪]. During the COVID-19 pandemic, the RISE LC began to adapt PRO tools for collection via telemedicine [46▪]. Participant rheumatologists reported difficulties in collecting the RAPID3 during telemedicine visits due of barriers surrounding patient access to a portal necessary for electronic administration of survey questions, lack of sufficient staff capable of deploying questions verbally, or language and health literacy barriers. In response to these challenges, the RISE LC developed a brief PRO survey tool that combined items for pain, physical function, and fatigue from the Multidimensional Health Assessment Questionnaire, which was deployed by physicians during a telemedicine visit. The initial piloting supported feasibility and acceptability by rheumatologists for use during a telephone or video visit [46▪].

A mobile application that digitally transmitted PROs daily in patients with RA demonstrated excellent adherence and better disease control most notably among older patients aged at least 65 years [48▪]. Such applications enable collection of PRO data between visits and may support assessment during telemedicine visits, thus potentially representing a viable option to engaging older patients in self-care. Another mobile application, which collected PRO measures in patients with RA reported very high adherence, retention after 3 months of use, and satisfaction with the patient-physician interaction [49▪].

Adoption or expansion of eConsult services

eConsult services are an asynchronous web or electronic health record-based system consultation in which a referring provider can securely share health information with a subspecialist who can offer clinical advice without directly seeing the patient [50▪]. These programs hold the potential to provide more timely rheumatology consultative services for underserved rural patients [50▪,51▪]. eConsult services may allow primary care providers to solicit advice or answers to questions as an alternative to a face-to-face specialist referral, which avoids prolonged wait time, or provide basic recommendations to support patients awaiting in-person evaluation [50▪,51▪,52].

For example, asynchronous secure eConsults have been utilized effectively to address questions about abnormal serologies (e.g. positive ANA) in the absence of systemic symptoms without significant increase in the utilization of laboratory testing and imaging studies [50▪,51▪] and use of eConsults was associated with decreased wait times for in-person visits [50▪]. In a descriptive study, rheumatologists agreed that eConsults have the potential to address specific questions (e.g. drug-related questions, or questions about diagnosis, management, or procedures) that otherwise would become routine consultations [51▪].

In addition, eConsults could potentially mitigate the rheumatology provider workforce shortage in rural areas. An expanding patient base relative to a shrinking rheumatology workforce may exacerbate existing inequities in access for rural patients. The 2015 American College of Rheumatology (ACR) Workforce Study projected that by 2030 adult rheumatology providers will decline by 25%, which will result in demand exceeding the supply of providers by 102% [12]. The imbalance of supply and demand is anticipated to be greater in rural areas [12,53]. eConsults could be useful in connecting rural patients with rheumatology provider recommendations, particularly for patients in whom long travel distance is a key barrier to accessing care [52].

Innovative virtual strategies for improving delivery of bone health services

Significant disparities in the availability and quality of medical care have been described for rural patients with osteoporosis, and many patients with associated fragility fractures are not treated for underlying osteoporosis [54,55]. Telemedicine may improve delivery of bone health services for underserved populations by coordinating laboratory and bone mineral density assessment, providing osteoporosis education and adherence follow-up via telemedicine. A mixed methods study of a multidisciplinary telemedicine osteoporosis management program determined that patients residing in underserved or remote areas were comfortable with virtual osteoporosis care, and furthermore, felt that virtual and in-person osteoporosis care were comparable [56▪▪].

In addition, a remote or virtual fracture liaison service (FLS) offers a solution to address key gaps in the delivery of secondary fracture prevention for vulnerable populations [57]. One such service introduced a virtual FLS telephone clinic as an alternative to an in-person visit [58▪▪]. Patients with a low trauma fracture were identified and underwent fracture risk assessment and counseling on behaviors supporting bone health by phone. Patient satisfaction with the virtual fracture liaison service was very high [58▪▪].

Virtual or remote telementoring represents another unique mechanism designed to create knowledge networks and empower primary care providers to develop and provide skilled care for patients with osteoporosis in underserved communities [59]. Bone Health TeleECHO convenes a weekly multidisciplinary videoconference with the goal to address existing gaps in care for best practices in bone health [60▪]. This strategy may enable rural and underserved patients to receive osteoporosis management by their primary care provider with greater convenience and lower cost than referral to a specialist.

Development of prediction models to stratify patients for in-person vs. telemedicine follow-up care

There has been concern that not all patients may be suitable for telemedicine visits and best practices to determine appropriateness for virtual vs. in-person follow-up are not yet available but prediction models may help fill this knowledge gap. Members of the RISE LC endorsed the utility of a brief survey tool deployed during telemedicine visits as a triage instrument to determine who would require an in-person visit as their next encounter [46▪]. Patient-reported data may be useful to predict appropriateness of visit types in the future. A recent study of patients with inflammatory rheumatic diseases evaluated the reliability of virtual video-assisted follow-up visits in identifying the need for treatment adjustment because of inadequate disease control [61▪]. Virtual video consultations demonstrated high sensitivity and specificity compared with in-person visits in identifying the need for changes in treatment, with the highest discordance between visit types in patients with SLE. Collectively, these data suggest that underlying diagnosis and disease activity are important to consider when risk-stratifying patients for telemedicine or in-person follow-up care [61▪].

Another study evaluated the feasibility of instituting teleconsultation for rheumatology care among the socioeconomically marginalized segments in India. The authors built a model to predict whether a subset of patients might be transitioned to telemedicine. Results suggested that patients in remission or low disease activity taking a stable dose of DMARDs could benefit from transitioning to telemedicine [62▪].

CONCLUSION

Worsening disparities in delivery of medical care to vulnerable populations may be an unintended consequence of the large-scale deployment of telemedicine in rheumatology prompted by the COVID-19 pandemic. We found in the recent literature several examples where the benefits of telemedicine did not fully reach the populations with the greatest opportunity to benefit.

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There are no conflicts of interest.

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The safety of glucocorticoids in the treatment of inflammatory rheumatic disease: new evidence

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Purpose of review
Glucocorticoids justifiably remain a cornerstone in the treatment of many inflammatory rheumatic diseases but many are opposed to their use because of the side effects, most of them known to be dose-dependent. Most concerns regarding glucocorticoids stem from observational studies which are affected by several forms of bias, mainly confounding by indication, that may result in overestimation of harm. Solid evidence regarding the safety of low-dose glucocorticoids remains remarkably scarce.

Recent findings
Several observational studies showed heterogeneous results and two 6-month trials showed no increase of harm. The GLORIA trial of 5 mg/day prednisolone vs. placebo in patients aged 65+ is the first randomized control trial with glucocorticoids safety as coprimary outcome. The benefits of glucocorticoids in terms of symptoms and structural damage were confirmed, but the proportion of patients with at least one adverse event of special interest (serious or glucocorticoids-related) was increased by 24%, mostly due to nonsevere infections.

Summary
Based on current evidence the benefit–risk balance of low-dose glucocorticoids in rheumatoid arthritis, and probably in other rheumatic diseases is generally favourable. Physicians should be aware of the risks and mitigate them, but avoid the negative effects of unfounded fear.

Keywords
glucocorticoids, risk, safety, toxicity

INTRODUCTION

More than 70 years after the initiation of their regular use, one would expect to know everything there is to know about glucocorticoids. However, while their efficacy in many inflammatory rheumatic diseases is well established, controversy remains regarding their safety and most adequate positioning in treatment strategies. Most glucocorticoids-related adverse events are dose and time-dependent raising the questions of how much is too much, how long is too long, and what is just right. Experts have defined a maximum of 7.5 mg/day prednisolone-equivalent (PDN-eq) as cut-off to define low-dose glucocorticoids, and maintenance therapy for most inflammatory rheumatic diseases is at or below this cut-off [1]. This review focuses on low-dose glucocorticoids in rheumatoid arthritis (RA). We will use two previous comprehensive reviews by our group, published in 2014 and 2019 [2,3▪], as a starting point to our literature search. Glucocorticoids safety in other inflammatory rheumatic diseases and of higher doses will be briefly covered at the end.

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KEY POINTS

- Glucocorticoids justifiably remain a cornerstone in the treatment of rheumatoid arthritis with proven efficacy in symptom relief, control of disease activity and damage prevention.
- There has been a lack of evidence, both in quantity and quality, to support firm conclusions on the safety of low-dose glucocorticoids, which is partially overcome by the GLORIA trial.
- Based on current evidence there is no good justification to quickly taper and withdraw low-dose glucocorticoids.
- Observational studies on glucocorticoids-related adverse event remain popular and are produced at an ever-increasing rate. Nevertheless, the occurrence rates from these reports are severely biased upwards due to confounding by indication, making them unfit for policy decisions.
- The most commonly reported glucocorticoids-related adverse events in association with low-dose glucocorticoids are infection risk and fragility fractures but they are usually nonsevere, provided that appropriate (personalized) assessment prophylaxis and treatment is applied, and adherence is monitored.

GLUCOCORTICOIDS: THE FALL (AND REVIVAL) OF A HERO

Glucocorticoids are one of the oldest pharmacological therapies used in rheumatology and remain one of the most commonly and widely used today [4]. In RA, the vast majority of patients receives glucocorticoids at some point in their life, and about 30% of patients are on glucocorticoids at any given time [5,6].

Before the advent of disease-modifying antirheumatic drugs (DMARDs) and biological and targeted synthetic disease-modifying therapies, glucocorticoids were the cornerstone and often only therapy available for most inflammatory rheumatic diseases. With over seven decades of accumulated experience there is irrefutable evidence of efficacy [7,8] but also documentation of an extensive panoply of adverse events. The concern for adverse events has heavily tarnished the image of the glucocorticoids and established glucocorticoids-free treatment as a major therapeutic target [9,10]. Many medications actually gained momentum on the basis of their putative glucocorticoids-sparing properties, more than on their intrinsic efficacy and safety. The first of these were of course the nonsteroidal anti-inflammatory drugs.

In previous reviews, we have argued that many fears of toxicity with low-dose glucocorticoids were exaggerated and derived from poor-quality observational studies and that most occurred at higher dosages including indications outside of rheumatology. A recent survey within the GLORIA project queried 1221 RA patients and 414 rheumatologists and showed broad satisfaction with the efficacy of low-dose glucocorticoids, but also concerns regarding the frequency of adverse events that were way above what is justified even by the low-quality available evidence [11]. Such fears obviously compromise optimal use of glucocorticoids. Despite their longstanding use, high-quality evidence on the actual toxicity of low-dose glucocorticoids remains scarce. However, this is finally starting to change.

LOW-DOSE GLUCOCORTICOIDS IN RHEUMATOID ARTHRITIS: WHERE DO WE STAND?

In our previous comprehensive reviews, we found that low-dose glucocorticoids therapy carries a trend towards higher rates of cardiovascular events, infections, diabetes and overall mortality in observational studies while showing a safety profile similar to placebo in most randomized control trials (RCTs) [2,3▪]. Since then, three RCTs and eight observational studies have been published or presented (Table 1). None of the RCT showed any suggestions of higher toxicity with low-dose, but exposure was only 6 months and not all endpoints were comprehensively assessed. The observational studies, in alignment with previous similar studies tend to show a dose-dependent and time-dependent increase in a variety of adverse events, with emphasis on infections and fragility fractures.

Observational studies, the overwhelming majority of publications, carry a high risk of bias, especially through confounding by indication (also known as channeling bias, where more severe patients have a higher risk of adverse events, but also a higher risk of exposure to glucocorticoids). This can lead to a strong overestimation of the rates of glucocorticoids-related adverse events. Especially in the case of glucocorticoids, with their extremely negative reputation, this bias cannot be corrected by multivariable regression or propensity score modelling [12]. Consequently, the high toxicity profile reported had not been corroborated by RCTs. However, these are only few, and they are of limited size and duration, focus more on benefit than harm and may not fully represent the routine clinic population.

The pragmatic GLORIA trial was designed to overcome these limitations and provide the best possible quality of evidence in this field. It is now completed, and its results are available in abstract:

Table 1. Adverse events in randomized control trials and observational studies on low-dose glucocorticoids in rheumatoid arthritis included in this review

Author, year	N	Population	Outcomes (P/S)	GC doses	Treatment duration	Follow-up	Results[a]			
							Outcome	GC	Non-GC	P
Randomized controlled trials										
Hua, 2020 [4]	80	Early RA (treatment-naive)	GC-related AE (S)	(1) GC (10 mg/day for 3 months followed by 5 mg/day for 3 more months) + MTX + HCQ (2) Placebo + MTX + HCQ	6 Months	1 Year	Gastrointestinal Liver dysfunction Upper respiratory tract infection: nonsevere/severe Fracture Hypertension Hyperglycaemia	5 (12) 4 (10) 2 (5)/0 0 0 0	3 (8) 4 (10) 3 (8)/0 0 0 0	ns ns ns ns ns ns
Burmester, 2020 [16▪▪]	259	RA (stable low disease activity)	GC-related AE (S)	(1) GC 5 mg/day for 24 weeks + TCZ (2) GC 5 mg/day tapered at week 16 + TCZ	24 Weeks	24 Weeks	No statistically significant difference between groups			
Boers, 2021 [13▪▪]	451	≥65 years-old RA (active disease)	Patients with ≥1 serious or GC-related AE (P)	(1) No GC (2) GC 5 mg/day	2 Years	2 Years	≥1 Serious or GC-related AE (%) Infections (mostly nonsevere) accounted for the largest contrast between groups. Numbers not reported	60	49	0.02
Observational studies										
Ince-Askan, 2019 [30]	117	Children born to women with RA	Altered cortisol concentration, body composition and blood pressure (P)	(1) No GC during pregnancy (2) GC ≥ 5 mg/day (mean dose 7.5 mg/day)	≥6 Months	NS	No association found between low-dose antenatal GC exposure and long-term elevated cortisol and cortisone concentrations, an altered body composition or higher blood pressure in prepubertal childhood			
George, 2020 [24]	230320	RA	Hospitalized infectious events (P)	(1) No GC (2) GC ≤ 5 mg/day (3) GC 5–10 mg/day (4) GC > 10mg/day	≥3 Months	1 Year	Hospitalized infectious events [adjusted HR (95% CI)]	GC ≤5 mg 1.54 (1.49, 1.59)	GC 5–10 mg 2.31 (2.22, 2.42)	GC > 10 mg 3.34 (3.11, 3.58)
Nowak, 2021 [27]	150	Inflammatory rheumatic disease	GC-induced glucose intolerance (P)	GC ≤ 7.5 mg/day	81.2 (19.2–160.1) months	NS	GC daily dose ($P=0.82$) and cumulative dose ($P=0.66$) were not predictors of GC-induced glucose intolerance			
Kim, 2021 [20]	933	RA	Annual ΔBMD (P)	(1) No GC (2) GC ≤ 7.5 mg/day	≥ 1 Year	21 Years	Contributors to annual ΔBMD (lumbar spine/femoral neck): Baseline DAS28-ESR: $P=0.01/P=0.74$ Change in DAS28-ESR: $P<0.01/P<0.01$ GC dose (cumulative): $P=0.914/P=0.07$ Annual ΔBMD according to GC dose (<2.5/≥2.5 mg): Femoral neck: $P<0.01$ Lumbar spine: $P=0.147$			
Roubille, 2021 [25]	608	Early RA	Death, CV disease, severe infection and fracture (P)	(1) No GC (2) GC ≤ 7.5 mg/day	NS	10 Years	All GC-related AE Death CV disease Severe infection Fracture GC-related AE increased over time: 1 year: 0.46 (95% CI 0.23, 0.90) 10 years: 6.83 (95% CI 2.29, 20.35)	71 (18) 9 (2) 15 (4) 30 (8) 17 (4)	24 (11) 1 (1) 3 (1) 5 (2) 15 (7)	0.04 0.10 0.18 0.01 0.14

Table 1 (*Continued*)

Author, year	N	Population	Outcomes (P/S)	GC doses	Treatment duration	Follow-up	Results[a]			
							Outcome	GC	Non-GC	P
Lee, 2021 [22]	148	Inflammatory rheumatic disease	Vertebral, nonvertebral and fragility fractures (S)	No GC GC 2.5–7.5 mg/day	3.9 ± 4.2 Months	NS	Vertebral fractures Nonvertebral fractures Fragility fractures	18 (20) 10 (11) 22 (25)	3 (5) 3 (5) 6 (10)	0.01 0.20 0.03
Abtahi, 2021 [21]	15 123	RA	Osteoporotic fracture (P)	(1) Current GC use ≤7.5 mg/day (2) Current GC use 7.5–15 mg/day (3) Current GC use ≥15 mg/day (4) Recent GC use (past 6 months) (5) Past GC use (past 7–12 months) (6) Nonuse GC	3.7 Years	8.1 ± 4.9 Years	OP fracture [adjusted HR (95% CI)]	GC ≤7.5 mg 1.14 (0.98, 1.33)	GC 7.5–15 mg 1.38 (1.11, 1.73)	GC ≥ 15 mg Recent GC No GC 1.84 (1.23, 2.74) 0.71 (0.51, 1.00) 0.94 (0.83, 1.07)
Ocon, 2021 [17]	19902	RA (GC naive)	CV events (P)	(1) No GC (2) GC 1–5 mg/day (3) GC 5–9 mg/day (4) GC ≥ 10 mg/day	18 Months	NS	CV events [adjusted HR (95% CI)]	GC 1–5 mg 0.94 (0.55, 1.59)	GC 5–9 mg 1.56 (1.18, 2.05)	GC ≥ 10 mg 1.91 (1.31, 2.79)

[a]Count (%) unless otherwise noted.
AE, adverse event; BMD, bone mineral density; CI, confidence interval; CV, cardiovascular; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; HCQ, hydroxychloroquine; HR, hazard ratio; MTX, methotrexate; ns, not significant; NS, not specified; OP, osteoporosis; P, primary; RA, rheumatoid arthritis; S, secondary; TCZ, tocilizumab.

adding PDN 5 mg/day to standard treatment in people with active RA, aged 65+, for 2 years, significantly improved disease activity over placebo and significantly decreased radiographic damage accrual. There was, however, a 24% increase in the proportion of patients with at least one adverse event either serious or possibly associated with glucocorticoids use (60 vs. 49%; relative risk (RR) 1.24), most being nonsevere infections [13▪▪]. The authors (including three coauthoring this review) concluded that low-dose glucocorticoids therapy in RA has a generally favourable balance of benefit and harm, even in this high-risk population.

Withdrawal studies

The 2019 EULAR recommendations on RA management advocate the use of glucocorticoids only as bridging therapy advising their withdrawal as soon as possible. Failure to withdraw glucocorticoids after the bridging phase should be regarded as therapeutic failure and prompt therapy intensification [14]. The 2021 recommendations of the American College of Rheumatology conditionally advise against glucocorticoids [15].

The double-blind SEMIRA trial [16▪▪] aimed to investigate a glucocorticoids tapering scheme in patients with RA and low disease activity on treatment with tocilizumab and 5 mg/day of PDN. A total of 259 patients were randomized to taper or continue PDN. At week 24, the continued-PDN group showed safer (3 vs. 5% of severe glucocorticoids-related adverse events) and better (77 vs. 65% of sustained low-disease activity) disease control compared with the tapered-PDN group. Almost one third of tapered patients flared.

Cardiovascular risk

Cardiovascular risk in RA is strongly linked to disease activity, through chronic inflammation and accelerated atherosclerosis, but is also a well recognized adverse event of glucocorticoids. Ocon *et al.* found less than 5 mg/day of PDN-eq to be relatively safe in a large real-world cohort of RA patients. Cardiovascular risk was also directly associated with cumulative dose and duration of use of glucocorticoids [17].

Bone mineral density and fracture risk

Glucocorticoids-induced osteoporosis can be devastating and may affect 30–50% of chronic glucocorticoids users [18]. While oral bisphosphonates remain the first-line therapy, several other therapeutic options have been proved efficacious in recent years [19]. Despite the intense focus, observational

studies and RCT universally report low testing and undertreatment of established osteoporosis in glucocorticoids-treated patients.

Three new observational studies reported heterogeneous results on bone health. A retrospective study including 933 patients compared patients on low-dose glucocorticoids and patients who had discontinued glucocorticoids for at least 12 months regarding annual change in bone mineral density (BMD) and rate of osteoporotic fractures [20]. This study failed to prove an increased risk of fracture as also could not find a significant difference in the annual rate of change in BMD. In fact, the only variable associated with an accelerated loss of BMD was erythrocyte sedimentation rate, suggesting that the benefits of low-dose glucocorticoids therapy in attenuating inflammation compensate for the risk of BMD lost and osteoporotic fracture, provided that appropriate preventive measures are adopted [20]. Another study including over 15 000 patients with RA found glucocorticoids, both short and long-term (cut-off 12 months), to be associated with a higher risk of clinical vertebral fracture in a dose-dependent manner, but not with nonvertebral fracture or overall osteoporotic fracture [21]. Similar results were reported in a third study that compared chronic glucocorticoids users (treatment duration >3 months) to controls [22].

In the GLORIA trial [23], about one-third of patients had osteoporosis at baseline (history or imaging) but only 13% were treated with antiresorptive drugs; the protocol advised cotreatment with calcium and vitamin D which was instituted in 81% of patients (Boers M, personal communication). In the spine, PDN patients lost mean 1%, whereas placebo gained 3% bone mass ($P < 0.001$), with no change at the hip in either group. Symptomatic and asymptomatic fractures occurred at slightly (but not significantly) higher rates in the PDN group (Boers M, personal communication). The bone density results in GLORIA were limited by losses to follow-up testing owing to the COVID-19 pandemic.

Infection

Infection is one of the most recognized adverse events of glucocorticoids therapy. However, the relative risk is still controversial as it relies on several other factors such as disease activity, age, comorbidities and comedications.

A cohort study looked into the 1-year cumulative incidence of hospitalized infections in over 200000 RA patients on different glucocorticoids doses and stable DMARD therapy. Infections increased in a dose-dependent manner, with significant risk even at doses 5 mg/day or less PDN-eq [24]. Infection was also the most common severe glucocorticoids-related adverse event reported in the 10-year analysis of the ESPOIR cohort [25]. Among 608 patients, 65% received low-dose glucocorticoids for an average of 45 months. Severe glucocorticoids-related adverse events (defined as needing hospitalization) occurred in 24% of these patients, 42% of which were infections. The risk of severe infection was increased in patients with higher cumulative glucocorticoids dose (≥8.4 g PDN-eq). Again, no adjustment for disease activity was made [25]. A recent review, including the two studies above, suggested that even low-dose glucocorticoids are associated with an increased risk of infection [26].

In the GLORIA trial [23], low-dose glucocorticoids were also associated with increased infection risk but the majority of events were nonsevere.

Endocrine and metabolic dysfunction

Glucocorticoids are known to cause insulin resistance and increase in postprandial hyperglycaemia. A recent study found that 20% of patients on long-term low-dose glucocorticoids and with normal fasting glucose concentration had impaired glucose tolerance [27]. However, a small study by Den Uyl *et al.* revealed that over half of patients with early RA not on glucocorticoids also have impaired glucose metabolism or even overt (but undetected) type 2 diabetes. In these patients, 1 week of PDN 30–60 mg/day caused progression to diabetes in about half, but complete reversal to normal in the other half [28]. These studies show that, similar to osteoporosis, adverse event typically associated with glucocorticoids are also features of inflammatory disease and can be mitigated by glucocorticoids [29]. In line with previous RCT of low-dose glucocorticoids in RA, the GLORIA trial found no increase in cases of new-onset diabetes (Boers M, personal communication).

Another common concern relates with the metabolic risk for children born to women under glucocorticoids during pregnancy. Ince-Askan *etal.* [30] found no altered body composition or hypertension in prepubertal children born to women with RA and under low-dose glucocorticoids therapy during most of the pregnancy. There are no studies addressing the issue of adrenal insufficiency.

LOW-DOSE GLUCOCORTICOIDS IN OTHER RHEUMATIC CONDITIONS

Axial spondyloarthritis

Low-dose glucocorticoids have been successfully used in most chronic inflammatory rheumatic

diseases, with the exception of axial spondyloarthritis, perceived as refractory to glucocorticoids except in high doses [31]. A recent RCT [32] tested a step-down regimen of glucocorticoids in axial spondyloarthritis, similar to the COBRA regime for RA: a starting dose of PDN 60 mg/day was progressively withdrawn to 5 mg/day over 6 weeks and kept thereafter for 18 weeks. A BASDAI50 response was achieved in 37.5% (vs. 9.1% in the placebo group) at 24 weeks. The most common glucocorticoids-related adverse events were cushingoid facies, acne and transient weight gain. No serious adverse events were reported. This suggests a potential role for low-dose glucocorticoids in axial spondyloarthritis, even though higher doses may be needed earlier in the disease course. However, this is a proof-of-concept study with a small sample size and short follow-up.

Systemic lupus erythematosus

Similar to the SEMIRA trial in RA, a recent RCT tested the efficacy and safety of maintenance vs. withdrawal of 5 mg/day of PDN in systemic lupus erythematosus (SLE) patients with quiescent disease. During the 52 weeks of the study, low-dose glucocorticoids was associated with a reduced flare rate (7% in the maintenance group vs. 27% in the withdrawal group). No severe glucocorticoids-related adverse events were reported. Adverse events were, overall, rare and did not differ between study groups [33]. These results were confirmed in a meta-analysis, which added that the benefit of withdrawing low-dose glucocorticoids in terms of further damage is marginal, at best [34].

In SLE, glucocorticoids have been associated with neuropsychiatric adverse events at high-dose, but there is no data regarding lower doses. Miyawaki *et al.* [35] performed a cross-sectional study using a patient-reported outcome scale (LupusPRO) and found low-dose glucocorticoids to be associated with worse emotional health in a sample of 175 patients with low-disease activity SLE. LupusPRO scale assesses not only anxiety and depression, but also patients concerns regarding the disease impact on the future and the risk of losing income, which increases the risk of bias by indication. Also, important confounding factors were not taken into consideration, namely socioeconomic status and previous and cumulative glucocorticoids doses.

Osteoarthritis

The use of glucocorticoids in osteoarthritis remains a controversial topic. Osteoarthritis is not a classic inflammatory rheumatic disease but inflammatory flares are increasingly recognized, especially in hand osteoarthritis. In the HOPE trial [36], patients with symptomatic hand osteoarthritis and signs of inflammation (both clinically and ultrasonographically) were randomized to receive a short-course of PDN (10 mg/day for 6 weeks tapered over 2 additional weeks) or placebo. This resulted in a significant improvement (in pain, function and imaging markers of inflammation), with no increase in adverse events, in the glucocorticoids group after 6 weeks; effects disappeared after withdrawal.

HIGHER DOSES AND PARENTERAL FORMULATIONS

High-dose glucocorticoids are an integral part of any induction scheme in the treatment of vasculitis. However, there is a growing concern about the increased risk of severe and opportunistic infections associated with high-dose glucocorticoids as infection is currently the main cause of death in the first year among patients with these conditions [37,38]. Two recent RCTs call into question the need for such high doses of glucocorticoids in ANCA-associated vasculitis. The PEXIVAS trial [39] randomized 704 patients to a standard vs. reduced glucocorticoids regimen (50% of standard dose). The two regimens had similar efficacy, as well rates of death and of progression to end-stage kidney disease, while a significant reduction in severe infections at 1 year was seen in the reduced glucocorticoids group. All other adverse events were similar between the groups.

A second trial, using similar treatment groups in newly diagnosed patients with ANCA-associated vasculitis, found reduced-glucocorticoids regimen to be noninferior to standard treatment with regard to induction of disease remission at 6 months. All severe adverse events (inducing death, disability and/or hospitalization), including severe infections, were lower in the reduced glucocorticoids group [40].

Glucocorticoids are also associated with opportunistic infections, including Pneumocystis pneumonia (PCP). Park *et al.* [41] looked into the incidence and risk factors of PCP in patients with rheumatic diseases exposed to PDN-eq less than 15 mg/day or 15– 30 mg/day, over a 14-year period. The higher dose, but not lower dose glucocorticoids therapy, was associated with increased risk of PCP. The most significant risk factors for PCP were concomitant glucocorticoids pulses and baseline lymphopenia.

CONCLUSION

There has been a longstanding lack of sound evidence to support firm conclusions on the safety of

low-dose glucocorticoids, with observational studies continuing to pile up and large long-term RCT still missing from the literature. The GLORIA trial filled part of this gap by becoming the first RCT explicitly focusing both on glucocorticoids safety and benefit. In addition to a large sample size and relatively long follow-up, it targets a typically high-risk population when it comes to glucocorticoids use – the elderly – with very flexible inclusion criteria overcoming a frequent limitations of RCT in general, that is the limited representativeness of a real-world setting.

The GLORIA trial confirmed that in older persons, PDN 5 mg/day for 2 years increases the overall risk of adverse event, mostly nonsevere infections, without relevant increases in a variety of other glucocorticoids-associated adverse events.

Fragility fractures can be prevented, but only when assessment and prophylaxis, according to the latest recommendations, are actually implemented [15,42,43]. The same studies that document glucocorticoids-related osteoporosis also show that physicians and patients are woefully inadherent.

In sum, low-dose glucocorticoids are not free of adverse events but the most prevalent ones – infection risk and fragility fractures – are mainly nonsevere and (at least partly) preventable. Benefit and risk must be kept in perspective, and efforts must be put into minimizing glucocorticoids toxicity, but unsubstantiated fear is not a good advisor, and leads to suboptimal use of glucocorticoids in the treatment of rheumatic diseases.

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