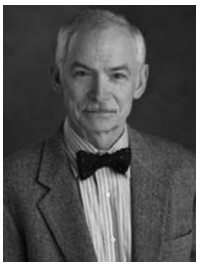
Editorial introductions

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

SECTION EDITORS

William J. McCune



Dr McCune is a graduate of Harvard College and the University of Cincinnati Medical School, USA. Following residency at the University of Michigan and fellowship at Brigham and Women's Hospital, USA, he joined the faculty of the University of Michigan, USA, where he is the Michael and Marcia Klein Professor of Rheumatic Diseases and Director of the Lupus Program.

Dr McCune has devoted much of his research career to systemic lupus. He reported the clinical and immunologic effects of monthly bolus cyclophosphamide for severe lupus using methods that were subsequently adopted as standard treatment for lupus nephritis. He has since focused on improving the efficacy and safety of immunosuppressive therapy, including the use of leuprolide for ovarian protection in women receiving cyclophosphamide. His work in medical imaging helped establish the importance of MRI in neurological complications of lupus and rheumatoid arthritis, and he was the first to describe ultrasound imaging of articular cartilage.

His current interests include the pathogenesis of cardiovascular disease in SLE, advanced MRI in SLE, and detailed population-based epidemiologic studies of the SLE in southeastern Michigan.

Jon T. Giles

Dr Giles's research interests are centered primarily within the inflammatory arthritides. His current projects center around understanding the inflammatory and non-inflammatory determinants of body composition abnormalities in rheumatoid arthritis and psoriatic arthritis, and their subsequent effects on health outcomes. Other current and past research involves the investigation of accelerated atherosclerosis and myocardial dysfunction in rheumatoid arthritis patients, understanding the determinants of rheumatoid arthritis-associated interstitial lung disease, and exploring the musculoskeletal side-effects of a class of medications used to suppress estrogen in women with certain forms of breast cancer. He is the recipient of grant support from the National Institutes of Health, the Arthritis Foundation, the Rheumatology Research Foundation, the Marianne Legato Foundation, and the Arthritis National Research Foundation.

Mycophenolate mofetil, for rheumatic diseases: should we monitor the area under the curve?

William J. McCune[a] *and Mousa Al Abbas*[b]

Mycophenolic acid (MPA) was first isolated from Penicillium Brevicompactum in 1893. Initially, it was used to treat anthrax and tested for additional antimicrobial and antitumor activity. Its use as an immunosuppressive agent began much later. In 1975, Jones *et al.* reported successful treatment of patients with psoriasis with MPA with target doses of 9600 mg/day for inpatients and 4800/day mg for outpatients. Not surprisingly, administration of these high daily doses – likely required because of the short half-life of MPA – resulted in frequent side-effects, especially affecting the gastrointestinal tract. The authors noted that 'clearly this is a drug that requires individualization of the dose; the doses required to clear psoriatic lesions are close to those at which many patients achieve adverse effects.'

Because of concerns that unfavorable kinetics and poor tolerance of MPA limited therapeutic use, mycophenolate mofetil (MMF) was developed and introduced in the early 1990s for prevention of transplant rejection. MMF's improved bioavailability and more consistent serum levels compared with MPA were associated with its rapid acceptance in transplantation as an alternative to azathioprine (AZA), and its subsequent adoption to treat rheumatic diseases, notably lupus and scleroderma. Despite these successes, it became evident that optimal drug exposure was frequently not achieved. In early allogeneic renal transplant studies, substitution of 2 g/day MMF for AZA for prevention of rejection in allogeneic renal transplant recipients achieved superior results in whites but not in blacks, and that blacks obtained a similar advantage over AZA with a 3 g/day target dose [1]. Proposed explanations have included racial differences in metabolism of MMF or other factors such as differing metabolism of coadministered calcineurin inhibitors, and differing concentrations of MPA required to achieve immunosuppressive effects. More recently, differences in MMF pharmacokinetics between races (Asians vs. whites vs. blacks) and between men and women have been described [2,3]. It has been suggested that lower maintenance doses be given to Asians, although there is not compelling evidence in our opinion that standard doses are harmful [2] or that lower doses will be equally effective.

Studies comparing individual patients have shown striking variation in metabolism, as illustrated by the report of Jacobson *et al.* of allogeneic bone marrow recipients receiving MMF 1 g i.v. or orally twice daily. With intravenous dosing, the area under the curve (AUC) ranged from 9.96 to 70.4 (mean 28.3) $\mu g \times h/ml$. With oral dosing, the AUC varied from 9.38 to 35.3 (mean 16.7) $\mu g \times h/ml$ and the median oral bioavailability was 72.3% with a range of 20.5–17.2%, with eight-fold variability [4]. Patients with lower AUC's of free MPA had higher incidences of graft vs. host disease and lower levels of engraftment. Wide variation in the AUC after standard dosing has also been reported in lupus patients [5].

Standardizing MPA exposure is especially challenging because the metabolism of MMF is complex. MMF is converted into MPA; which is in turn converted into the inactive metabolite MPA-glucuronide (MPA-G) which is primarily renally excreted. Enterohepatic recirculation of MPA-G is accompanied by deconjugation in the stool of MPA-G back to its active metabolite MPA. Levels are influenced by multiple factors including renal function and coadministration of drugs such as cyclosporine. In clinical practice, determination of a single blood level is not an accurate predictor of exposure; determination of the AUC of MPA by collection of multiple specimens over at least 3–6 h is needed to determine exposure [6].

An emerging literature suggests that monitoring the AUC of MPA in MMF-treated patients is associated with improved outcomes. Studies of transplant patients and pediatric nephritis patients have shown improved outcomes without documented

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increased toxicity in patients observed to have higher AUCs [7] and including studies in which patients have prospective dose adjustment according to the AUC [7–10].

Similarly, in lupus and lupus nephritis (LN) patients, there is increasing support for the utility of using the AUC in patient management [8,11] either by obtaining a full 12 h AUC or by abbreviated protocols. Lertdumrongluk *et al*. [12] showed in a study of Thai patient with LN that responders after 6 months had higher AUCs measured over a full 12 h. The mean AUC of responders was significantly higher than those not responding and successful treatment was correlated with areas more than 45 mg h/l. Zahr *et al*. [13] demonstrated a correlation of AUC with overall lupus activity. Sagcal-Gironella reported that in pediatric lupus patients, AUC bit not individual blood samples correlated with disease activity, results consistent with those of Alexander *et al*. [14]. Recognizing the unreliability of individual blood samples, numerous investigators have tested abbreviated methods for estimating AUC with briefer periods of sampling with varied success.

What are the implications of recognizing the high variability of blood levels of one of our most important drugs for the treatment of lupus? Although the evidence that careful dose adjustment of MMF using serial MPA AUC determinations improves outcome is still in the early stage, it behooves us to understand how individual patients metabolize the drug. There are enough data to recommend measuring at least an abbreviated AUC at the initiation of therapy and for developing efficient methods for dose adjustment thereafter. The data we have also encourage us to measure the AUC of MPA in patients, particularly with LN, who have suboptimal responses to MMF as an aid to deciding whether to increase dosage for patients with suboptimal AUCs (e.g. significantly below the currently proposed target of approximately 45 pg-ml/h), or change to a different regimen. However, the data do not currently establish a need for dose reduction for patients who are tolerating somewhat higher levels than expected without apparent toxicity.

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Conflicts of interest

There are no conflicts of interest.

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Recent advances in the treatment of rheumatoid arthritis

Tina D. Mahajan[a] *and Ted R. Mikuls*[a,b]

Purpose of review
Therapies for rheumatoid arthritis (RA) continue to expand rapidly. The purpose of this review is to discuss novel treatment options, including biosimilars, that are available, as well as to highlight promising agents in development. The purpose is also to discuss new emerging safety signals associated with these drugs and to discuss strategies in tapering therapy.

Recent findings
There are several novel RA therapies. These include the interleukin-6 (IL-6) receptor blocker sarilumab, which was approved in 2017. In aggregate, the sarilumab studies show that it is effective in RA, including patients with incomplete responses to methotrexate and anti-tumor necrosis factor inhibitor, and showing superior efficacy when used in higher dose (200 mg every 2 weeks) to standard-dose adalilumab. Other drugs that are currently being studied include the IL-6 cytokine blocker sarikumab, the small targeted molecule filgotinib, and many new biosimilars. Baracitinib failed to achieve approval by the Food and Drug Administration primarily over perceived safety concerns. The two biosimilar drugs currently approved are CT-P13 and SB2, which are based on the reference product infliximab. Although this review summarizes trials examining biologic tapering, additional data are needed to guide clinicians in regards to treatment de-escalation in RA.

Summary
With the greatly expanded armamentarium of RA treatment options available, it is important for clinicians to understand the data regarding drug efficacy and safety. With remission increasingly attainable, effective drug tapering strategies are needed. Although tapering trials do exist, more studies will be needed to help guide clinical practice.

Keywords
biosimilars, rheumatoid arthritis, sarilumab, tapering, treatment

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive disease that, left untreated, leads to progressive joint destruction and disability. Although there are many RA treatment options available, many agents are at best only partially effective or induce remission in only a minority of patients. Therefore, there remains an unmet need for treatments that provide excellent response and are cost-effective. The goal of this review is to identify novel therapies including both biologic and targeted synthetic disease modifying antirheumatic drugs (DMARDs), emerging safety issues with available agents, and data addressing the possibility of tapering therapies once remission is achieved.

NOVEL TREATMENTS

Interleukin-6 inhibition

Approved by the U.S. Food and Drug Administration (FDA) in 2017, sarilumab is the newest biologic for the treatment of RA. A human monoclonal antibody directed against the alpha subunit of the interleukin-6 (IL-6) receptor complex, it has a unique structure and a higher affinity for the receptor compared with tocilizumab, the first IL-6 inhibitor to be approved in RA [1]. In addition to its association with chronic inflammation, IL-6 exhibits multiple immune regulatory effects [2]. IL-6, for instance, activates the Janus kinase (JAK) signaling inflammatory pathway by binding to the IL-6 receptor and gp130, a transmembrane protein. The IL-6 receptor has two isoforms, including the soluble and membrane form. Although

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KEY POINTS

- Recent advances in RA treatment include the availability of biosimilars as well as novel agents inhibiting IL-6 and Janus kinase.
- Recent findings have identified risk factors the development of herpes zoster complicating tofacitinib in RA and these include older age, concomitant glucocorticoid use, geographic region of residence, and smoking status.
- Although several promising trials suggest that biologic therapies can be successfully tapered in some patients with RA, further study is needed to identify optimal candidates and approaches of treatment de-escalation.

the soluble and membrane-bound receptors demonstrate similar affinity for IL-6, the soluble IL-6 receptor produces a wider range of biologic effects due to its broader distribution [3]. In turn, IL-6 blockade potently reduces the production of acute phase proteins, acts as an antipyretic [4], and decreases osteoclast formation and reduces bone erosion, the latter a characteristic feature of RA [5].

Sarilumab is indicated for the treatment of moderate-to-severe active RA with inadequate response or intolerance to methotrexate and can be used with or without concomitant methotrexate. The recommended dose is 150–200 mg subcutaneously every 2 weeks. In the wake of promising phase II findings [6], the efficacy of sarilumab was demonstrated in separate phase III studies. In a 1-year study of RA patients with moderate-to-severe RA and inadequate responses to methotrexate, the addition of sarilumab (150 or 200 mg every 2 weeks) to weekly methotrexate led to greater American College of Rheumatology (ACR)-20 treatment responses (58–66%) vs. placebo (33%, $P < 0.0001$). Similar advantages of sarilumab over placebo were observed for the coprimary endpoints of radiographic progression and physical function [7]. In a separate 24-week study enrolling tumor necrosis factor-inhibitor (TNFi) incomplete responders receiving background conventional DMARD therapy, sarilumab administration resulted in similar benefit over placebo [8]. Finally, in a randomized double-blind head-to-head comparison of sarilumab (200 mg every 2 weeks) with adalimumab (40 mg every 2 weeks) monotherapy, sarilumab was statistically superior in terms of the change in 28-joint disease activity score at 24 weeks (mean -3.28 vs. -2.20, $P < 0.0001$)[9▪▪].

The tolerability of sarilumab was assessed in all of the above investigations, displaying a safety profile that was relatively consistent across studies. The most common serious adverse effects reported included neutropenia, serious infections, hypersensitivity, and gastrointestinal perforations [10]. Neutropenia was seen in a significant percentage of patients, with varying degrees of severity, although no connection between neutropenia and infection risk could be established. There were significant liver function test (LFT) abnormalities (>3× upper limit of normal) in 3–8% of patients with a frequency of lipid abnormalities that approach that observed with tocilizumab [1]. Of note, in the head-to-head comparison, neutropenia and injection site reactions were more common with sarilumab than with adalimumab, whereas headache was more common with the latter [9▪▪]. In aggregate, these studies show that sarilumab is effective in RA (including patients with incomplete responses to methotrexate and TNFi), showing superior efficacy when used in higher dose (200 mg every 2 weeks) to standard-dose adalimumab (a TNFi) with similar tolerability.

Biosimilars

Biosimilars represent an important new class of drugs in the rheumatologic armamentarium. Due to the complex molecular structure of biologics, generic versions of these drugs are not possible. Defined as a product that 'has no clinically meaningful differences from an existing FDA-approved reference product' [11], regulatory agencies require that biosimilar agents pass stringent pharmacokinetic and pharmacodynamic testing, as well as immunogenicity assessments.

Two biosimilar products based on the monoclonal antibody infliximab are now approved for RA treatment in the United States. The first to be approved was CT-P13 (Inflectra) in 2016. Approval was based in part on results from two 52-week, randomized double-blind, multinational, parallel group studies in which CT-P13 was compared with reference product. Primary endpoints included efficacy defined by ACR20, ACR 50, and ACR70 responses, immunogenicity defined by antidrug antibodies (ADAs), and safety defined as treatment emergent adverse events [12,13]. Recently, a 102 week, open-label extension study was completed to evaluate the safety and efficacy of switching to CT-P13 in patients already on the reference product and to evaluate the longer term safety and efficacy of CT-P13 in patients who continue the agent for over 2 years [14▪]. Across these studies, there were no significant differences in efficacy, immunogenicity, or safety in patients taking (or switched to) CT-P13. In addition, the latter study showed that CT-P13 demonstrated persistent efficacy and tolerability

over time, throughout the 102 weeks of observation [14▪].

SB2 (Renflexis) is the most recent infliximab biosimilar to be approved in the United States. Approval in 2017 was based on two randomized double-bind, multinational, parallel group studies comparing SB2 to reference product. Compared to the reference product (infliximab), SB2 demonstrated a similar safety profile as well as efficacy over 24–54 weeks of follow-up, both in terms of treatment response (ACR20) as well as retarding radiographic disease progression [15]. The most recent study of SB2 was an extension of the 54-week study, in which subjects receiving infliximab were re-randomized to either switch to SB2 or to continue on infliximab for up to 70 weeks [16▪]. The efficacy, safety, and immunogenicity profiles were similar between all of the groups as assessed at week 78. Additionally, there were no treatment related immunogenicity issues arising in subjects switching from infliximab to SB2.

Emerging therapies

Interleukin-6

In contrast to available IL-6 inhibitors, sirukumab is a monoclonal antibody that selectively binds to the cytokine, rather than its receptor. In a phase III multinational, randomized double-blind study, sirukumab (50 mg every 4 weeks and 100 mg every 2 weeks) was compared with placebo in RA patients who had failed conventional DMARDs [17]. Both coprimary endpoints of ACR20 response at 16 weeks and radiographic progression at 52 weeks were met, with similar efficacy observed between the high and low-dose sirukumab groups. A similar phase III study examined the use of sirukumab in RA patients failing prior anti-TNF therapy [18]. This trial met its primary outcome measure of ACR20 response at 16 weeks, again demonstrating similar efficacy across active treatment groups (ACR20 of 45% with high dose and 40% with low dose) vs. placebo (24%; $P < 0.0001$). Safety signals in these trials were similar to that of other IL-6 inhibitor drugs with the most common adverse events including LFT abnormalities, upper respiratory tract infections, and minor injection site reactions.

Biosimilars

There are several biosimilars in various stages of development. Table 1 [13,14▪,15,16▪,19–21] outlines biosimilars approved in the United States and those that are currently under evaluation by regulatory agencies.

Targeted synthetic disease modifying antirheumatic drugs

Bioavailable with oral administration, the targeted synthetic DMARDs that are currently available (tofacitinib) or in development target kinases involved in cell signaling. JAKs are intracellular cytoplasmic tyrosine kinases that signal cytokine signaling from membrane receptors to the cell nucleus. Four different types of JAKs are known: JAK1, JAK2, JAK3, and Tyk2. JAK1 and JAK3 transduce proinflammatory cytokine signaling, whereas JAK2 signals for a wider array of cytokines and is downstream of a number of growth factors involved in hematopoiesis [22]. Tofacitinib is a pan-JAK inhibitor, and the only drug in this class currently approved for use in the United States. [23]. Baracitinib, another pan-JAK inhibitor, failed to gain approval in April of 2017, with the FDA citing the need for further dosing and safety data [24]. The major phase III study of baracitinib involved 527 patients with refractory RA, defined as those failing one or more previous TNFi, other biologic, or both [25]. More patients receiving baracitinib (4 mg daily) achieved the primary endpoint of ACR20 response at 12 weeks than placebo (55 vs. 27%; $P < 0.001$). Although rates of serious adverse events or those leading to study discontinuation were similar across treatment assignments, more patients treated with baracitinib 2 or 4 mg daily

Table 1. Current biosimilars on the market and pending approval in United States.

Drug (Trade name)	Reference pproduct	Approval status	Trial
CT-P13 (Inflectra)	Infliximab	Approved in the United States in 2016	PLANETRA, PLANETRA extension [13,14▪]
SB2 (Renflexis)	Infliximab	Approved in the United States in 2017	Choe *et al.* [15] Smolen *et al.* [16▪]
SB4 (Benepali, Brenzys)	Etanercept	Approved in Europe, Current US clinical trial	ClinicalTrials.gov:NCT01895309 Emery *et al.* [19]
ABP501	Adalilumab	Current US clinical trial	ClinicalTrials.gov:NCT01970475 Cohen *et al.* [20]
GP2013	Rituximab	Current US clinical trial	ClinicalTrials.gov:NCT01274182 Smolen *et al.* [21]

Table 2. Summary of filgotinib (selective JAK-1 inhibitor) trials

Trial	Type	Length	Number	Efficacy	Safety
DARWIN 1 [30]	Phase IIb, multicenter, multinational, including United States	24 weeks	594 received placebo vs. drug at various doses and methotrexate	Drug met ACR endpoints at 12 weeks for doses 100 mg and 200 mg, but not for lower doses	No significant differences in adverse events between placebo and drug groups
DARWIN 2 [31]	Phase IIb, multicenter, multinational including US	24 weeks	283 received placebo vs. drug at various doses, no methotrexate	Drug met ACR endpoints starting at week 12 and persisted week 24	No significant difference in adverse events between placebo and drug group
[28]	Phase IIa, proof of concept study done in Republic of Maldova	4 weeks	36 received placebo vs. drug at 100 or 200 mg dose	Drug met ACR endpoints vs. placebo	No major safety signals. Hemoglobin went up, decrease in neutrophils without neutropenia
[28]	Phase IIa, dose ranging study in Republic of Maldova, Ukraine, Russia, and Hungary	4 weeks	91 received placebo various doses of drug	85% of 300 mg dose group had a ACR 20 response but this was not significantly better than placebo	No major safety signals. Hemoglobin went up, decrease in neutrophils without neutropenia

ACR, American College of Rheumatology.

(71–77%) experienced an adverse event than with placebo (64%) after 24 weeks. Adverse events occurring more commonly with baracitinib included infections (44 and 40% vs. 31%), decreased neutrophil counts, and slight increases in low-density lipoproteins that were accompanied by increases in high-density lipoprotein concentration. In a more recent open-label extension study with up to 128 weeks of treatment exposure, the safety and tolerability profile of baracitinib (4 and 8 mg doses) remained consistent with earlier observations, whereas efficacy was maintained throughout the open-label period [26▪▪]. One particular safety concern cited by the FDA was the possible increased risk of thromboembolic events [deep venous thrombosis (DVT) and pulmonary embolus] related to baracitinib use. One recent study reviewed data from the FDA Adverse Event Reporting System to screen for thromboembolic events related to tofacitinib and ruxolitinib, the latter a JAK inhibitor used in certain myeloproliferative disorders. Although there was no evidence for elevated reporting of either DVT or pulmonary embolus for the individual agents, there were trends in the data suggesting that pulmonary embolism could represent an emerging class-wide adverse effect [27].

Filgotinib (GLPG0634/GS-6034) is a potent and selective inhibitor of JAK1 currently under development [28]. Pharmacokinetic and pharmacodynamic studies of filgotinib and its active metabolite suggest that both structures contribute to its pharmacodynamic properties, rendering a relatively long treatment half-life [29]. Filgotinib was initially found to be efficacious in two 4-week randomized trials conducted for proof-of-concept and dose finding purposes [28]. In separate phase II studies, filgotinib (100 or 200 mg, dosed once or twice daily) was significantly more efficacious than placebo in achieving ACR20, -50, and -70 responses while demonstrating similar adverse event rates [30,31]. Importantly, the trial patients receiving filgotinib showed slight increases in hemoglobin during observation, in contrast to patients on pan-JAK inhibitors who can develop anemia, likely mediated by JAK2 inhibition [22]. Table 2 [28,30,31] summarizes the current filgotinib trials.

Herpes zoster as an emerging safety issue

Herpes zoster incidence has been increasingly identified as an adverse event in RA treatment trials, with data suggesting that its risk may be disproportionately higher with tofacitinib use. An initial study identifying all cases from phase II, -III, and long-term extension RA trials of tofacitinib showed that the herpes zoster incidence rate was 4.4 per 100 person years [95% confidence interval (CI) 3.8–4.9] [32]. Importantly, complicated herpes zoster cases were rare in these studies and there were no cases of visceral dissemination or death from these databases. More recently, a study was done to identify other risk factors for herpes zoster complicating the course of tofacitinib treatment in RA [33▪]. Using similar datasets as described above and multivariable Cox regression, the authors identified several other potential independent risk factors including: older age (hazard ratio 1.41; 95% CI 1.31–1.52 per 10 years); glucocorticoid use (hazard ratio 1.49; 95% CI 1.22–1.82 for more than 0 mg to or less 5 mg/day of prednisone equivalent or hazard ratio 1.41; 95% CI 1.12–1.77 vs. 0 mg); region of enrolment (with Asians having the highest risk); and former or never smoking status (hazard ratio 1.32; 95% CI 1.04–1.69 vs. current smoker).

With known risk for herpes zoster, vaccination of patients is an important consideration. A recent phase II, randomized controlled trial compared the

safety and immunogenicity of the live zoster vaccine in RA patients (all receiving background methotrexate) treated with tofacitinib (5 mg twice daily) versus placebo administered 2–3 weeks postvaccination [34▪]. Importantly, this study showed similar vaccine-mediated immune responses in those receiving tofacitinib versus placebo. Moreover, the vaccine appeared to be well tolerated in all but one patient who lacked preexisting viral immunity and who developed cutaneous vaccine dissemination 2 days after initiating tofacitinib (16 days after being vaccinated). These data suggest that the live zoster vaccine may be an effective tool in mitigating this adverse effect and may be administered safely in a majority of patients within 2–3 weeks of initiating tofacitinib. In October of 2017, the FDA approved a non-live shingles vaccine consisting of a recombinant VZV antigen and an immune adjuvant [35]. A recent study was done to evaluate the immunogenicity and safety of the inactivated vaccine in patients with autoimmune disease on immunosuppressive agents (both biologic and nonbiologic). The vaccine was found to elicit robust humoral and cell-mediated responses and was relatively well tolerated with the most common adverse effect being injection site reactions. Two serious adverse events in the vaccine group were determined by investigators to be related to vaccine including one case of keratitis and another of amnesia [36]. Additional comparative effectiveness studies of the vaccines in the context of RA and DMARD and biologic use are needed.

Tapering therapies

With the advent of multiple new therapies for RA, disease remission is now a more achievable goal. In patients who achieve remission by any definition, the concept of tapering therapy is an important consideration. In fact, recent treatment guidelines suggest tapering either DMARDs or biologic therapies in patients with established RA who are in remission. The quality of evidence, however, endorsing this practice is low [37]. Although several de-escalation studies have been undertaken, these are difficult to compare due to clinical heterogeneity of the populations studied as well as differences in methodologies.

A systematic review of de-escalation studies was done in 2014 [38]. This review aimed to assess the literature supporting 'biologic downtitration'. The authors identified 10 studies in the report, only

Table 3. Summary of recent de-escalation trials.

Trial	Methods	Results
PRESERVE: [40] To evaluate whether patients can maintain LDA despite tapering or stopping of ETA	RCT in moderately active RA, three arms: ETA 50+MTX, Enbrel 25 +MTX, placebo + MTX	Author conclusion: standard and reduced doses of etanercept are more effective at maintaining remission than MTX alone
PRIZE: NEJM 2014 [41] To evaluate whether patients with early RA, after induction, can maintain LDA without ETA	RCT in early RA patients, three groups: ETA 25+MTX, MTX, and placebo	Author conclusion: After early, aggressive treatment of tapering of RA achieving LDA, tapering biologic is appropriate, reduced dose of ETA is more effective at maintaining remission than MTX alone
OPTIMA: [42] To assess different treatment adjustment strategies in early RA patients attaining (or not) LDA with ADA + MTX vs. MTX alone	RCT in early RA patients, patients phase 1 (24 week) treated with either MTX or MTX +ADA, then those who achieved LDA were either continued on their regimen or ADA removed for phase 2 (additional 52 week)	Author conclusion: Patients who achieved LDA initially on MTX+ADA who then withdrew ADA mostly maintained good clinical responses
RETRO: [39] To assess different tapering strategies in established RA patients.	RCT in established RA, three arms: continue all meds, tapering DMARD or biologic, stopping all medications at 6 months after tapering, endpoint was an Interim Analysis of relapse at 12 months	Author conclusion: There was a significant difference in relapse rates between the groups that continued and stopped the medications, but no difference between the groups that were continued and those that were tapered
tREACH: [38] To compare different tapering strategies and to determine whether remission could be regained after flare	RCT in early RA patients, patients in DAS remission were tapered according to protocol, outcomes were sustained remission, rates of flare, and remission after flare	Author conclusion: There was a similar rate of flare when tapering biological vs. conventional DMARDs (37 vs. 47%). After flare, 65% of flare patients regained remission after increasing therapy
NORD-STAR: Trials 2017 [43]	Prospective RCT, arms: Immediate taper, slow taper, stop meds	Trial ongoing currently

ADA, adalimumab; DAS, disease activity score; DMARDs, disease modifying antirheumatic drugs; ETA, etanercept; LDA, low disease activity; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial.

three of which were randomized controlled trials (RCTs). On the basis of the limited data available at the time, the authors concluded that it was difficult to determine which patients needed to remain on therapy and which patients could be safely undergo biologic tapering without flaring and that more studies were needed. Since then, several additional RCTs have been completed (Table 3) [38–41,42,43].

Further studies have aimed to help determine predictors of flare with treatment tapering. The tREACH and RETRO studies examined rates of flare with tapering of either conventional synthetic DMARDs or biologics [44,39]. Of note, the RETRO study was published as a 1-year interim analysis and reported that disease relapses were associated with the presence of anticitrullinated protein antibody. In a follow-up to this, 94 baseline serum samples from RETRO subjects were tested for immune responses to 10 different modified (citrullinated, homocitrullinated, and acetylated) peptides. Among these patients undergoing standardized DMARD/biologic tapering or discontinuation, the more antimodified protein antibodies a patient had, the more likely their disease would relapse [45]. The proportion flaring ranged from 18% in those with none or one autoantibody positive to 55% in those with more than five positive autoantibodies. Both the RETRO study and tREACH trials showed that female sex was also a predictor of flare. Finally, one recent 18-month noninferiority study examined the utility of a baseline multidisease biomarker disease activity (MBDA) score to predict flare in RA patients (all in sustained remission at baseline) whose medication was tapered or stopped [46]. The results showed that the baseline MBDA score, although associated with the occurrence of flare in those receiving usual care, was not a good predictor of disease relapse in those tapering therapies.

Another important aspect of tapering therapy is whether patients can regain remission if therapy is resumed after being stopped. The tREACH trial showed that approximately 65% of patients regained remission within 6 months of treatment intensification [44]. This is consistent with the systemic review of studies done before 2014 [38]. Of note, the tREACH population was an early RA group and it is unclear whether those with more established RA would respond similarly.

Many trials suggest that tapering the dose or frequency of the biologic drug, rather than completely stopping it, may be a more effective alternative in maintaining RA treatment response. The PRESERVE and PRIZE trials showed that patients on a reduced dose of etanercept (25 mg s.c. weekly) maintained remission as well as those on full dose etanercept (50 mg s.c. weekly), but those whose etanercept was stopped were far less likely to maintain remission [40,41]. The OPTTIRA trial was an open-label trial that also looked at this concept [47▪], comparing tapering of TNFi (adalimumab or etanercept) by either 33 or 66% percentage to stable-dosed treatment. Compared with those receiving stable, standard TNFi dosing, 66% tapering was associated with a reduced time-to-flare in survival analysis, an effect that was not observed with 33% tapering.

CONCLUSION

The RA treatment armamentarium has expanded substantially over the last 20 years. In this review, we have summarized the latest biologics/biosimilars and targeted small molecule drugs on the market, other promising agents in development, as well as emerging safety signals associated with newer treatment options. With these many treatment options, remission has become increasingly obtainable and the question of tapering strategies has become highly relevant in the day-to-day management of RA patients. Future trials will continue to help guide clinicians in best practices in the treatment of RA.

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Conflicts of interest

There are no conflicts of interest.

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This is an open label trial looking at the concept of reduced dose of a biologic (adalilumab or etanercept). It showed that reduction by 66% was associated with a reduced time-to-flare in survival analysis, but reduction by 33% did not have this same association.

Management of Behçet's disease

Fatma Alibaz-Oner[a], *Amr H. Sawalha*[b], *and Haner Direskeneli*[a]

Purpose of review
Current treatment modalities in Behçet's disease will be summarized in light of new studies published within the last 2 years.

Recent findings
There is an increasing interest in the treatment of refractory mucocutaneous symptoms of Behçet's disease, and results were quite promising with apremilast, anakinra, and ustekinumab. Data from large case series confirmed both the efficacy and safety of tumor necrosis factor-α inhibitors for the treatment of refractory major organ manifestations such as ocular, neurologic, vascular, and gastrointestinal involvement. In refractory ocular disease, long-term results also confirmed the efficacy and safety of interferon-α. Interleukin-1 inhibitors and tocilizumab seem to be alternative options in patients with refractory ocular involvement.

Summary
Prospective and controlled studies for the management of major organ involvement in Behçet's disease are still limited. Data from primarily retrospective studies confirmed better outcomes of major organ involvement with tumor necrosis factor-α inhibitors and interferon-α. There were also acceptable results with interleukin-1 inhibitors for the management of refractory ocular disease, and with apremilast, anakinra, and ustekinumab for refractory mucocutaneous involvement.

Keywords
Behçet's disease, interferon-α, interleukin-1 inhibitors, tumor necrosis factor-α inhibitors, tocilizumab

INTRODUCTION

Behçet's disease is a chronic, multisystemic, inflammatory disease characterized by recurrent attacks of mucocutaneous, ocular, musculoskeletal, vascular, central nervous system (CNS), and gastrointestinal manifestations. Approach to the management of Behçet's disease requires the assessment of disease severity and prognostic factors such as gender and age. Major organ involvement such as uveitis, vascular, neurologic, and gastrointestinal disease needs a more aggressive approach with long-term immunusuppressive agents. Young males are the group with the highest risk of morbidity and mortality [1]. The aim of this review is to summarize current approaches to treatment of Behçet's disease in light of new studies published within the last 2 years.

MUCOCUTANEOUS INVOLVEMENT

Colchicine is the preferred agent as the first-line treatment of mucocutaneous involvement; however, without definitive evidence of efficacy in oral ulcers [2]. Azathioprine, interferon (IFN)-α-2a, and tumor necrosis factor (TNF)-α inhibitors are suggested for refractory mucocutaneous lesions in the Management Recommendations by the European League Against Rheumatism (EULAR) [3,4].

In a recent phase 2 study, apremilast which is an oral phosphodiesterase 4 inhibitor, was observed to be highly effective in suppressing oral ulcers [5]. A 52-week, multicenter, double-blind, phase 3 trial of apremilast has just completed the recruitment of patients (ClinicalTrials.gov Identifier: NCT02307513). Being already approved for psoriasis, apremilast seems to be a promising agent for mucocutaneous Behçet's disease, but its role in major organ disease is currently unknown.

Grayson *et al.* [6▪▪] recently reported the safety and efficacy of anakinra, an interleukin-1 receptor antagonist, for the treatment of refractory oral and

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KEY POINTS

- Apremilast and anakinra may be effective options in refractory mucocutaneous involvement in Behçet's disease.
- TNF-α inhibitors are effective and well tolerated in the management of all major organ involvements in Behçet's disease refractory to conventional immunosuppressive treatments.
- IFN-α, interleukin-1 inhibitors, and tocilizumab may be alternative agents in the treatment of refractory ocular involvement.

genital ulcers in Behçet's disease. Anakinra at a dose of 100 mg/day (with dose increments up to 300 mg/day) was given to six patients. The primary outcome, defined as no ulcers for 2 consecutive monthly visits, was achieved in 2 patients, and partial responses were achieved in 5 patients. Ustekinumab, a humanized monoclonal antibody targeting interleukin-12/interleukin-23, was also studied for the treatment of refractory oral ulcers in 14 Behçet's disease patients. At week 12, 64% of patients were in complete remission defined as no ulcers, and 21% had partial responses. Overall, ustekinumab was well tolerated. After a follow-up period of 7 months, 10 patients were still receiving ustekinumab treatment, and relapse developed in 4 patients [7]. These results suggest that ustekinumab may also be a promising new agent in patients with refractory oral ulcers.

Although, interleukin-6 is one of possible therapeutic targets in Behçet's disease, use of tocilizumab in mucocutaneous Behçet's disease is controversial. Data from case reports suggest that mucocutaneous manifestations appear to respond only mildly, or even worsen, with tocilizumab treatment [8].

OCULAR INVOLVEMENT

Azathioprine and systemic corticosteroids were suggested as the first choice for the treatment of ocular involvement, especially in posterior segment disease according to the EULAR recommendations. In refractory patients, cyclosporine-A, TNF-α inhibitors, or IFN-α-2a were suggested as alternative options [2].

Recent open, nonrandomized series showed efficacy of anti-TNF-α therapies in uveitis patients. In a retrospective study comparing the efficacy and safety of infliximab versus adalimumab in 160 patients with noninfectious uveitis (Behçet's disease in 36%), infliximab and adalimumab were found to be equivalent regarding efficacy, with overall response rate of 95–97%. There were also no differences regarding rates of complete response or event-free survival [9]. In another study of 42 patients, adalimumab induced clinical remission in all patients. However, relapse developed in eight patients during 24 months of follow-up during adalimumab therapy [10]. In another series of 40 patients, 95% responded to 12 months of treatment with adalimumab [11]. Although the number of Behçet's disease patients was very low in the VISUAL I and II studies, the efficacy of adalimumab for idiopathic uveitis will possibly lead to its increased use for uveitis in Behçet's disease [12,13].

Patients with recent onset disease (≤18 months) had better visual outcomes with infliximab therapy, putatively because treatment reduced background vascular leakage before the development of permanent ocular damage [14]. Guzelant *et al.* [15] also reported that earlier initiation of infliximab in Behçet's disease uveitis led to a milder course of ocular involvement. The efficacy of intravitreal adalimumab in breakthrough panuveitis was assessed in Behçet's disease patients on subcutaneous adalimumab (>3 months). Among 13 attacks developed during a follow-up of 24.5 months, three attacks resolved with only one injection and 10 attacks required an average of 2.4 injections (range 2–3) [16]. In patients who are refractory, intolerant, or refusing corticosteroids, and maintained on systemic adalimumab, intravitreal injections of the same drug during breakthrough inflammation might be a practical, well tolerated, and cost-effective option. However, this approach warrants further investigation.

The effectiveness of IFN-α-2a in ocular Behçet's disease was demonstrated in two new case-series [17,18] Weekly administered Pegylated IFNs (IFN-α-2a and b) were also shown to be effective and well tolerated in Behçet's disease patients with uveitis in two other studies [19,20]. Fabiani *et al.* [21] assessed interleukin-1 inhibitors, anakinra and canakinumab, in a multicenter retrospective study demonstrating good efficacy. The combination of any immunusuppressive agent with interleukin-1 inhibitors had no added benefit compared to interleukin-1 inhibitors alone. The safety and efficacy of gevokizumab, a recombinant, humanized, monoclonal antibody that binds to interleukin-1β, was demonstrated by Tugal-Tutkun *et al.* [22▪▪] in Behçet's disease uveitis. Gevokizumab controlled the acute exacerbations of Behçet's uveitis rapidly with no increase of corticosteroids dosage, and was also well tolerated.

In a double-blind, placebo controlled study, intravenous administration of 1000 mg methylprednisolone added to standard immunusuppressive therapies demonstrated better outcome with less flares during a 6-month follow-up [23].

Another biological agent targeting T-cells, alemtuzumab, an anti-CD52 antibody, was also studied as remission-induction therapy in the treatment of refractory and relapsing Behçet's disease. After the first alemtuzumab course, 84% of patients achieved partial or complete remission. All patients with severe ocular and CNS disease achieved remission with profound lymphocyte depletion. Mild-to-moderate infusion reactions (27%) and symptomatic autoimmune thyroid disease (25%) were the most common adverse effects [24]. Alemtuzumab might be an alternative agent in refractory Behçet's disease, but probable adverse effects should be taken into account.

There are also case reports suggesting the efficacy of tocilizumab (TCZ) treatment in Behçet's disease uveitis refractory to conventional immunusuppressives and TNF-α inhibitors [25–27].

VASCULAR INVOLVEMENT

There are no randomized controlled trials for the management of major vascular involvement (VBD) in Behçet's disease. According to EULAR recommendations, only immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide, or cyclosporine-A are recommended for VBD. Anticoagulants, antiplatelet, or antifibrinolytic agents are not recommended. IFN-α-2a, methotrexate, and TNF-α inhibitors can also be used in refractory patients [28]. In a multicenter, retrospective study evaluating different treatment modalities in VBD, the relapse rate was observed to be similar between patients using only immunusuppressives and those using anticoagulants together with immunusuppressives (29.1 vs 22.4%, $P = 0.08$). In multivariate analysis, development of vascular relapse negatively correlated with immunosuppressive treatments, and adding anticoagulants to immunusuppressives had no additional positive effect [29]. All data for anticoagulant treatment in VBD comes from retrospective studies. There is a clear need for randomized controlled studies for clarifying the role, if any, of anticoagulants in VBD. Previous studies demonstrated the efficacy of TNF-α inhibitors for the treatment of refractory VBD [30,31]. Similar new small case-series supported these observations [10,32] with clinical remissions observed in more than 90% of patients [33]. In a recent case report of 2 VBD patients with pulmonary aneurysms refractory to cyclophosphamide, TNF-α inhibitors were found effective [34]. There are also a few case reports suggesting the efficacy of anakinra in VBD [35]. Recently, as another approach in refractory cases, pulmonary endarterectomy was reported to be well tolerated and effective in Behçet's disease patients with pulmonary hypertension due to thrombi [36].

NEUROLOGIC INVOLVEMENT

There are also no controlled studies of the management of neurologic involvement in Behçet's disease (NBD). In an International Concensus Report, high-dose pulse IV methylprednisolone for 5–10 days was recommended for the acute stage of neurologic involvement and azathioprine together with oral corticosteroids as the first-line therapy afterward [37,38]. Alternatives include mycophenolate mophetil, methotrexate, and cyclophosphamide. Anticoagulant treatment for dural sinus thrombosis is controversial. TNF-α inhibitors were recommended for parenchymal disease when the first-line treatment fails or the disease relapses [38]. In two recent case-series, anti-TNF-α treatments for NBD were reported to be effective in inducing remission for most patients [39,40]. However, awareness for opportunistic infections should be high in Behçet's disease patients especially for tuberculosis [41,42].

There are also a few case reports suggesting the effectiveness of IV immunoglobulins and rituximab in refractory NBD [43–45].

GASTROINTESTINAL INVOLVEMENT

5-Aminosalicylic acid (ASA) derivatives are suggested to be the first-line of therapy for mild gastrointestinal involvement in Behçet's disease patients with or without corticosteroids [46]. Azathioprine may be an alternative in patients refractory to 5-ASA derivatives, or as a first-line therapy in more severe cases with gastrointestinal involvement [47]. Thalidomide and TNF-α inhibitors may also be used in refractory cases [48]. In a retrospective series of 60 Behçet's disease patients by Hatemi *et al.* [49], azathioprine was utilized in 73 with 65% remission rate – without any relapse during a mean follow-up of 68.6 months. In new series using anti-TNF-α therapies, 20–61% complete remission rates were observed for refractory gastrointestinal disease [50,51].

CONCLUSION

Data derived primarily from case reports, case series, retrospective analyses, and a limited number of recent clinical trials suggest the safety and potential efficacy of newer biological agents in the treatment of Behçet's disease. Sfikakis *et al.* [52] recently reported long-term drug-free remissions after infliximab therapy in 41% of Behçet's disease patients. With similar

data previously reported for interferon-α2a, these reports suggest that, at least in some patients, better management of Behçet's disease can now be achieved. However, there is still a clear need for randomized controlled clinical trials in Behçet's disease, especially to guide the management of major organ involvement. For refractory mucocutaneous involvement, recent results were quite promising with apremilast, anakinra, and ustekinumab. New data from a number of case series confirmed both the efficacy and safety of TNF-α inhibitors for refractory major organ involvements such as ocular, vascular, neurological, and gastrointestinal involvement. In refractory ocular disease, long-term follow-up also confirmed the efficacy and safety of IFN-α. Interleukin-1 inhibitors and tocilizumab seem to be alternative options in patients with refractory ocular involvement.

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Current management of sarcoidosis I: pulmonary, cardiac, and neurologic manifestations

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Purpose of review
Sarcoidosis is a systemic disease characterized by noncaseating granulomatous inflammation of multiple organ systems. Pulmonary, cardiac, and neurologic involvements have the worst prognosis. Current recommendations for the therapeutic management and follow-up of sarcoidosis involving these critical organs will be reviewed.

Recent findings
In those sarcoidosis patients requiring immunosuppressive therapy, corticosteroids are used first at varying doses depending on the presenting manifestation. Patients with symptomatic pulmonary, cardiac, or neurologic involvement will be maintained on corticosteroids for at least a year. Many require a second immunosuppressive agent with methotrexate used most commonly. Anti-tumor necrosis factor agents, especially infliximab, are effective and recommendations for their use have been proposed.

Summary
Evidence-based treatment guidelines do not exist for most sarcoidosis clinical manifestations. Therefore, clinical care of these patients must rely on expert opinion. Patients are best served by a multidisciplinary approach to their care. Future research to identify environmental triggers, genetic associations, biomarkers for treatment response, and where to position new steroid-sparing immunosuppressive agents is warranted.

Keywords
cardiac sarcoidosis, neurosarcoidosis, pulmonary sarcoidosis, sarcoidosis treatment

INTRODUCTION

Sarcoidosis is a systemic inflammatory disease of unknown cause characterized by noncaseating, granulomatous inflammation of two or more organs [1,2▪▪]. Virtually, any organ can be involved. It occurs worldwide, affecting both sexes and all races/ethnicities but with marked variations in clinical presentation and disease severity. The clinical manifestations are diverse ranging from an abnormal chest radiograph in an asymptomatic individual to severe multiorgan involvement [3]. Evidenced-based treatment guidelines do not exist for most presentations [4▪]. This paper reviews current recommendations for management of the life-threatening manifestations of sarcoidosis. Other than corticosteroids, none of the therapies is Food and Drug Administration-approved for use in these sarcoidosis presentations. A subsequent paper will review the management of other clinical presentations.

CLINICAL MANIFESTATIONS AND DIAGNOSIS: OVERVIEW

The presenting and cumulative clinical manifestations are shown in Table 1. Although sarcoidosis most commonly involves the lung, up to 30% of patients present with extrapulmonary sarcoidosis as their initial manifestation. During the course of follow-up, over 90% have pulmonary involvement, 50% have extrathoracic involvement, and 2% have isolated extrathoracic involvement. The diagnosis of sarcoidosis is established by a combination of well recognized clinical, radiographic, and laboratory findings supported by histologic evidence of widespread noncaseating epithelioid granulomas in more than one organ system. Other granulomatous diseases must be rigorously excluded. Not all patients will require a tissue biopsy (e.g. Lofgren's syndrome). However, in all doubtful cases and in cases in which immunosuppressive treatment is likely to be needed, histologic confirmation in

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KEY POINTS

- Sarcoidosis causing significant symptoms due to involvement of the lung parenchyma, pulmonary vasculature, heart, or neurologic system frequently causes residual organ dysfunction and when progressive can lead to death.
- Patients with critical organ involvement and poor prognostic signs should receive immunosuppressive medications with multidisciplinary assessment and follow-up by physicians skilled in the evaluation and treatment of patients with sarcoidosis.
- High-dose prednisone is initially started to control organ inflammation, tapered to 10 mg daily by 6 months, and continued for at least a year.
- A second immunosuppressive agent, most commonly methotrexate, is added if a patient fails to respond to prednisone or cannot be tapered to a well tolerated dose without a relapse.
- An anti-TNF agent, most commonly infliximab, may effectively control disease progression in patients with critical organ involvement resistant to other immunosuppressive therapies.

Table 2. Recommended initial evaluation of patients with sarcoidosis

1. History (occupational and environmental exposure, symptoms)
2. Physical examination
3. Chest radiograph (and HRCT lung)[a]
4. Pulmonary function tests: spirometry and DL_{CO}; Six minute walk with oximetry
5. Peripheral blood counts: White blood cells, red blood cells, platelets
6. Serum chemistries: calcium, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), creatinine, BUN
7. 25OH vitamin D and 1,25OH vitamin D
8. Urinalysis (and 24 hr urine for creatinine and calcium)[a]
9. Electrocardiogram (and echocardiogram)[a]
10. Ophthalmologic examination (slit lamp, fundoscopic, tonometric)
11. Tuberculin skin test or IGRA

[a]Many experts recommend HRCT scan of lung, 24 h urine calcium, and an echocardiogram as part of the initial evaluation especially in patients with poor prognostic signs.
BUN, blood urea nitrogen; DL_{CO}, diffusing capacity of the lung for CO; HRCT, high-resolution computed tomography; IGRA, interferon gamma release assay.

one organ is mandatory. Clinical criteria for additional organ involvement without the need for more tissue biopsies have been published [5].

Once the diagnosis is established, a comprehensive baseline evaluation is recommended (Table 2); although it may be less extensive in patients presenting with classic Lofgren's syndrome [1]. This evaluation will assess the extent and severity of organ involvement, quality of life, and functional limitations that will be used to determine what treatment, if any, is necessary. Importantly, many sarcoidosis patients (50–60%) will not need immunosuppressive therapy, which should only be used in patients with critical and/or progressive organ involvement or symptoms that significantly affect quality of life.

Table 1. Clinical features of sarcoidosis

Manifestation	Presenting (%)	Cumulative (%)
Respiratory tract	25–50	90–95
Constitutional	25	33–70
Adenopathy	10–20	15–40
Joint disease	1–14	25
Ocular	5	10–20
Hepatosplenomegaly	4	5–20
Cutaneous	3	15–30
Other		
Heart	<1	5–10
Neurologic	<1	5–10
Muscle	<1	1–5
Bone	<1	1–13
Renal	<1	1

NATURAL HISTORY AND PROGNOSTIC SIGNS

The extent of organ involvement in many patients is defined at presentation with fewer than 25% of patients developing new organ involvement within 2 years of follow-up. However, who will progress is difficult to predict in an individual patient [6]. Therefore, during the first 2–3 years after disease onset, a complete review of systems, physical examination, certain tests [chest radiograph, pulmonary function tests (PFTs), calcium levels, or any abnormal baseline test] should be repeated every 3–6 months and others [eye examination, ECG] every 12 months or sooner if symptoms develop. Advanced testing [high-resolution computed tomography (HRCT) scan of chest, MRI, fluorodeoxyglucose-PET (FDG-PET) scan, echocardiogram, and Holter monitoring] are ordered as indicated by symptoms or based on other abnormal tests.

Up to 50–60% of sarcoidosis patients undergo spontaneous remission within 3 years of diagnosis. An additional 10–20% experience resolution with corticosteroid therapy, whereas 10–30% have a

chronic course requiring prolonged therapy. Overall, at least 50% of patients experience some degree of permanent organ dysfunction. Poor prognostic signs include three or more organs involved, black race, disease onset after 40 years of age, symptom duration of longer than 6 months, advanced radiographic stage pulmonary disease, pulmonary hypertension, and extrathoracic involvement (cardiac, neurologic, lupus pernio, panuveitis, hypercalcemia, and bone involvement).

The probability of a spontaneous remission without treatment may be predicted by a patient's initial presentation. Up to 80% of patients with Scadding radiographic stage I pulmonary disease (hilar adenopathy alone) at presentation experience spontaneous resolution. Those with hilar adenopathy as part of Lofgren's syndrome have the best overall prognosis. Up to 60% of patients with radiographic stage II disease (hilar adenopathy with nonfibrotic reticulonodular infiltrates), 10–20% with stage III (nonfibrotic reticulonodular infiltrates only), and 0% with stage IV (end-stage pulmonary fibrosis) experience spontaneous remission. Patients who develop pulmonary hypertension or extrathoracic disease manifestations have a worse overall prognosis and are unlikely to undergo spontaneous remission.

MANAGEMENT

Patients with good prognostic signs and noncritical or limited organ involvement (Lofgren's, radiographic stage I or II pulmonary disease with normal PFTs, mild skin involvement) should be observed for the first 3–6 months without immunosuppressive therapy due to the potential for spontaneous resolution. Patients with progressive disease, critical organ involvement, or symptoms that interfere with quality of life should receive systemic corticosteroid therapy (Table 3). Adjunctive and other immunosuppressive therapies should be used when needed to reduce corticosteroid exposure and side effects [7]. A multidisciplinary approach involving specialists skilled in caring for patients with sarcoidosis affecting organs in their area of expertise is strongly recommended.

Pulmonary disease

Over 90% of sarcoidosis patients develop lung disease, but only half of these patients will require systemic therapy [8▪]. Dyspnea, cough, and chest pain are the most common symptoms. Pulmonary physical examination is normal in over 80% of patients even in those with an abnormal chest radiograph. Patients who are asymptomatic, have a normal or stage I chest radiograph (hilar adenopathy alone), and have normal PFTs should be followed without therapy. For patients with a mild cough, inhaled corticosteroids may be beneficial especially in patients with reactive airways disease. Patients with parenchymal lung disease (radiographic stage II and III) who have dyspnea and/or a progressive decrease in PFTs or worsening chest radiograph need a trial of prednisone (or equivalent) 20–40 mg/day [9]. Expert opinion recommends this dose be continued for at least 3 months with a slow taper to 10 mg/day by 6 months. Patients are then maintained on 10 mg daily for an additional 6 months before a further attempt to taper. Many patients require maintenance corticosteroids because treatment withdrawal is associated with a 30–80% relapse rate.

Table 3. Indications for immunosuppressive therapy in sarcoidosis

Progressive radiographic stage II and III pulmonary disease
Moderate or severe symptoms: cough, dyspnea
Decrease in pulmonary function tests
Decrease FVC > 15%
Decrease TLC > 10%
Decrease DL_{CO} > 20%
Worsening reticulonodular infiltrates on chest radiograph
Cardiac disease
Arrhythmia
Heart failure
Neurologic disease
Ocular pain or loss of vision
Symptomatic hypercalcemia
Nephrocalcinosis
Severe or disfiguring skin lesions (e.g., lupus pernio)
Symptomatic musculoskeletal disease unresponsive to NSAIDs
Significant end-organ dysfunction or failure: hepatic, other
Disabling systemic constitutional symptoms (relative indication)

DL_{CO}, diffusing capacity of the lung for CO; FVC, forced vital capacity; TLC, total lung capacity.

Patients with persistent symptoms, progressive parenchymal lung disease, worsening PFTs, inability to taper prednisone to less than 10 mg daily, and those who experience intolerable steroid side effects are candidates for additional immunosuppressive therapy. Methotrexate has been used most commonly in doses up to 15–20 mg weekly. Azathioprine (2 mg/kg/day), leflunomide (10–20 mg/day), and mycophenolate mofetil (1000–1500 mg BID) have also been used successfully in open-labelled case series. It may take up to 6 months for any of these cytotoxic agents to be effective and only 66% of patients will respond. Some patients require lifelong immunosuppressive medications.

Failure to respond to the combination of prednisone and at least one cytotoxic agent is an indication

for anti-tumor necrosis factor (TNF) therapy. However, patients must first have other causes of dyspnea, such as pulmonary hypertension, heart failure, and end-stage pulmonary fibrosis excluded before starting this treatment. With those ruled out, patients with moderate to severe dyspnea, forced vital capacity (FVC) less than 55%, reticulonodular infiltrates on chest radiograph, and increased uptake in the lungs on FDG-PET scan are the best candidates for an anti-TNF agent, which is usually added to existing therapy. After loading doses (0, 2, 6 weeks), infliximab at a dose of 5 mg/kg every 4–6 weeks appears to be the most effective. It may take 2–6 months to show an effect and this therapy will need to be continued for at least a year or indefinitely because relapses are common (50%) when it is discontinued. Adalimumab may be effective but only if able to be used at high doses (40 mg subq weekly) [10].

Other medications used in open-labelled case series for patients who have refractory disease or are intolerant to or have contraindications to the use of anti-TNF agents include rituximab (1000 mg 2 weeks apart, total two doses) and Acthar gel. Rituximab is an anti-CD20 monoclonal antibody resulting in B cell depletion [11]. Acthar gel is adrenocorticotropic hormone that may have additional immunomodulatory effects by stimulating melanocortin receptors in addition to the adrenal cortex. Overall experience with both these medications in pulmonary sarcoidosis is limited.

Patients with symptomatic parenchymal lung disease who are treated with immunosuppressive medications must be followed every 3 months to evaluate if therapy is effective. A response to therapy is defined as a decrease in symptoms, a reduction in radiographic abnormalities, and physiologic improvement (10–15% increase in FVC and a 20% increase in DL_{CO}). A decrease in lung activity on FDG-PET scan is also objective evidence of a treatment response.

Pulmonary vascular involvement by sarcoidosis causing precapillary pulmonary hypertension has been treated with endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostanoids with or without immunosuppressive medications but response has been variable [12▪▪]. In patients with parenchymal lung disease who fail immunosuppressive therapy and develop end-stage pulmonary fibrotic disease, lung transplantation may be lifesaving, although asymptomatic recurrence of sarcoidosis in the allograft can occur in 50% of patients.

Cardiac disease

Symptomatic cardiac sarcoidosis occurs in 5% of patients and can be the first manifestation of sarcoidosis [13]. Clinically, silent cardiac involvement is present in at least 25% of patients. Clinical features of symptomatic cardiac sarcoidosis include conduction abnormalities, ventricular arrhythmias, sudden death, and heart failure. All sarcoidosis patients should be asked about cardiac symptoms (palpitations, syncope, presyncope, orthopnea) at each visit. All patients should have a baseline ECG and many recommend an echocardiogram. Over 50% of patients with symptomatic cardiac sarcoidosis will have an abnormal ECG and echocardiogram, whereas fewer than 10% with clinically silent cardiac involvement will have an abnormal test. A 24 h Holter monitoring and an exercise ECG should be performed in all patients with cardiac symptoms and/or arrhythmias or conduction disturbances on ECG. Electrophysiologic studies are often done as part of the risk assessment for sudden cardiac death. Advanced cardiac imaging including cardiac MRI with late gadolinium enhancement and fasting cardiac FDG-PET scan have high sensitivity (89–100%) and specificity (78%) for detecting myocardial inflammation [14▪▪]. The presence of increased activity on advanced cardiac imaging portends a worse cardiovascular prognosis [15]. This imaging is not recommended for asymptomatic patients with a normal baseline ECG and echocardiogram. Endomyocardial biopsy is rarely necessary and often negative (80%) due to the heterogeneous nature of cardiac sarcoidosis lesions.

Symptomatic cardiac sarcoidosis due to second degree (Mobitz type II) or third degree atrioventricular heart block, frequent or sustained ventricular arrhythmias, or left ventricular dysfunction who have evidence of myocardial inflammation on advanced cardiac imaging must be treated aggressively with immunosuppressive medications and antiarrhythmic medications (usually beta blockers) when indicated [13,16▪▪]. Patients are initially treated with prednisone (or equivalent) 40–60 mg/day for 2–3 months. A cardiac FDG-PET scan may be performed after 3 months of treatment and if there is no abnormal uptake then prednisone is tapered over the next 3 months to 10–15 mg/day. This dose is continued for another 6 months before further tapering. If the FDG-PET scan at 3 months shows continued abnormal uptake or if the cardiac sarcoidosis relapses during the prednisone taper, a second immunosuppressive agent is added. Methotrexate is most commonly used although azathioprine, cyclophosphamide, and infliximab have also been used with success. In patients with a severe presentation of cardiac sarcoidosis , cyclophosphamide or infliximab may be used early in combination with prednisone. Patients with unexplained syncope/near-syncope, spontaneous or inducible sustained ventricular

arrhythmias, or a left ventricular ejection fraction (LVEF) less than 35–50% despite optimal medical management should be evaluated for an implantable cardioverter-defibrillator to prevent sudden death. Patients with conduction abnormalities and preserved LVEF may be candidates for a pacemaker. Catheter ablation can be useful in patients with ventricular arrhythmias refractory to immunosuppressive drugs and antiarrhythmic therapy. Patients with cardiac sarcoidosis who fail medical management are candidates for heart transplantation.

Patients with symptomatic cardiac sarcoidosis who respond to prednisone alone with no recurrent symptoms, preserved LVEF, no ventricular arrhythmias, and no cardiac uptake on FDG-PET scan may be candidates for tapering off prednisone after 12 months of therapy. They must be followed off therapy every 3–6 months for development of cardiac symptoms. Every 6–12 months for at least 3 years they should also have an ECG and echocardiogram. In patients who relapse, prednisone should be restarted and a second agent (usually methotrexate) added. Patients will then remain indefinitely on the lowest doses of immunosuppressive medications that will prevent relapse of cardiac sarcoidosis. Serial FDG-PET scans may be necessary to document control of myocardial inflammation.

At the present time, there is no consensus on the appropriate treatment, if any, or the prognosis of patients with clinically silent cardiac sarcoidosis. These patients must be followed every 3 months for the development of cardiac symptoms and have an ECG and echocardiogram every 6–12 months. Some physicians may elect to treat asymptomatic patients with immunosuppressive medications who have a baseline abnormal ECG and/or extensive myocardial inflammation evident on advanced cardiac imaging.

Neurologic disease

Sarcoidosis can cause symptomatic involvement of the central (5%) and peripheral nervous systems (10–15%) [17▪▪,18▪]. Up to 33–50% of patients who develop neurosarcoidosis have manifestations either preceding or coincident with the initial diagnosis of sarcoidosis. Neurosarcoidosis most commonly present as an aseptic basilar meningitis or involvement of one or both of the seventh or second cranial nerves. Multiple other neurologic presentations are possible. Brain MRI with gadolinium enhancement is best to document sarcoid involvement and to follow response to therapy. Cerebrospinal fluid (CSF) analysis most commonly shows an elevated protein (70%), lymphocytic pleocytosis (50%), and a high immunoglobulin G index with oligoclonal bands (50%). Brain biopsy is occasionally necessary if sarcoid involvement cannot be documented in other tissues.

Patients presenting with peripheral facial nerve palsy should receive prednisone (or equivalent) 20–40 mg daily for a month with taper over the next 1–6 months and discontinuation if the weakness resolves [19▪]. Patients with isolated aseptic meningitis or a mild peripheral neuropathy may also respond to this abbreviated prednisone regimen. However, patients with moderately disabling neurologic manifestations (cranial nerves II and VIII, mass lesions, hydrocephalus, central nervous system (CNS) parenchymal disease, spinal cord lesions, peripheral neuropathies) should receive prednisone 40–60 mg in divided daily doses, whereas patients with severe neurologic symptoms should receive IV methylprednisolone (1 g daily for 3–5 days) followed by prednisone 60–80 mg in divided daily doses for 4–6 weeks. If the patient improves, the prednisone can be tapered by 5 mg every 2 weeks to 10 mg daily by 6 months. The patient should remain on 10 mg daily for at least another 6 months before any further attempt to taper prednisone.

Patients with moderate to severe neurologic symptoms frequently require a second immunosuppressive agent to facilitate prednisone tapering. Many experts recommend starting a second agent at the same time as the prednisone, whereas others add these drugs only in patients who fail to respond to or relapse as the prednisone is tapered. Methotrexate or azathioprine is added in patients with moderate symptoms. Mycophenolate mofetil has also been used but may be associated with more neurologic relapses compared to methotrexate [20]. Cyclophosphamide or anti-TNF therapy (infliximab 5 mg/kg monthly after loading doses) is used for severe neurologic presentations [21▪,22▪]. The recognized effectiveness of anti-TNF therapy for neurosarcoidosis suggests it should be used as early as possible.

Hydroxychloroquine (or chloroquine) is sometimes added as an adjuvant therapy [23]. Antiepileptics should be used in patients with seizures. CSF diversion for hydrocephalus and surgical debulking of mass lesions may be required. CNS radiation has been used in patients who fail to respond to immunosuppressive medications [24].

CONCLUSION

Patients with sarcoidosis affecting critical major organs with poor prognostic signs need immunosuppressive therapy with corticosteroids and oftentimes with a second immunosuppressive agent. These patients need lifelong follow-up and longitudinal

assessment of their clinical status every 3–6 months. Up to 50% of these patients will relapse as therapy is tapered or discontinued. Many patients with major organ involvement will require lifelong immunosuppression. Therefore, patients must be monitored for adverse effects and prophylactic measures used to prevent medication toxicities, such as *Pneumocystis jiroveci* pneumonia, osteoporosis, and hyperglycemia. Overall 5% of sarcoidosis patients die with half dying from progressive lung disease and the other half dying of cardiac or neurologic complications. Patients with pulmonary fibrosis (radiographic stage IV) and a vital capacity less than 1.5 l have a 25–40% mortality rate. Five-year survival in patients with pulmonary hypertension is only 55% [12▪▪]. Patients with severe left ventricular dysfunction (ejection fraction < 30%) have a 60% 5-year survival rate, whereas those with normal left ventricular function have over a 90% 5-year survival [25▪]. The prognosis for patients with neurosarcoidosis varies depending on the presenting manifestation and treatment response. Retrospective studies report that up to 33% of patients with neurosarcoidosis may stabilize but do not improve on therapy and 5–10% will die [26▪▪,27]. Prospective cohort studies and randomized controlled trials evaluating which patient subsets need early aggressive therapy and how best to follow response to that therapy are urgently needed.

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Conflicts of interest

There are no conflicts of interest.

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Hydroxychloroquine: balancing the need to maintain therapeutic levels with ocular safety: an update

Nada Abdulaziz[a], *Anjali R. Shah*[b], *and William J. McCune*[a]

Purpose of review
Antimalarial drugs including chloroquine, its less toxic quinolone-derivative hydroxychloroquine (HCQ), and quinacrine have become cornerstones in the treatment of autoimmune diseases including systemic lupus, rheumatoid arthritis, sarcoidosis, and Sjogren syndrome; cutaneous disorders, antiphospholipid syndrome, and have recently been employed at higher dioses in oncology. Benefits include anti-inflammatory effects, protection against thrombosis, and improved control of hyperglycemia and hyperlipidemia. In general, both the therapeutic advantages and the toxic effects of the drugs correlate with the dose and the duration of therapy. Here we summarize the current literature regarding the administration and the safety profile of HCQ in management of rheumatologic disease and focus on the most recent revised American Academy of Ophthalmology (AAO) guidelines for prevention and detection of hydroxychloroquine retinopathy to help guide therapeutic decision-making for patients.

Recent findings
The risk of antimalarial-induced retinal toxicity is better predicted by calculating the daily dosage based on 5 mg/kg total body weight rather than 6.5 mg/kg lean body weight and reducing dosage in patients with risk factors such as renal failure. The risk of retinal toxicity after 5 years is substantially increased even when these guidelines are followed; hence dose reduction is appropriate with long-term use. Newer techniques provide improved detection of early signs of retinal damage. These advances are reflected in the revised AAO guidelines 2016, which are in part based on the retrospective study by Melles and Marmor of HCQ toxicity.

Summary
The most important changes in practice guidelines include dose calculation based on total body weight, dose reduction after long-term use, and intensified screening with techniques including optical coherence tomography (OCT) after 5 years.

Keywords
antimalarial, blood levels, hydroxychloroquine, renal insufficiency, retinopathy, spectral domain optical coherence tomography

INTRODUCTION

Administration of quinine for systemic lupus erythematosus (SLE) was described by Payne in the 1894 [1]. Quinacrine was first synthesized in 1931 and chloroquine in 1934. These compounds were used for antimalarial prophylaxis in World War II and it was documented that soldiers suffering from either rashes that were later diagnosed as autoimmune skin disease or inflammatory arthritis improved after taking quinacrine or chloroquine [2]. Hydroxychloroquine was introduced in 1946 [3], and by the 1950s, chloroquine and hydroxychloroquine were widely utilized often at higher doses than currently recommended [4], leading to recognition of multiple adverse effects, particularly retinopathy. Quinacrine but not chloroquine use was notable for the absence of any retinal toxicity in more than two million soldiers in World War II.

CLINICAL USE AND DOSING

The rheumatic diseases for which the 4-aminoquinolines (4AQs), chloroquine and hydroxychloroquine,

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KEY POINTS

- The recommendation for calculation of the initial dose of hydroxychloroquine in individuals with no risk factors has changed from 6.5 mg/kg (ideal body weight) to 5 mg/kg (real body weight).
- Reduce dose after 5 years; exercise additional caution with longer drug administration or high cumulative doses.
- Reduce the initial dose in renal insufficiency, tamoxifen use, retinal/macular disease.
- In low-risk patients, annual exams are recommended by current guidelines only after 5 years of HCQ use including OCT.

and or quinacrine are most frequently prescribed are lupus and rheumatoid arthritis, accounting for more than 80% of treated patients. The daily dose recommendation for HCQ treatment of rheumatic diseases has recently changed from 6.5 mg/kg lean body weight to 5 mg/kg total body weight for patients without additional risk factors [5▪▪], with a maximum of 400 mg during the first 5 years of treatment. 4AQs are also used in dermatology for discoid lupus, cutaneous sarcoidosis, and granuloma annulare, sometimes at higher doses than those used for rheumatic diseases [6]. Antimalarial use in oncology has expanded over the past several years, and much higher doses are often used (800–2000 mg HCQ daily for short courses) [7–8] Interestingly higher initial doses have been associated with more rapid onset of toxic retinopathy, raising concern about use of loading doses in rheumatology and dermatology, which has not been reported to increase the risk of retinopathy [9].

ROLE OF BLOOD VERSUS PLASMA LEVELS?

There is a lack of consensus in studies about the approach used to evaluate drug concentration. The proportion of drug distributed in plasma or serum, whole blood appears to vary considerably with the concentration in plasma being the least, and that in whole blood being the most [9]. The higher concentration in serum as opposed to plasma is attributed to release of the drug contained in platelets into the serum during coagulation. The concentration of HCQ in whole blood is estimated to be almost five-fold higher than in plasma. These variances make determination of therapeutic and toxic levels challenging.

Several studies assessing the role of therapeutic monitoring have suggested positive correlation of achieving therapeutic levels with compliance and to some extent improved control of disease activity [10]. In the French (PLUS) study, dose adjustment to therapeutic level did not correlate with number of flare reductions [11–12]. Cunha *et al.*, in a recent retrospective study of 171 patients with lupus nephritis, proposed that HCQ-level monitoring could identify noncompliance and suggested a minimum target level of at least 0.6 mg/l to reduce renal flare rate [13].

DOSE–RESPONSE AND USE OF LOADING DOSES

HCQ sulfate and chloroquine have bioavailability of approximately 70% and are extensively sequestered in the tissues; deposition may persist for up to 5 years. Steady-state levels, and onset of clinical efficacy are achieved more rapidly with chloroquine (approximately 1 month) than hydroxychloroquine (3–6 months). Delay in achieving steady-state concentrations, and corresponding delay in clinical responses, has led to use of loading doses.

Chasset *et al.* [14] reported that in the patients who had been diagnosed with refractory cutaneous lupus, a progressive increase of the dose of HCQ up to measured concentrations of more than 750 ng/ml was associated with satisfactory responses in 81% of cases, and proposed adjustment of the dose of HCQ in these patients to reach these concentrations to optimize monotherapy to achieve this level, higher doses of hydroxychloroquine were prescribed.

Costedoat-Chalumeau *et al.* randomized 171 stable lupus patients with baseline hydroxychloroquine blood concentration levels ranging from 100 to 750 ng/ml. These patients received either their usual dose or dose adjustment to reach peak HCQ concentrations of more than 1000 ng/ml. After 7 months, they reported that the rate of lupus flares did not significantly diminish in the cohort that received higher doses. However, concentrations of HCQ that were lower at baseline were associated with a more active disease process [11–12].

Furst *et al.* randomized 212 rheumatoid arthritis patients initiating treatment with HCQ to either initially receive loading doses of 1200 or 800 mg/day for the first 6 weeks of treatment or begin treatment with the maintenance dose of 400 mg/day. Improved outcomes with dose-loading were documented at 6 weeks in a group of patients with predominantly seronegative rheumatoid arthritis. There was no dose–response relationship in relation to adverse events. Most dropouts were because of gastrointestinal symptoms. Significant ophthalmologic changes included abnormal color vision and macular abnormalities [9–15].

INCIDENCE AND RISK FACTORS FOR RETINOPATHY WITH HYDROXYCHLOROQUINE AND CHLOROQUINE USE

Chloroquine-induced retinopathy was described in the year 1959 by Hobbs and Calnan [16]. Hydroxychloroquine retinopathy in rheumatic disease patient was reported by Braun-Vallon in 1963 [17]. Older retrospective series, using relatively insensitive diagnostic techniques such as visual field testing and fundoscopy, reported retinal toxicity in 1–3% of HCQ-treated lupus or rheumatoid arthritis patients. Recent advanced diagnostic studies such as multifocal electroretinography (mfERG), optical coherence tomography (OCT), and fundus autofluorescence (FAF) have enabled earlier identification of retinopathy, often before patients experience symptoms, and report higher incidences especially after long-term use [18–19]. Recently, Melles and Marmor in a very influential study reported retinopathy in 7.5% of patients who had used HCQ for at least 5 years [5▪▪].

DOSAGE AND DURATION

A debate addressed by Melles and Marmor concerns the use of ideal versus real body weight to calculate hydroxychloroquine doses. As 4AQs were felt to be poorly absorbed in fatty tissues, previous recommendations suggested calculating dose by ideal body weight, that is, 6.5 mg/kg ideal body weight in patients with normal renal function, to cut down the postulated risk of giving overdoses to patients who are overweight or obese. In Melles and Marmor's series, the risk at a given dose per kilogram was actually more closely correlated with actual weight than ideal weight. Patients at ideal body weight were at more risk of toxicity where the dosage was determined using 6.5 mg/kg ideal weight (as previously recommended). They determined that the prevalence of retinal toxicity in relation to milligrams per kilogram of actual bodyweight was essentially independent of body habitus, whereas the risk happened to be much greater in thin individuals whenever calculated with the ideal body weight, the well tolerated dose during the first 5 years was calculated to be 5 mg/kg total body weight with normal renal function [18] (Fig. 1a and b).

The study also showed that patients who used an average daily dose of more than 5 mg/kg had a heightened risk of retinal toxicity. The toxicity approaches 10% in the first decade and increased significantly to 40% after usage for more than 20 years. However, the annual risk remains less than 1% in the first 10 years for those who use 5 mg/kg or less and rises to about 4% after 20 years [18].

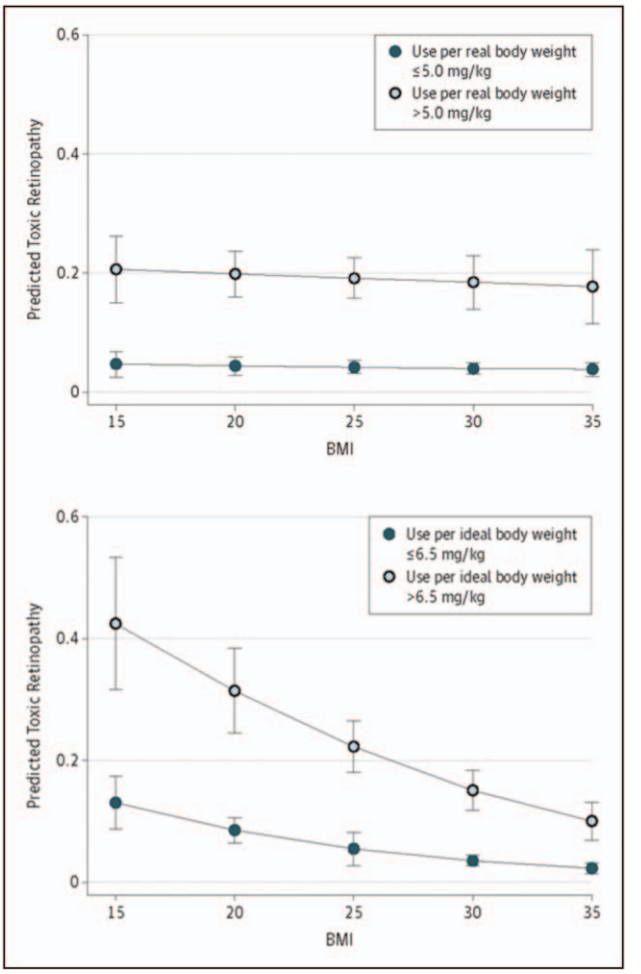

FIGURE 1. (a) Risk versus body habitus based on real body weight (5.0 mg/kg cutoff). (b) Risk of retinopathy versus body habitus based on ideal body weight (6.5 mg/kg cutoff). Effect of body habitus on the rate of retinal toxicity, comparing a daily use cutoff level of 5.0 mg/kg real body weight (a) to a cutoff level of 6.5 mg/kg ideal weight (b). Body habitus is indicated by BMI (calculated as weight in kilograms divided by height in meters squared). The lines show adjusted predictions after logistic regression analysis of BMI and retinal toxicity with 95% CIs [18]. Reproduced with permission from [18]. CIs, confidence intervals.

American Academy of Ophthalmology guidelines in 2011 stated that a cumulative dose of more than 1000 gm increased risk of antimalarial retinopathy, but this was disregarded in recent guidelines because of lack of consistent data [5▪▪,6–19,20▪].

Lyons and Severn in 2007 retrospectively assessed 62 patients who had been referred for evaluation of hydroxychloroquine retinal toxicity. Characteristic mfERG abnormalities in those with cumulative dose of HCQ of more than 1250 g (equivalent to 81/2 years at 400 mg/day) was 41%, versus an incidence of 10% in cumulative doses under 1250 g. The authors proposed that cumulative dose

was more predictive of mfERG abnormalities than daily dose or duration of treatment. It is unclear, however, whether the authors used ideal body weight or actual body weight whenever calculating daily dose [21].

Wolfe *et al*. studied 3995 patients with rheumatoid arthritis or SLE who were current or past users of HCQ. They screened patients with self-reported toxicity. Positive cases were followed by specialists for confirmation and 50.5% of the patients examined annually, whereas 40.4% of the patients examined every 6 months. Results showed definite or probable toxicity in only 0.65% (95% confidence interval 0.31–0.93). The apparent risk of toxicity was lower during the first 7 years of medication use and increased 5-fold after 7 years of usage (or 1000 gm total exposure) [22].

RENAL DISEASE

Hydroxychloroquine and chloroquine are predominantly excreted from the body through the kidney. Renal insufficiency increases the circulating level of these medications and their metabolites, therefore, increasing the risk of toxicity [23]. Patients with renal disease, especially if unstable, may develop unpredictably high levels of the drugs in blood levels. It is, therefore, imperative that the dosage administered, and screening frequency are continuously adjusted to prevent from developing toxicity.

Melles and Marmor calculated the risk of HCQ retinopathy in relation to glomerular filtration rate (GFR) and reported a two-fold increase in the rate of HCQ retinopathy in association with 50% decline in GFR (odds ratio (OR) 2.08). Though HCQ is partially cleared by the liver, no increased risk of toxicity has been noted in patients with liver disease (Fig. 2) [18].

Chloroquine and hydroxychloroquine equilibrium levels have been reported to be 70 and 25–30% higher, respectively, in anuric patient whenever compared with induvial with normal renal clearance [24].

From the PLUS study, multivariate analysis demonstrated lower HCQ blood concentrations in association with higher estimated CrCl ($P < 0.001$). Lupus patients with chronic renal insufficiency (estimated median CrCl ~52 ml/minute) on daily HCQ 400 mg demonstrated significantly higher median blood HCQ than that in the 509 who received similar daily dose. Jallouli *et al*. also evaluated HCQ blood concentrations in three long-term dialysis patients receiving 200–400 mg plaquenil/day at the beginning and end of one dialysis session. Blood HCQ concentrations were measured before and after dialysis and did not change significantly and remained undetectable in all three patients in the dialysis bath [25].

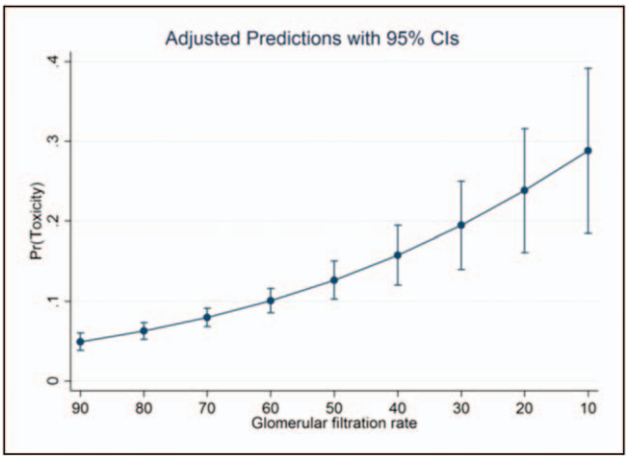

FIGURE 2. Effect of kidney function on the risk of retinal toxicity. Adjusted predictions of toxicity after logistic regression of glomerular filtration rate (GFR), with 95% confidence intervals. The predicted risk of toxicity rises as kidney function decreases [18]. Reproduced with permission from [18].

TAMOXIFEN USE

Tamoxifen is known to cause central retinal changes similar to antimalarials. Combining tamoxifen and hydroxychloroquine can significantly raise the risk of toxicity, reportedly by synergistically altering lysosomal enzyme activity in retinal cells [20▪,21–26]. On the other hand, estrogen analogs such as anastrozole, also used to treat breast cancer, have not demonstrated an association with HCQ toxicity to date [18].

PREEXISTING RETINAL AND MACULAR DISEASE

Revised American Academy of Ophthalmology (AAO) recommendation on screening for HCQ retinopathy 2016 include caution in patients with underlying retinal and macular disease as this may impede proper interpretation of screening tests to detect early toxicity. There is no clear evidence to suggest increased risk of toxicity in these patients, although the consequences of toxicity may be more dire. The frequency of monitoring is determined by the treating ophthalmologist [5▪▪].

OCULAR TOXICITY

The most frequently encountered ocular toxicities of antimalarials affect the cornea and retina. Corneal deposits are more common with chloroquine

than HCQ with use at recommended doses and directly related to higher dosage. Corneal deposits can create halos and cause photosensitivity. They are reportedly reversible upon discontinuation of the medication.

Retinopathy is the most serious ocular complication of therapy with chloroquine and hydroxychloroquine [27] but does not occur with quinacrine. Photoreceptor damage as a result of antimalarial and retinal pigment epithelium (RPE) interaction can lead to permanent vison loss.

Early retinal toxicity is often asymptomatic, with no abnormalities on clinical fundus exam. Visual field and OCT testing may also demonstrate only subtle changes, showing suggestive, but not definitive deficits in visual function. Typical findings include decreased retinal sensitivity in the 2–6° range on visual field testing, and perifoveal thinning of outer retinal layers on OCT. In situations where routine screening tests such as visual fields and OCT are concerning, mfERG – an objective measure of photoreceptor function – should be performed to confirm true toxicity. Characteristic changes on mfERG show depressed photoreceptor function in a ring-shaped pattern around the fovea [28].

Advanced macular disease and retinopathy may cause a 'bull's eye' lesion in the macula resulting from central loss of pigmentation surrounded by a ring of hyperpigmentation [29]. Patients may present with difficulty reading, photophobia, visual field defects within the 2–6° range, and decreased color vision, despite very good central visual acuity. These anatomical changes and their resulting visual function loss are not reversible and may continue to progress after the drug discontinuation.

HCQ toxicity in Asian ancestry population may not present with the classic 'bulls eye' pattern of paracentral visual field defects. Instead, changes in these patients may extend further out into the visual field, necessitating the use of wider range visual field-screening techniques and methods [30▪].

Results of clinical studies do not support the previously held view that HCQ-induced changes differ from chloroquine-induced changes in that they are likely to be reversible whereas changes induced by chloroquine are not. Though reports of reversal of retinopathy when the drug is stopped in very early stages of toxicity exist, large clinical studies do not support reversibility in the majority of patients [31–42].

SCREENING METHODS

Current guidelines from the American Academy of Ophthalmology for screening patients on chloroquine or HCQ favor at least one objective test in addition to visual field testing (subjective test), as current data suggests that subtle defects on central visual field testing can present earlier prior to the evidence of structural changes on other screening modalities [31–32].

Visual field testing is the most sensitive subjective evaluation of HCQ toxicity. Areas of decreased visual sensitivity may be the first evidence of HCQ retinopathy. Visual defects can manifest with paracentral loss in early disease or ring scotoma in advanced disease. As mentioned above, Asian patients may have need wider field visual testing to detect lesions beyond the standard 10° visual field radius. As this test is very dependent on patient reporting, abnormal findings should be confirmed with objective testing methods [33].

Spectral-domain OCT (SD-OCT) is a very widely used objective test that provides cross sectional images of the macula and enables early detection of structural abnormalities-related HCQ toxicity. Typical findings include parafoveal changes and thinning or loss of photoreceptor layers [34]. Wide-field SD-OCT may be necessary for screening in Asians to detect extramacular early changes.

Fundus autofluorescence is an objective test to screen for antimalarial toxicity by imaging the fundus using laser light of 488 nm wavelength to detect lipofuscin autofluorescence and area of dysfunctional changes within the RPE [35].

mfERG was first used in 1999 to detect early HCQ retinopathy before visual field testing showed abnormalities [36]. It is the most sensitive objective screening test [36]. It measures bioelectric signals from photoreceptors to elaborate depressed retinal sensitivity. It is the gold standard to confirm HCQ retinopathy in patients with suspicious findings on other screening exams.

In one study, the sensitivity and specificity of screening tests used to detect presymptomatic disease were examined. Sensitivity of 10–2 HVF, mfERG, and OCT to detected HCQ retinopathy were found to be 85.7, 92.9, and 78.6% respectively, with specificities of 92.5, 86.9, and 98.1%. The negative-predictive values were calculated at 99% for all tests [36].

APPROACH TO ADMINISTERING AND MONITORING ANTIMALARIAL DRUGS BASED ON CURRENT RECOMMENDATIONS

Guidelines for diagnosing and managing HCQ and chloroquine retinal toxicity have changed significantly in the past 30 years. Understanding the evolution of testing informs interpretation of reports of toxicity in different eras. As late as 1978, Dubois

proposed that screening for toxicity should only involve clinical examination and that routine application of visual fields, color vision testing, and a myriad of other different ancillary modalities was not necessary. Subsequent recommendations variously included funduscopic examination, visual field testing and perimetry, usually annually. As recently as 1998, the Royal College of Ophthalmology recommended referral to an ophthalmologist only for patients with a baseline visual impairment or development of blurred vision or reduced acuity during treatment [37].

Beginning in 2003, guidelines began to include the use of sophisticated techniques to detect ocular toxicity, consideration of duration of drug use, and changes in recommendations on initial dosage and dosage with long-term use. The following recommendations are largely based on the current 2011 and revised 2016 American Academy of Ophthalmology recommendations.

Approach to administering antimalarial drugs based on current recommendations:

(1) Calculate initial daily dose based on total (not ideal) body weight: for low-risk users HCQ 5 mg/kg; chloroquine 2.3 mg/kg.
(2) Reduce the initial dose for renal insufficiency, retinal/macular disease, and possibly old age.
(3) Consider reducing baseline dose after 5 years; exercise additional caution with longer drug administration, or high cumulative doses.
(4) Consider substituting quinacrine or combining quinacrine with very low doses of HCQ for long-term use [38].
(5) Exercise extreme caution in combining hydroxychloroquine or chloroquine with tamoxifen.

Approach to monitoring antimalarial drugs based on current recommendations:

(1) Screen within 1 year of starting HCQ/chloroquine with automated visual fields and SD-OCT to exclude preexisting maculopathies and establish baseline testing results.
(2) Other objective tests can be used as needed or if available including mfERG and FAF.
(3) Annual examinations are recommended for patients with high risk: for example, renal disease, tamoxifen use, daily dose greater than 5 mg/kg total body weight, preexisting macular disease.
(4) In low-risk patients, annual exams are recommended by current guidelines only after 5 years of HCQ use. (Further experience with newer and more sensitive modalities for detection of early toxicity will provide additional data to determine whether a full 5-year interval between the first and second examinations for patients without known risk factors is optimal.)
(5) There are no clear guidelines for screening after cessation, but it is deemed appropriate in cases of suspected or confirmed retinal toxicity.

GUIDELINES FOR MONITORING FOR HYDROXYCHLOROQUINE OR CHLOROQUINE TOXICITY

Baseline screening with automated visual fields and SD-OCT should be performed within 1 year of starting HCQ/CQ. In Asian patients, wider field testing should be strongly considered. Other objective tests that can be used include mfERG and FAF. Fundus exam, Amsler grid evaluation, color testing, and fluorescein angiography are not recommended for screening because of lack of sensitivity in detecting subtle early changes. Annual examinations are not recommended until year 5 except in patients with high risk: for example, renal, disease tamoxifen use, daily dose greater than 5 mg/kg total body weight. After 5 years, annual screening is recommended for all patients [5▪▪].

SCREENING AFTER CESSATION

There are no generally accepted guidelines for monitoring after initial diagnosis of retinal toxicity, though continued surveillance is frequently practiced. Michaelides *et al.* [39] monitored 10 patients with retinal toxicity from chloroquine and HCQ. Six patients showed evidence of retinopathy progression; in one case, continued decline in visual function was noted up to 7 years after cessation of HCQ. Ruiz and Saatci [40] recommended follow-up every 9 months after cessation; whereas Easterbrook [41] recommended a follow-up evaluation 3 months after a diagnosis of definite 4AQ retinopathy is made, and then annually [41].

CONCLUSION

Current guidelines importantly recommend maximum initial daily HCQ dosage of 5 mg/kg or less calculated on the basis of actual (not ideal) body weight, (with a maximum initial dose of 400 mg in most patients) and dose reduction after long-term use or achieving high cumulative dosage. Use of quinacrine in addition to a very low dose of HCQ with very long-term use has been suggested. We are unable to identify evidence-based guidelines for HCQ-dose adjustment in renal insufficiency. We suggest that dose adjustment be considered

whenever the eGFR is less than 50% and using great caution whenever administering HCQ to dialysis patients. There are no evidence-based guidelines for well tolerated antimalarial use in patients using tamoxifen, which can add substantially to the risk of developing retinal toxicity. Similarly, there are no guidelines for dose adjustment in the frail or elderly, or patients with preexisting macular disease, all of whom may be at increased risk.

Newer methods of surveillance allow for earlier detection of maculopathy will be invaluable in facilitating safe use of these compounds.

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Conflicts of interest

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Emergence and treatment of chikungunya arthritis

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Purpose of review
To review the emergence, clinical features, pathogenesis, and treatment of acute chikungunya (CHIK) fever and chronic CHIK arthritis.

Recent findings
Since 2004, CHIK, an arboviral infection, has spread throughout the world, infecting millions of people. The illness occurs in two phases: an acute viremic infection followed by chronic arthritis. In less developed countries, there are limited resources and effective treatment. For acutely ill CHIK fever patients, management is symptomatic. The treatment of chronic CHIK arthritis should be determined by an understanding of pathogenesis. Is chronic CHIK arthritis a persistent viral infection or a postinfectious inflammatory process? Multiple proinflammatory cytokines, chemokines, and growth factors have been identified in chronic CHIK arthritis. Attempts to isolate CHIK virus from synovial fluid have been unsuccessful. Given pathogenetic similarities (as well as differences) compared with rheumatoid arthritis and the painful, disabling nature of the arthritis, it is not surprising that disease-modifying antirheumatic drugs such as methotrexate have begun to be used.

Summary
CHIK infection has emerged with major arthritic epidemics for which evidence-based therapy is limited. But there is an opportunity to improve the treatment of chronic CHIK arthritis and, from this disease, to gain understanding of the pathogenesis and treatment of inflammatory arthritis more generally.

Keywords
chikungunya fever, chikungunya virus, chronic postchikungunya arthritis, methotrexate, postviral inflammatory arthritis

INTRODUCTION

Chikungunya (CHIK) fever (CHIKF), caused by the CHIK virus (CHIKV), is a rapidly emerging, global pandemic. CHIKV is a single-stranded RNA virus of the Togaviridae family that includes arthritogenic alphaviruses such as the Ross River Virus and neuropathic viruses such as Western equine encephalitis virus [1]. Since 2004, the emergence of CHIKF has resulted from the global spread of two mosquito vectors, *Aedes aegypti* and *Aedes albopictus,* that carry CHIKV, migrating from Africa and Asia to cause disease throughout Africa, Asia, Oceania, Europe, and the Americas – with millions of cases reported [2].

Vector spread throughout tropical and subtropical regions has been possible because of rapidly expanding urban populations, limited vector control, globalization promoting human migration, climate change, and increased environmental disasters (i.e., flooding) [3]. Almost all cases are arthropod-borne, but intrapartum maternal–fetal transmission and transmission via blood products and organ transplantation have occurred [4].

To date, over 45 countries have reported CHIKV outbreaks, including travel associated cases in 46 of the United States and locally acquired cases in Florida [5]. Phylogenetic studies demonstrate three distinct CHIKV Genotypes: East/Central/South Africa that has spread throughout Africa/Asia/Europe, Asian genotype that spread to the Americas in 2013, and the ancestral West African genotype [2]. CHIKF is causing epidemics of acute illness followed by persistent disabling arthritis. This review will examine the clinical manifestations, pathogenesis, and treatment of both early and late stage disease.

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KEY POINTS

- CHIK, like dengue virus or Zika virus infection, is an emerging arboviral infection, transmitted by *Aedes* mosquitoes, causing explosive epidemics.
- CHIK causes a biphasic illness, acute viremic infection followed in many patients by chronic inflammatory arthritis.
- Because CHIK causes chronic, painful inflammatory arthritis in some patients and because chronic CHIK arthritis may be a postinfectious inflammatory arthritis with parallels to rheumatoid arthritis, disease-modifying drugs, such as methotrexate, are being evaluated.

CLINICAL FEATURES

Early disease

Following exposure to CHIKV, up to 95% of infected individuals develop acute symptoms 2–6 days after an infecting mosquito bite [6]. After this incubation, CHIKF begins abruptly with high fever, polyarthalgia, myalgia, rash (often maculopapular), headache, and back pain [7]. CHIKF is often similar to dengue viral infection. Both diseases present with fever and myalgia and are transmitted by the same mosquito vectors. Generally, however, arthralgias are more prominent in CHIKF and hemorrhage, when present, is a feature of dengue viral infection [7]. Other acute symptoms of CHIKF include intense fatigue, anorexia, nausea, vomiting, and diarrhea [6]. Viremia lasts 5–10 days and can be followed by a 6–21-day post-viremic phase with pyrexia, polyarthrlagia/arthritis, lymphadenopathy, fatigue, and anorexia [8,9]. Arthralgias are often symmetrical, affecting ankles, wrists, hands, elbows, shoulders, knees, and feet [10–12]. Joint pain is more distal than proximal, although axial skeleton involvement is noted in up to half of cases. Synovitis is seen in ankles, hands, wrists, toes, and less commonly, in larger joints. Atypical joint involvement includes the spine, temporomandibular, or sternoclavicular joints. There may be ligamental pain causing pubalgia, talalgia and myalgias in the arms, thighs, and calves without objective evidence of myositis [13,14].

In addition, many CHIKF patients have dermatologic manifestations. The most common rash is generalized, maculopapular and often pruritic, but nodular, vesicular, bullous, and desquamative skin lesions occur, as well as vasculitic and apthous lesions [7,15–17]. Additional skin manifestations include hypermelanosis, hyperpigmentation, photosensitivity, exfoliative dermatitis, and erythema nodosum like lesions. Patients with preexisting skin disease such as psoriasis may have exacerbations. CHIKF skin lesions affect the extremities, trunk, and face, and tend to be transient, resolving after 2–5 days [14,18].

More severely affected acute CHIKF patients have other extra-articular manifestations. Neurologic complications include encephalitis, facial paralysis, sensorineural deafness, and Guillen–Barre syndrome [19]. Ocular manifestations, including optic neuritis, uveitis, retinitis, and conjunctivitis, are also described [20]. A small number of patients have myocarditis, cardiac arrhythmias, sepsis, and septic shock [21]. During widespread CHIKF epidemics, excess mortality has been reported, primarily in newborns and the elderly [22].

Both nonspecific and specific laboratory abnormalities occur with CHIKF. During acute illness, transient leukopenia and lymphopenia, mild thrombocytopenia, elevated inflammatory markers, and abnormal liver function tests are observed [7]. More specific diagnostic tests are also available. During the viremic phase, CHIKV is detectable by viral culture and reverse transcriptase PCR [1,23]. After about 5 days of illness, following viremia, CHIKF can be diagnosed serologically, by ELISA, or by immunofluorescence [6,24].

Late disease

To describe painful arthritis, the word 'Chikungunya' means 'that which bends up' in the Tanzanian dialect [25]. The transition from acute CHIKF to chronic CHIK arthritis is variable. Some patients have continuous symptoms, whereas others experience a biphasic illness, acute disease followed by transient remission, and then persistent arthritis [26]. Chronic CHIKV symptoms include arthralgia, arthritis, and edema involving hands, wrists, ankles, and knees, typically in a symmetrical pattern [27,28]. In a Colombian study of 152 patients evaluated 26 weeks after onset of CHIKF, morning stiffness (53.7%), joint edema (49.5%), and polyarthralgia and morning stiffness concurrently (38.2%) were the main arthritic symptoms. Overall, 53.7% of the patients had persistent rheumatologic symptoms at 6 months [26]. Among 88 patients in the US Virgin Islands, chronic arthritis was reported in 93, 57, 47% at 3, 15, 24 months, respectively [29]. Other studies report a 4–82% incidence of persistent, unremitting joint symptoms, ranging from months to years [10,30,31].

To better define the risk of chronic arthritis, a systematic review evaluated 5700 CHIKF patients and found that 25–35% progressed to chronic joint symptoms, with 50% developing inflammatory arthritis characterized as rheumatoid arthritis

(RA), postviral polyarthritis, or seronegative spondylitis [32]. To characterize clinical patterns of arthritis, Javelle *et al.* [33] evaluated 159 individuals and found that 112 with CHIKV arthritis for at least 2 years had chronic inflammatory rheumatism; 33 patients fulfilled criteria for spondyloarthritis, 40 for RA, and 21 for undifferentiated polyarthritis.

In addition to arthritis, a variety of extra-articular manifestations occur with chronic CHIK. In one cohort, new-onset Raynaud's phenomenon developed in the second or third month in 20% of patients [31]. In another report, neurological symptoms including neuropathic pain syndromes, cerebral disorders, sensorineural impairment, and paresthesia's were reported, as well as depression [10]. Also present were carpal/tarsal/cubital tunnel syndromes, bursitis, tenosynovitis, and frank synovitis. Some patients had digestive disorders. Considering the large numbers of individuals affected, these widespread and severe symptoms underscore the severity of pain and disability presented by chronic CHIKV infection [14].

PATHOGENESIS

Early disease

During acute CHIKF, a high viral load develops quickly with viral replication in musculoskeletal tissues, particularly tissue fibroblasts, epithelial cells, endothelial cells and macrophages [34]. Viremia promotes a robust immune response dominated by plasmacytoid dendritic cells, monocytes and lymphocytes and a rapid rise in plasma levels of IFN-α and IFN-γ. Control of viremia is IFN-α dependent and rising IFN-α levels coincide with onset of symptoms [10,35]. Several animal studies demonstrate that CHIK infection is lethal in type 1 interferon deficient mice and that mice lacking IFN-α/β have severe arthritic symptoms [36,37]. Similarly, a strong interferon response correlates with milder disease in alphavirus infected mice [38]. In acutely infected patients, elevated viral load and defective interferon type 1 signaling also correlate with disease severity and symptoms [36]. To promote viral replication and signaling, alphaviruses have developed mechanisms to inhibit host interferon induction [39].

A complex array of other proinflammatory/anti-inflammatory cytokines, chemokines, and growth factors are involved in monocyte trafficking and activation of natural killer (NK)/T cells in early CHIKF [40]. Elevated levels of IL-1Ra, IL-6, IL-8, IL-10, IL-13, IL-16, IP-10, MCP-1, MIP1Beta, CCL2, migration inhibition factor, CCL4, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor (GM-CSF), and vascular endothelial growth factor have all been reported [24,41,42,43▪].

Transition from early to late disease

As patients with CHIKF transition from acute to chronic disease, typically between 4 weeks and 3 months after infection, proinflammatory cytokines such as IL-6 and IL-17 persist, as do increased serum concentrations of the growth factor GM-CSF [35]. The mechanism of progression from acute infection to persistent arthritis is uncertain, but could include macrophage virus tropism, local viral persistence, or unabated inflammatory responses [14]. However, attempts to recover CHIKV from synovial fluid have been unsuccessful, suggesting that the pathogenesis of chronic CHIK arthritis may be a postinfectious, inflammatory process [44▪▪]. CHIKV RNA has also not been found in synovium during chronic disease [44▪▪,45,46].

Molecular mimicry is a possible mechanism for chronic CHIK arthritis, but no specific autoantigen has been described [47▪]. In both mice and human models, CD4+ T cells and improperly functioning NK cells have been linked to chronic arthritis [40,48]. It is postulated that myeloid cells, including cellular debris-clearing macrophages, may act as a source of pathogen-associated molecular patterns that generate chronic inflammation [43▪]. These several lines of evidence suggest that progression from acute infection to chronic CHIKV arthritis could result from a postinfectious, inflammatory host response that resembles other auto-immune, inflammatory rheumatic diseases.

Late disease

In addition to the failure to demonstrate CHIKV in synovial fluid in chronic CHIK arthritis patients, the cytokine profile in chronic infection mimics the cytokines seen in RA, including IFN-α, IL-1β, IL-5, IL-6, IL-10, IL-7, IL-15, and TNF-α [49]. Despite these similarities, 95.8% of CHIKV arthritis patients are rheumatoid factor and anticitrulline antibody negative [50].

IL-17 may drive chronic CHIK inflammation, inciting extracellular matrix/bone destruction through stimulation of IL-6, tumor necrosis factor, IL-1, matrix metalloproteinases proteinases, and the receptor activator of nuclear factor kB-receptor activator of nuclear factor kB ligand (RANKL) system [51]. As in RA, IL-6 participates in chronic CHIKV arthritis, in part by stimulating RANKL and inhibiting osteoprotegerin released by osteoblasts. In mouse models of chronic CHIK arthritis,

osteoclastogenesis and substantial bone loss occur via this pathway [52–55]. Elevated levels of IL-1β and IL-6 along with decreased regulated on activation, normal T cell expressed and secreted correlate with more severe disease, whereas increased IL-1 and IL-8 coincide with more destructive arthritis demonstrating the complex, concerted interaction of multiple proinflammatory factors [46,50].

TREATMENT

None of the treatments to be discussed have been approved by the Food and Drug Administration or other regulatory authority.

Prevention

Vector control strategies of *Aedes* mosquitoes have been used, particularly in affluent countries with temperate climates, but have had limited success in India, Africa, and other major reservoirs of disease [56]. Alphavirus vaccines, including an effective CHIKV vaccine, are technically achievable, but have not yet found a viable commercial market. This limitation is changing as a result of the spread of the CHIK pandemic, tourism, and the needs of the military [57]. Vaccines have reached human trials and may have a preventive impact in the future [58].

Early disease

A variety of antiviral strategies are under investigation in the treatment of CHIKF and other alphavirus infections, but none, including chloroquine, acyclovir, ribavirin, IFN-α, corticosteroids, and newer agents, including favipiravir, the trypanosomiasis drug suramin, and the turmeric-derived compound curcumin have been validated [59▪,60–64]. At the present time, early treatment is supportive care, including rest, adequate hydration, antipyretics, and analgesics [65]. Severely ill and frail patients may need to be hospitalized for intravenous fluids and monitoring of electrolyte imbalances, organ dysfunction, pain, and fever. As corticosteroids are immunosuppressive, NSAIDs have been recommended for early treatment of joint symptoms [1,9], but concern exists that aspirin or NSAIDs should be used cautiously if there is possible dengue coinfection given the potential for hemorrhagic complications [6]. Thus, in acute infection, acetaminophen, tramadol, codeine, or oxycodone are preferred [66]. Maintaining mobility is important.

Following acute infection, some patients experience postacute (week 4 to month 3) symptoms of tendinitis, arthritis, and arthralgias. Treatment includes NSAIDs, corticosteroids for severe arthritic manifestations, and gabapentin and pregabalin for neuropathic pain control [9]. Acute symptoms often resolve within weeks, but some patients remain symptomatic with joint pain and depression [33].

Late disease

Chronic CHIKV arthritis causes joint damage and impacts quality of life as severely as RA [46]. The goals of treatment of chronic CHIK arthritis include pain relief and preventing joint destruction. This phase of the illness is increasingly referred to as post-CHIK chronic inflammatory rheumatism (pCHIK-CIR) [29,33]. Treatment options for pCHIK-CIR include NSAIDs, corticosteroids, hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide, methotrexate (MTX), and biologics [33] (Table 1).

NSAIDs and corticosteroids

Corticosteroids improved tenosynovitis, polyarthritis, and ability to ambulate in patients treated months after acute illness [31]. In 147 patients with pCHIK-CIR, there was better symptomatic improvement with corticosteroids compared with NSAIDs and acetaminophen [67]. Padmakumar *et al.* [68] demonstrated that an NSAID (aceclofenac 200 mg/day) in combination with corticosteroids (prednisolone 10 mg/day) improved quality of life and reduced pain more than NSAID monotherapy or combination NSAID/HCQ (400 mg/day) therapy. No benefit was achieved with the addition of HCQ.

Hydroxychloroquine and chloroquine

Antimalarial therapy has not been demonstrated to be effective in pCHIK-CIR. Sebastian *et al.* [69] found no reduction in joint pain comparing chloroquine with placebo. Other studies demonstrated no difference in the duration of arthralgia or viremia with chloroquine vs. placebo [70]. Chloroquine was not superior to meloxicam in controlling chronic arthritis pain in 70 pCHIK-CIR patients [8,71].

Methotrexate

If chronic CHIKV arthritis may be a postinfectious, inflammatory arthritis, MTX therapy should be considered [72]. MTX increases adenosine and inhibits proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α [73]. These cytokines, especially IL-1, IL-6, IL-17, have been associated with greater disease severity in both RA and chronic CHIKV arthritis [49,51]. There is no prospective, placebo controlled trial evaluating the efficacy and safety of MTX monotherapy in the treatment of chronic CHIK arthritis [74]. We believe that such a study is warranted and have had success treating individual

Table 1. Rheumatic disease treatment in chronic chikungunya arthritis

Drug	Type of study	Number of patients	Outcome measure	Evidence of efficacy	Reference, country
NSAIDs/ Corticosteroids/ Hydroxychloroquine	Prospective Randomized Parallel Group Study	120	VAS ADL IADL	Group C [aceclofenac (200 mg/day) + prednisone (10 mg/day)] & Group D [aceclofenac (200 mg/day) + prednisone (10 mg/day) + HCQ (400 mg/day)] showed statistically significant improvements in VAS/ADL/IADL compared to Group A (aceclofenac alone) & Group B (aceclofenac + HCQ)	Padmakumar *et al.* [68], India
Hydroxychloroquine	Double-blinded, placebo controlled, randomized trail	54	Viremia; Duration of febrile arthralgia	HCQ group (600 mg Day 1 → 300-mg BID Days 2/3 → 300-mg QD) showed no significant difference between placebo group in terms of duration of febrile arthralgia or decrease of viremia between days 1 and 3. At Day 200, patients who received chloroquine treatment complained of arthralgia more frequently than those who received placebo (*P* 0.01)	De Lamballerie *et al.* [70], French Reunion Island
Chloroquine/Meloxicam	24-week, 2-arm, parallel efficacy trial	70	VAS; Cytokine levels	Although both groups showed clinical improvements, no significant difference found between the chloroquine (250 mg/day) and meloxicam (7.5 mg/day) in terms of VAS and inflammatory cytokine levels. No advantage of chloroquine over meloxicam to treat early musculoskeletal pain and arthritis following acute CHIK virus infection. Therapeutic efficacy of chloroquine was not ruled out	Chopra *et al.* [71], India
Methotrexate/ sulfasalazine/ Hydroxychloroquine	24-week prospective, randomized parallel group open-label study	72	DAS28-ESR; EULAR good response; HAQ; pain VAS	Patients with persistent CHIKF arthritis received either triple combination therapy (MTX 15 mg/week, SSZ 1 g/day, HCQ 400 mg/day) vs. monotherapy with HCQ 400 mg/day. At 24 weeks, combination therapy group showed significant improvement in both DAS28-ESR and HAQ. At study end pain VAS was significantly less in combination therapy group	Ravindran and Alias [75▪▪], India
Methotrexate/ sulfasalazine/ Hydroxychloroquine	Prospective	16	TJC; SJC; ESR; DAS28; HAQ	All patients given NSAIDs (Etoricoxib 90 mg/day) for 2 weeks and 2–4 weeks of steroid (prednisolone 5–10 mg/day). Patients then given sulfasalazine 1–2 g/day with HCQ 200 mg/day and subsequently methotrexate added to those having poor to moderate response after 3 months. Treatment with sulfasalazine with and without methotrexate produced good response in 71.4 and 12.5%, respectively	Ganu and Ganu [76], India
Methotrexate	Retrospective	159	MTX treatment considered successful if there was no need for dose escalation or additional drug therapy	MTX 15 mg/week was clinically effective in 54 of the 72 patients (75%) with efficacy of 67% in rheumatoid arthritis patients, 80% in spondyloarthritis, 100% in undifferentiated polyarthritis	Javelle *et al.* [33], French Reunion Island

ADL, activities of daily living; BID, twice daily; CHIK, chikungunya; CHIKF, chikungunya fever; DAS28-ESR, disease activity score 28-joint count erythrocyte sedimentation rate; EULAR-European League Against Rheumatism; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; IADL, Instrumental activities of daily living; MTX, methotrexate; QD, once daily; SJC, Swollen joint count; SSZ, sulfasalazine; TJC, tender joint count; VAS, visual analogue scale.

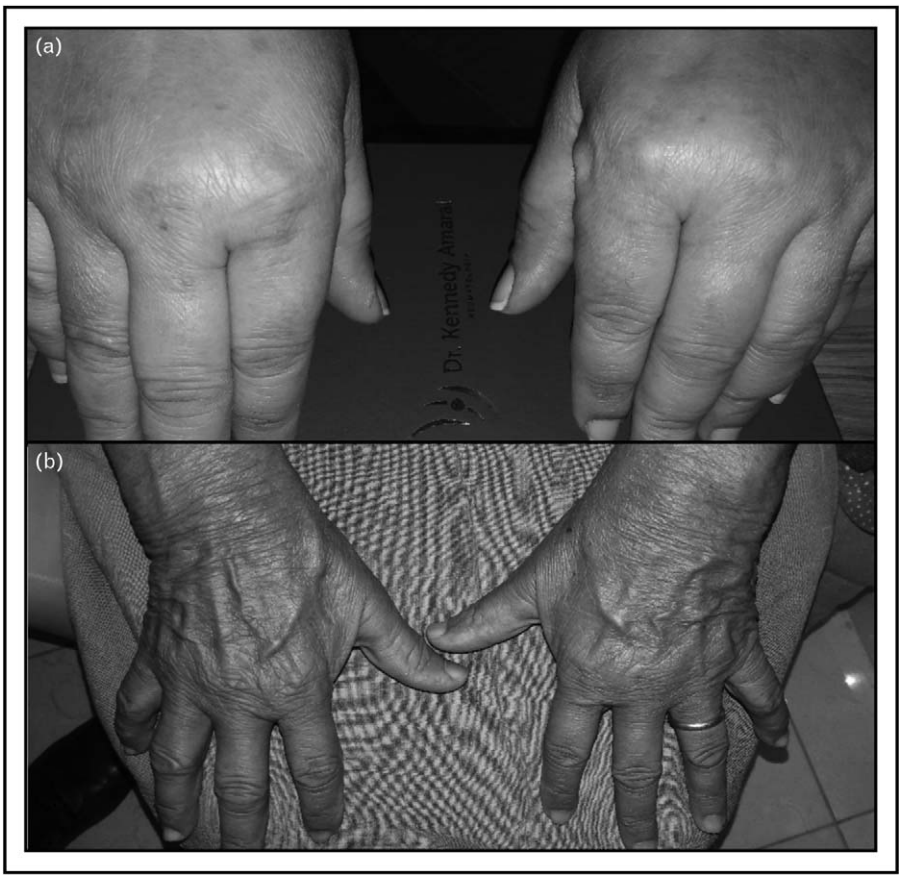

FIGURE 1. A patient with chronic chikungunya arthritis. (a) Before methotrexate treatment. (b) Following methotrexate 7.5 mg/week for 4 weeks.

chronic CHIK arthritis patients with MTX (Fig. 1). In the best available CHIK arthritis MTX study, Ravindran and Alias [75▪▪] demonstrated superiority of triple therapy (MTX 15 mg/week, HCQ 400 mg/day, and SSZ 1 g/day) compared with HCQ monotherapy (DAS28-ESR < 3.2 at 24 weeks, 84 vs. 14%, respectively, *P* value <0001) (Fig. 2).

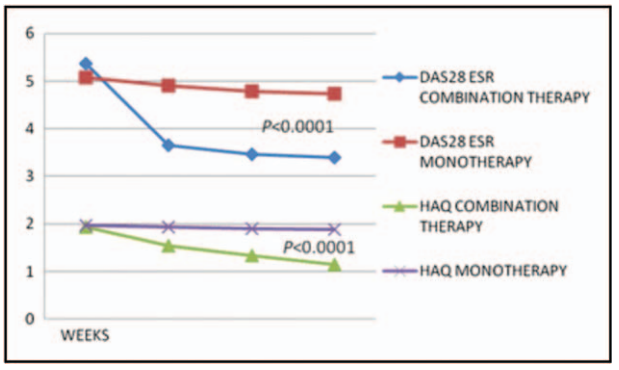

FIGURE 2. Triple therapy including methotrexate is superior to hydroxychloroquine. Disease activity and disability at weeks 8th, 16th, and 24th. DAS, disease activity score; HAQ, Health Assessment Questionnaire in Combination therapy with methotrexate, sulfasalazine, hydroxychloroquine vs. monotherapy with hydroxychloroquine. Reproduced from [75▪▪].

Other uncontrolled studies support the use of MTX in chronic CHIK arthritis. Ganu and Ganu [76] found that adding MTX to SSZ and HCQ in non-responders after 3 months resulted in significantly better clinical responses. Javelle *et al.* [33] noted 'good therapeutic response' in 75% of the 72 patients treated with MTX 15 mg/weekly with pCHIK-CIR who met criteria for RA, spondyloarthropathy, or undifferentiated polyarthritis.

Biologic therapy

There is limited information regarding use of biologic therapies in pCHIK-CIR. In a murine model, anti-TNF-α therapy with etanercept exacerbated tissue damage in mice with alphaviral arthritis [77]. During the CHIK outbreak on Reunion Island, however, 12 patients with chronic CHIK arthritis who escalated to treatment with antitumor necrosis factor therapy after MTX failure showed 'beneficial effect' [33]. Significantly, another report from the Dominican Republic indicated that 53 of 328 RA

patients developed CHIKV arthritis while on prior biologic therapy, suggesting that biologic therapy does not protect against CHIK arthritis [78]. In a murine model, the CD4+ T-cell suppressive drug fingolimod was joint protective [79]. Also in a mouse model, Miner *et al.* [80] showed benefit for the CTLA-4 fusion protein, abatacept, used in the treatment of RA, when combined with anti-CHIKV neutralizing antibodies.

CONCLUSION

In just 10 years, CHIKF has become a global disease affecting millions of people. Attempts to limit the *Aedes* mosquito vectors or to prevent the disease through vaccination may have a future impact on this disease. In the meantime, primary care physicians practicing in CHIK endemic areas, treat acute disease symptomatically as we have outlined in this review.

For the rheumatologist, treating patients with chronic CHIK arthritis, a central question about pathogenesis will determine how the disease should be managed. CHIKF begins as an alphavirus infection. Evidence, by no means certain, suggests that in the progression of acute illness to chronic arthritis, the infection may become a postinfectious inflammatory arthritis. This may provide treatment options beyond supportive management with disease-modifying drugs such as MTX. But before confident recommendations can be made, there is a need for more research both on the pathogenesis of CHIK arthritis and on randomized controlled trials evaluating therapy.

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Getting personal: towards individualized management of rheumatoid arthritis

Jon T. Giles

I am certain that I am not alone in using the term 'toolbox' to explain the treatment options available to the patients with rheumatoid arthritis that I see in my practice. I use this analogy to conjure up a box filled with different treatment options that will 'fix' their symptoms. If one tool does not work to our satisfaction, there is surely another in that box that will, even if it may take several tries. However, this is not how tools in a toolbox are used in real-life. To loosen a screw, one does not reach in for the 'standard starting tool' and then try another only if that tool fails to work. In real life, one first analyses the characteristics of the screw to be loosened and then selects the most appropriate screwdriver to fit the task. Even after selecting the right tool, there may still be barriers to effective loosening. The screw head may be worn or the screw tightly embedded, requiring adapting how the same tool is being used (i.e. more force), augmenting the tool with another tool, or changing to an entirely different tool. Even after this, some screws remain stubborn and beyond the ability of the best tools to remove them. This analogy is a good fit for the concept of truly personalized management of rheumatoid arthritis. Ideally, we would have a data-driven approach at all stages of therapy to guide decisions based on the treatment that will best suit my patient, both in maximizing efficacy and safety, based on their individual characteristics; clinical features that will allow me to adapt management after treatment has begun; and, finally, inform me whenever optimal management has been reached. In this section of *Current Opinion in Rheumatology*, each of the reviews addresses an aspect of these questions.

The first three reviews in this edition address differing aspects of adapting and optimizing rheumatoid arthritis management. Whenever patients do not achieve efficacy targets with a biologic, we do not currently know if the failure is because of not achieving adequate levels of the drug or, in the case of loss of response, whether antidrug antibodies have developed. Measuring both drug levels and antidrug antibodies to guide therapeutic decision-making [i.e. therapeutic drug monitoring (TDM)] is commonplace in inflammatory bowel disease (IBD) management, and the recent American Gastroenterological Association Institute Guideline [1] advocates the use of drug levels and antidrug antibody testing to guide treatment changes for IBD patients with active disease despite treatment with a tumor necrosis factor (TNF) inhibitor. There has been great enthusiasm for using a similar approach in the use of biologics in rheumatoid arthritis management. Despite this enthusiasm, as den Broeder *et al.* (pp. 266–275) carefully summarize in their review, there is a lack of strong evidence for TDM in rheumatoid arthritis. The authors point out that this lack of evidence may be related to deficiencies in study design, leaving the possibility for scenarios in which TDM in rheumatoid arthritis may have clinical utility, as with IBD. However, even the American Gastroenterological Association (AGA) guideline developers make their recommendation conditionally, acknowledging very low-quality evidence. Thus, the search for an external data source to guide management continues.

One possible source could derive from tracking patient-generated data between office visits. Office follow-up visits tend to be brief, occur relatively infrequent, and may not capture patients at times when their disease is at its most active. Moreover, they may focus more on the tangible aspects of a patient's disease (e.g. quantifying joint swelling) with less emphasis on the less tangible aspects (e.g. fatigue). Using technology, such as mobile phone apps or wearable trackers, is an intriguing way to collect such data. However, as argued by Dixon and Michaud (pp. 276–281) in their review, what data to collect, optimal ways to collect it, and how to efficiently integrate it into clinical practice

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in a way that adds value to care have yet to be established. One certainty is that with advancing technology, and the desire of providers and patients to have the electronic health record function as a dynamic interface that enhances the provision of care, additions that allow providers to objectively measure the day-to-day experience of their patients in a way that allows them to tailor care will be a welcome addition to rheumatoid arthritis management.

Tools that support accelerating care for patients with active rheumatoid arthritis tend to be the focus of most management initiatives, but how do we know when management has been optimized? The law of diminishing returns asserts that greater and greater efforts are typically required to achieve smaller incremental gains. Clearly, treating a rheumatoid arthritis patient from high-disease to low-disease activity has large benefits on symptoms, function, and quality of life. But, how much additional benefit is gained in taking a patient from low-disease activity to remission, particularly when the offset may require shifting from a disease-modifying antirheumatic drug (DMARD) felt effective and tolerated to one of uncertain efficacy or tolerability, or adding on DMARDs that may add burden in their administration, safety concerns, lifestyle restrictions (i.e. alcohol, travelling with refrigerated medications, etc.), and additional monitoring requirements? As reviewed succinctly by Bergstra and Allaart (pp. 282–287) in this issue, it still remains uncertain where the optimal goal posts for the finish line should be set.

Embracing an aggressive treat-to-target approach in order to achieve this hoped for sustained meaningful clinical response requires access to the entirety of the therapeutic toolbox. However, since the beginning of the biologic era, the looming specter of malignancy accompanying the use of biologics has led to the exclusion of biologics from most patients with prior malignancy. Having the word 'tumor' in the name of an entire class of biologics has raised a justifiable concern that biologic therapy, and TNF inhibitor therapy in particular, may impair an assumed important regulator of tumorogenesis, especially among those with prior malignancies. In their review, Strangfeld and Regierer (pp. 288–294) comprehensively summarize the current observational experience of biologic use in those with prior malignancy, including what is known for specific forms of malignancy. Although certainty in the area is not yet established, there are differing treatment recommendations in national and international guidelines for rheumatoid arthritis patients with prior malignancy, particularly in the recommendation of rituximab use for those with prior malignancy, to which the authors are justifiably critical.

Finally, the ability to optimize our therapeutic choices based on the key pathologic specificities of an individual's immune system also requires a deeper understanding of how our pharmacotherapies affect the immune system in both their 'on-target' and 'off-target' effects. In particular, whereas the therapeutic efficacy of abatacept is primarily felt to act through its ability to reduce the activation of T cells, it has been shown to have a host of effects on other cells, such a T-regulatory cells, monocytes, macrophages, and B cells. As pointed out by Bonelli and Scheinecker (pp. 295–300), any of these may enhance or detract from the efficacy of the drug in ways that are currently not well delineated. In particular, interindividual differences in these 'off-target' effects may account for the success or failure of the drug between two otherwise similar rheumatoid arthritis patients.

What does the future hold for my rheumatoid arthritis toolbox? The addition of more tools is certain based on the current robust development pipeline. However, with just the currently available tools in place, continued optimization of the care of rheumatoid arthritis patients can be expected with the development and implementation of strategies to match therapies to patients individualized based on not only their immune system, but their beliefs, lifestyle, and comorbidity profile.

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Therapeutic drug monitoring of biologicals in rheumatoid arthritis: a disconnect between beliefs and facts

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Purpose of review
To give an overview of recently published articles covering therapeutic drug monitoring (TDM) of biological DMARDs (bDMARDs) in rheumatoid arthritis.

Recent findings
In the last 18 months, two clinical studies and nine reviews were found after a systematic literature search. Most (narrative) reviews conclude that TDM should be used to improve biological treatment in rheumatoid arthritis patients, whereas most of the clinical studies (including 13 studies identified earlier) whenever scrutinized do not support this conclusion. This disconnect between sobering data from prediction studies and test-treatment diagnostic studies and optimistic TDM beliefs in reviews is caused by failure to recognize incorrect study designs, false positives because of lack of validation after explorative multiple testing, cherry picking of studies, and incorrect interpretation of test characteristics.

Summary
Serum (anti)-drug level monitoring has been extensively studied in rheumatoid arthritis, but correctly designed and executed interventional prediction studies or test-treatment intervention studies are sparse and mostly negative. In contrast, many reviews advocate use of biological TDM in rheumatoid arthritis. On the basis of current evidence, therapeutic drug monitoring of biologicals cannot be recommended in the treatment of rheumatoid arthritis patients, although two clinical scenarios deserve further study.

Keywords
biologicals, review, rheumatoid arthritis, therapeutic drug monitoring

INTRODUCTION

The treatment of rheumatoid arthritis has seen a number of improvements in last decades, one of them being the increased availability of several biological Disease-modifying AntiRheumatic Drugs (bDMARD), including TNF inhibitors (TNFi) like adalimumab, etanercept and infliximab, and non-TNFi biologicals like rituximab, abatacept, and tocilizumab (Table 1). Since their introduction, the search for the most optimal treatment strategy using these drugs has resulted in many clinical studies. These studies addressed treatment initial dosing and comedication, increasing the dose, tapering or stopping whenever doing well, and finally switching in case of inefficacy. Result of these studies are included in current guidelines [1,2] and suggest that starting with authorized dose of any of the aforementioned biologicals, using a treat-to-target (low-disease activity or remission) strategy, and assess treatment effect at 3–6 months seems the best initial strategy. Cotreatment with conventional synthetic (cs)DMARD therapy is in general more effective, although by varying degrees between drugs. Whenever patients are doing well, treatment can safely be tapered stepwise, guided by disease activity, until discontinuation. Whenever disease activity increases or remains high, patients should be

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KEY POINTS

- TDM is suggested as a promising way to improve biological use in rheumatoid arthritis.
- Many data exist on pharmacokinetics and antidrug antibody development, but prospective prediction studies or test-treatment randomized controlled trials on the application of TDM are scarce and often negative.
- Although most suggested applications of biological TDM seem not supported by evidence, many TDM reviews are very positive about clinical use. These reviews are, however, more about the pharmacokinetics and pharmacodynamics, than about applied TDM.

switched to another bDMARD. This can either be within class (TNFi to TNFi) or between class, although the latter seems to be somewhat more effective [3]. Using these strategy choices, the vast majority of rheumatoid arthritis patients can reach low-disease activity or remission, and adverse effects and costs can be kept within optimal range.

The development of several assays to measure bDMARD levels and antidrug antibody levels, first by the pharmaceutical companies themselves, and later by commercial or academic parties [4] (www.theradiag.com/en/theranostic/lisa-tracker/; www.sanquin.nl/producten-diensten/diagnostiek/diagnostische-testen/; www.prometheuslabs.com/Products/Default.aspx?section=GIDiagnostics; www.immundiagnostik.com/en/home/products/kits-assays/skeletal-system.html), has spawned interest in the possibilities of therapeutic drug monitoring (TDM) to further improve these clinical treatment strategies. The underlying rationale of this approach includes the hypotheses that achieved drug levels after standard dosing differ between patients, that the lowest effective drug level does not differ between patients, and that knowing these two variables together with disease activity could prevent overtreatment and undertreatment, resulting in better treatment outcomes and lower costs and risk off side effects.

In this review, we set out to provide an overview of the current state-of-the-art of biological TDM in rheumatoid arthritis in this systematic narrative review.

Table 1. Overview of currently approved biological Disease-modifying AntiRheumatic Drugs in rheumatoid arthritis

Drug class	Class/mode of action	Drugs
Biological Disease-modifying AntiRheumatic Drug	Anti-TNF moab	Adalimumab Infliximab (bs) Golimumab
	Anti-TNF pegylated partial IgG	Certolizumab
	Anti-TNF receptor construct	Etanercept (bs)
	IL-1 receptor antagonist	Anakinra
	Anti IL-6 receptor moab	Tocilizumab Sarilumab
	Anti CTL4A moab	Abatacept
	Anti CD20 moab	Rituximab (bs)

bs, biosimilar available; IL-1, interleukin 1; moab, monoclonal antibody; TNF, tumor necrosis factor.

RECENT STUDIES ON BIOLOGICAL THERAPEUTIC DRUG MONITORING IN RHEUMATOID ARTHRITIS

We performed a systematic literature search on TDM of bDMARDS in rheumatoid arthritis. The search was performed in Medline and Cochrane database, using the search general and MESH terms for rheumatoid arthritis and TDM. The resulting 383 hits were screened using title and abstract, for the three included study types [prediction studies, test-treatment controlled trials (diagnostic studies), and reviews], for publication date between 1 April 2016 to 1 November 2017, and for subject (biological TDM in rheumatoid arthritis). Clinical studies had to have more than 20 patients, and follow-up 3 months or longer. Cross-sectional studies and modelling studies were excluded. Reviews were included if they discussed the subject of biological TDM in rheumatoid arthritis, summarized evidence, and made recommendations. We also incorporated results from our recent systematic review on this subject [5▪]. Results of the search showed two clinical studies on TDM, and nine reviews (Table 2). No further formal study grading or meta-analyses were done.

Clinical studies

Recent studies

The two new clinical studies firstly include the study of Bouman *et al.* [6▪], including more in-depth data from an earlier published study [7], and adding data on infliximab TDM. This study assessed in two prediction studies the predictive effect of serum (trough) levels of three TNFis: adalimumab, etanercept and infliximab, in rheumatoid arthritis patients undergoing disease activity-guided tapering of their

Table 2. Clinical studies on therapeutic drug monitoring of biological Disease-modifying AntiRheumatic Drugs in rheumatoid arthritis

Study	Design	Country	Patients and context	Biologic	Clinical question	Patient characteristics	Test	Results
l'Ami *et al.* [8▪▪]	RCT	The Netherlands	Rheumatoid arthritis patients with stable ADAL therapy and stable low disease activity, and serum trough ADAL level more than 8 mg/l	ADAL	Noninferiority in DAS change at month 3 after increasing the interval from 2 to 3 weeks compared with biweekly continuation	$N=55$, rheumatoid arthritis	Drug levels and anti-drug antibodies, Sanguin Diagnostic Services, the Netherlands	Tapering to 3 weeks is noninferior compared with biweekly continuation in these patients. No conclusion possible about TDM properties of (anti)ADAL measurement.
Bouman *et al.* [6▪]	Prospective cohort, explorative	The Netherlands	Rheumatoid arthritis patients with stable INFL therapy and stable low-disease activity	INFL (ADAL and ETA data published earlier ARD 2015)	Predictive effect of trough-timed ADA against and drug levels of INFL at moment of start of tapering for successful dose reduction or discontinuation (no flare, defined as DAS28 increase of more than 1.2 or more than 0.6 and current DAS28CRP more than 3.2) after 52 weeks	$N=51$, rheumatoid arthritis	Drug levels and anti-drug antibodies, Sanguin Diagnostic Services, the Netherlands	Neither INFL drug levels nor ADA were associated with successful dose reduction (ROC AUC 0.44, 95% CI 0.30–0.59) or stopping (ROC AUC 0.65, 95% CI 0.5–0.81) after 52 weeks

Reviews on therapeutic drug monitoring of bDMARDs in rheumatoid arthritis

Study	Design	Country	Patients and context	Biologics	Review question	Number of diagnostic accuracy test–treatment studies discussed[a]	Tests discussed	Conclusion summary
Bastida, 2017	Narrative review	Spain	Rheumatoid arthritis; context several scenarios (not clearly specified)	All TNFi, ABA, RTX, TOC	'To focus on the pharmacokinetics and pharmacodynamics of biologic agents approved for rheumatoid arthritis'	4	Drug levels and ADA, type of tests unclear	'A shift in daily practice for TDM should be encouraged, and population PKPD models could play an important role as a support tool for further dosage optimization'.
Medina, 2017	Narrative review	France	Rheumatoid arthritis; context several scenarios (not clearly specified)	All TNFi, ABA, RTX, TOC	'To examine the most relevant articles dealing with the concentration–response relationship, ADA detection and pharmacokinetics in rheumatoid arthritis patients receiving biopharmaceuticals' 'We aimed to assess the utility and clinical relevance of therapeutic drug monitoring (TDM) and immunogenicity testing of biopharmaceuticals in rheumatoid arthritis'	3	Drug levels and ADA, type of tests unclear	'Strategies based on TDM of TNF inhibitors seem promising for rheumatoid arthritis, but randomized controlled trials are required to support this'. 'Comparative effectiveness research in this field is a priority before implementation of TDM of biopharmaceuticals in clinical practice in rheumatoid arthritis'.

Table 2 (*Continued*)

Reviews on therapeutic drug monitoring of bDMARDs in rheumatoid arthritis								
Study	**Design**	**Country**	**Patients and context**	**Biologics**	**Review question**	**Number of diagnostic accuracy test–treatment studies discussed[a]**	**Tests discussed**	**Conclusion summary**
Sirotti, 2017	Narrative review	Italy	Not specified	All TNFi	'to describe the concept of personalized medicine and …… antidrug antibodies (ADA), to evaluate how these can help to …… choose the best option for treating and monitoring rheumatic patients in everyday practice'.	0	ADA, type of tests unclear	'Overall, the determination of ADA levels and anti-TNF-a drug may be useful in patients where the clinical efficacy of TNF-a inhibitor has dropped'.
Van Herwaarden *et al.* [5▪]	Systematic narrative review	Netherlands	Rheumatoid arthritis, PsA, Spa; several scenarios: prediction response after start of treatment, prediction Response next bDMARD, prediction successful dose Reduction/ discontinuation in case of low disease activity, prediction response to dose escalation in case of active disease, prediction response to bDMARD in case of flare.	All TNFi, ABA, RTX, TOC	'Evidence of clinical utility of TDM in bDMARD treatment is reviewed'.	14	Drug levels and ADA tests: Sanguin Diagnostic Services, the Netherlands, Immunodiagnostic AG, Bernsheim, Germany, Theradiag, Marne-La-Vallee, France, Progenika biopharma, Derio, Spain, Centocor research and development inc, Philadelphia, USA	'…available evidence concerning TDM of bDMARDs in treatment of inflammatory rheumatic diseases is very limited'. 'Therefore, TDM aimed at optimizing bDMARD use in clinical practice in these diseases cannot be advocated based on current data'. '…. worth investigating further, i.e. the use of ADA in case of inadequate response to TNFi to determine the next bDMARD and the use of serum drug levels in case of flare in disease activity to predict maintained response'.
Takeuchi, 2017	Narrative review	Japan	Rheumatoid arthritis; context not specified	INFL	'Summarize the background for biomarker research and introduce recent topics in the research and the possible clinical applications of biomarkers to guide treatment in rheumatoid arthritis (rheumatoid arthritis)'.	0	Drug level and ADA, type of test unclear	'The clinical application of measurement of serum infliximab level is realistic in Japan' 'The clinical usefulness should be determined'.

Table 2 (*Continued*)

Reviews on therapeutic drug monitoring of bDMARDs in rheumatoid arthritis								
Study	**Design**	**Country**	**Patients and context**	**Biologics**	**Review question**	**Number of diagnostic accuracy test–treatment studies discussed[a]**	**Tests discussed**	**Conclusion summary**
Martelli, 2017	Systematic review	France	Rheumatoid arthritis, IBD; context several scenarios, not specified	All TNFi	'to review, for the first time, all available studies comparing the cost-effectiveness of an empirical management of anti-TNF treatment versus a test-based strategy in patients with IBD or rheumatoid arthritis'.	0 (0 rheumatoid arthritis, 2 IBD, 5 modelling studies)	Drug level and ADA, type of test unclear	'All seven included studies showed that a test-based strategy with TDM of anti-TNF is more cost-effective than an empirical strategy in both IBD and rheumatoid arthritis patients, with no negative impact on efficacy'.
Kiely, 2016	Narrative review	UK	Rheumatoid arthritis; context several scenarios: outcome in TNFi nonresponders after switching to TNFi or non TNFi, individualise TNFi dose reduction	All TNFi	'This review summarizes those factors… which are known to influence efficacy and, when synthesized into the clinical decision-making process, will enhance optimization'.	4	Drug level and ADA, type of test unclear	'The measurement of trough levels provides a potential tool for patients who are not doing well to determine early whether to switch within the TNFi class (if levels are low) or to a biologic with an alternative mode of action (if levels are normal or high)'. 'The finding of supratherapeutic levels has the potential to enable individual patient selection for dose reduction without the risk of flare'.
Mok, 2016	Narrative review	Taiwan	Rheumatoid arthritis; context several scenarios: outcome in TNFi nonresponders after switching to TNFi or non TNFi	All TNFi	'This article reviews … the implications <of immunogenicity of biologic agents used in the treatment of rheumatoid arthritis> for clinical practice and treatment outcomes in Asian countries.	2	Drug level and ADA, type of test unclear	'To date, there are no evidence based recommendations to guide selection or switching of biologic therapies based on drug level and immunogenicity testing after failure of anti-TNF therapy, and the benefits of adopting such an approach would need to be balanced against the availability of reliable and reproducible tests and the costs of monitoring'.

Table 2 (*Continued*)

Reviews on therapeutic drug monitoring of bDMARDs in rheumatoid arthritis								
Study	**Design**	**Country**	**Patients and context**	**Biologics**	**Review question**	**Number of diagnostic accuracy test–treatment studies discussed[a]**	**Tests discussed**	**Conclusion summary**
Prado, 2017	Narrative review	Brazil, Denmark	Rheumatoid arthritis	All TNFi	'This review provides a comprehensive overview of ADA in rheumatoid arthritis patients treated with antiTNF immune-biologicals, and explores the concept of ,therapeutic drug monitoring (TDM) as an effective strategy to improve therapeutic management'	0 (1 study in CD)	Drug level and ADA, type of test reviewed and discussed	'…there are no recommendations based on circulating drug levels and ADA to guide selection and administration of anti-TNF drugs, including exchange biological therapy in case of secondary response failure. Hopefully, as more data becomes available, and more informative tests are developed, guidance strategies may be developed to individualize anti TNF therapies. The potential benefits of this approach should be balanced against the costs of TDM…'

ABA, abatacept; ADA, antidrug antibodies; ADAL, adalimumab; bDMARDs, biological Disease-modifying AntiRheumatic Drugs; CERT, certolizumab; ETA, etanercept; GOL, golimumab; INFL, infliximab; ROC AUC, receiver-operating curve area under the curve; RTX, rituximab; TDM, therapeutic drug monitoring; TNFi, TNF inhibitors; TOC, tocilizumab.

[a]The number of studies reviewed that tested TDM in clinical practice, either by testing predictive value of TDM for relevant clinical outcome in the future, or by test–treatment studies assessing the value of a clinical with TDM strategy compared with clinical only strategy, with $n > 20$ patients, follow-up at least 3 months. Excluded are cross-sectional studies, modelling studies.

TNFi. Results of this study show that serum (anti)-drug levels before start of tapering were not predictive for successful tapering or stopping. Although the design was in general correct, using a blinded test to predict a relevant clinical outcome in a scenario with clinical uncertainty, serum drug for adalimumab and etanercept levels were – in contrast with those of infliximab – random-timed instead of trough-level samples. Indeed, a subanalyses suggested that higher adalimumab trough levels might be predictive for higher success rate after tapering, although in a small number of patients. Furthermore, a significant relation in the other direction was found between drug level and successful tapering of etanercept, casting doubt on the validity of the subanalysis.

The second clinical study that was identified was the study by l'Ami *et al.* [8▪▪]. This study included rheumatoid arthritis patients doing well on adalimumab treatment, with a serum trough level greater than 8 mg/l, and randomized these patients between continuation or tapering to interval increase from 2 to 3 weeks. Although the study failed to meet the projected inclusion, the results clearly demonstrated noninferiority in DAS28 at 12 weeks between the tapered and continued patients. Because of the rather peculiar design of this study, however, interpretation with regard to clinical utility of TDM is limited [9]. Classically, in a diagnostic test–treatment trial, a strategy using a test and subsequent test-dependent strategy is tested against a clinical usual care strategy. This would enable the reader to infer whether addition of the test resulted in better outcomes (improved health outcomes of lower cost). Because of the design of the study by L'Ami *et al.* not randomizing for a test–treatment strategy, but only randomizing after the test, the only conclusion that can be drawn is that tapering from 2 to 3 weeks interval results in the same outcome as continuation of treatment in patients with drug-trough levels above 8 mg/l. However, in light of other data, it is plausible that this would also have been possible in patients with serum trough drug levels below 8 mg/l [10–12], making TDM of no value in this context.

Clinical studies: discussion

These two studies fit in well with the evidence from the 13 studies (with one double publication) that were earlier summarized in a systematic review by our group [5▪,13–26]. Results from this review suggest that TDM of biologicals in rheumatoid arthritis cannot rationally be supported in the context of treatment start and early response prediction or biological dose escalation or to guide dose tapering. Possible scenarios that remain promising are response prediction to the next biological based on current (anti)drug levels (supported, with some limitations, by three clinical studies) [16–18] and the use of serum drug levels in case of flare in disease activity to predict maintained response (supported by one study) [26]. Adalimumab through levels, as mentioned before, might also be helpful to guide dose reduction, although all the evidence whenever summarized is at least conflicting [6▪,8▪▪,9,20–22,30].

The current evidence from clinical studies is hampered by several issues. Firstly, no test-treatment randomized controlled trials (RCTs) have been done in this field. This kind of study is the highest level of evidence for clinical application of a test (Table 3). Also, all prediction studies are of the exploratory kind, with validation studies being absent. Further limitations include subpar reporting without following a reporting guideline like STARD and QUADAS [27,28]. For example, studies fail to state if the test was done blinded for clinical outcome, and test characteristics are often absent. In addition, other known predictors are almost never included.

The way to provide high-quality evidence for use of a test like TDM in clinical practice depends on following a five-step plan (recognized by the Cochrane diagnostic test accuracy group; http://methods.cochrane.org/sdt/welcome), which is summarized in Table 3. Whenever comparing these steps with current clinical studies, two aspects are remarkable: firstly, no step 3–5 studies have been done in this field at all (prediction studies with all other known predictors, or diagnostic RCTs). Secondly, as mentioned before, execution and reporting of step 2 studies (prediction studies with separate discovery and validation cohorts) has been done rather haphazardly.

In summary, a clear need remains for well designed validation and test–treatment studies in this field.

Reviews

Recent reviews

In addition to systematically searching for clinical trials, we also expanded the search to reviews. This was done to assess the number, quality, and conclusions of recent reviews in this field. Nine recent reviews were identified (Table 2). All reviews except two were nonsystematic, and none included grading or meta-analyses. No reviews mentioned following the PRISMA reporting guideline for reviews [29]. Eight out of nine reviews stated – in different words – that they aimed to describe use of serum

Table 3. Therapeutic drug-monitoring requirements filter

1	The test needs to be a reliable, precise and feasible measure of the variable it is supposed to measure. (no formal reporting guideline available)	
	Study type	(lab)validation studies: for example, spiked serum as golden standard (precision), and several test–retest measurements (reliability, for example, after thaw–freeze cycles). The test should be not too expensive or cumbersome and generally feasible for patients and for labs to perform (feasibility).
	Outcomes	CV%, agreement (kappa), regression/correlation coefficient, limits of agreement.
2	The test should be strongly associated with a relevant clinical outcome, thus resulting in clearly larger or smaller posttest chances *(QUADAS and STARD guideline on quality and reporting of diagnostic accuracy studies)*	
	Study type	Diagnostic accuracy study: cohort study in relevant patient population (relevant pretest chance for outcome), assessing the outcome, and establish association with test (being assessed blinded for outcome). In addition, validation in separate cohort, or adjustment using shrinking techniques like bootstrapping.
	Outcomes	Sensitivity and specificity, negative and positive-predictive value, area under the curve of receiver operator curves, likelihood ratios, odds ratio, relative risk, hazard rate.
3	The test should provide additional information (result in a clearly larger or smaller posttest chance for the relevant clinical outcome) beyond history taking, physical examination and simple routine testing. *(TRIPOD guideline on reporting of multivariate prediction modelling)*	
	Study type	Diagnostic accuracy study: see step 2, now also including multivariate prediction modelling with all other known predictors for the clinical outcome.
	Outcomes	Change in sensitivity and specificity, negative and positive predictive value, area under the curve of receiver operator curves, R^2 explained variance, tested with Wald test, −2 log likelihood testing, net reclassification improvement.
4	The use of the test should result in other medical treatment and/or follow up ('the result of the test should have consequences') and better outcomes for patients. *(CONSORT guideline on reporting of controlled trials)*	
	Study type	Diagnostic study or test-treatment study, two-arm RCT, one arm using optimal protocolized usual care strategy, the other arm using the same strategy but amended with the test and with different treatment based on test result.
	Outcomes	Better clinical disease outcomes, such as less morbidity and mortality, better quality of life.
5	The use of the test should be cost effective. *(CONSORT guideline on reporting of controlled trials)*	
	Study type	Diagnostic study or test-treatment study, two-arm RCT, one arm using optimal protocolized usual care strategy, the other arm using the same strategy but amended with the test and with different treatment based on test result.
	Outcomes	Cost-effectiveness is increased with an incremental cost effectiveness ratio lower than the society is willing to pay per gained quality adjusted life year (QUALY), usually below 40 000–80 000 euro per QUALY.

(anti)drug levels for clinical decision-making. The number of relevant studies that were included in these reviews ranged from 0 to 4, whereas one review with a systemic search identified 14 relevant studies [5▪]. The specific types of tests used and parties who provided the tests were mentioned in two of nine reviews.

The conclusions of the reviews ranged from critical to very positive. Five of nine reviews stated, in our eyes correctly, that based on current evidence – although sometimes appreciated as promising – TDM could not be endorsed for clinical practice. Four reviews were positive, suggesting that TDM with serum (anti)drug levels should be used in biological treatment in rheumatoid arthritis patients. Although four reviews suggest (nonvalidated) general test algorithms, none of the reviews provided specific recommendations (test cut-off threshold, sensitivity, specificity) in what patient and in what context to perform TDM, and what consequences for the treatment are.

Reviews: discussion

The reviews generally provide a wealth of information about the biologicals discussed, the way of measuring (anti)drug levels, and many cross-sectional and longitudinal pharmacokinetics–pharmacodynamics data, also on the relation between these markers and disease outcome. However, interestingly, many of them do not seem to focus on the objective they set out for, diagnostic test accuracy of

biological TDM, and nevertheless, conclusions are drawn about clinical utility of TDM.

The current issue seems rooted in a frequently observed 'blind spot' in basic science researchers for clinical research methodology (it goes without saying that the reverse is of course also often true). Here we would like to present a few examples that occur in the field of biological TDM in rheumatoid arthritis:

Firstly, finding cross-sectional correlation does not prove that a test is associated with a particular clinical outcome. For example, it has repeatedly been shown that antidrug antibodies are prevalent and associated with lower response rates. However, the evidence that is available suggests that in the selected patient population who are doing well, antidrug antibodies do not predict the ability to stop this presumably ineffective drug [5▪]. Another point that is commonly missed is that whenever a test is cross-sectionally correlated with, for example, disease activity, this also means that the information that is provided by the test is limited. To appreciate this, one might think of the most extreme case: perfect correlation between test and disease activity. This would make the test superfluous, as it does not deliver any more information than is already known.

A third issue concerns the failure to recognize a very high false-positive finding rate resulting from the toxic mix of low a priori chance for a successful biomarker, multiple testing, post hoc analyses, and lack of use of validation or shrinking techniques. It has been repeatedly shown that most research findings are not true, but in fact a false-positive result [31,32]. These are caused mainly by a perfect storm of low a priori chance of the phenomenon being tested being real (e.g. predictive value of TDM), use of multiple testing without correcting for it, not externally validating the findings, or using shrinking techniques such as bootstrapping, and publication bias. Considering all this, it is in fact very likely that all currently present invalidated evidence of the value of TDM in rheumatoid arthritis represents still an overestimation of the predictive value of TDM, even though only a few studies are positive.

Moreover, some inherent drawbacks of testing are often overlooked. Any testing costs money, and introduces treatment choice delay of often a few weeks. In addition, testing is always associated with false positives and negatives. All these things together further diminish returns on testing.

A final important issue is the general disregard for second-round or second-order effects in clinical practice, or put otherwise, overestimate the unmet need in clinical care. An example can be found in one of the modelling study on TDM-guided adalimumab dose reduction in rheumatoid arthritis [33]. The MARKOV model used in this study reports high-cost effectiveness of such a TDM-guided strategy compared with usual care. However, this is very dependent on a few critical assumptions. In addition to assuming perfect test characteristics – which really requires a giant leap of faith in light of the available data – this model compares with a control group without tapering at all. The cost effectiveness ratio is, therefore, driven not so much by using a TDM-guided strategy, but by tapering at all versus no tapering at all. Whenever considering current recommendations and usual clinical care, this is an unrealistic control condition. So, it is important to consider that whenever TDM is not available, clinical care alone also result in outcome optimization.

All the issues mentioned above are the reason that test validation steps have been designed in the last three decades as they are (Table 3). These steps protect against the scientific errors mentioned above, and any TDM strategy that finished step 5 successfully can be relied on as being valid and robust.

CONCLUSION

In conclusion, TDM of biologicals in rheumatoid arthritis currently seems to show a disconnect between evidence and beliefs. Clinical evidence is still limited and conflicting, and translation from promising pharmacokinetic–pharmacodynamic insights and cross-sectional data to well designed prediction or test–treatment studies is lacking. In contrast, many reviews support the clinical use of TDM to varying degrees, and suggest test algorithms, although some argue that these should first be tested in randomized clinical trials.

Future research effort should be aimed at developing and testing specific algorithms of whom to test, in what context, with what test, what should be done differently based on the test result, and finally, what the gains would be for patients and society. Involving methodology-trained clinical researchers could be worthwhile, to increase the chance of finding results that really matter to patients, and to reduce research waste.

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Conflicts of interest

There are no conflicts of interest.

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OPEN

Using technology to support clinical care and research in rheumatoid arthritis

William G. Dixon[a] *and Kaleb Michaud*[b]

Purpose of review
As digital technology becomes more ubiquitous, understanding the current state-of-the-art in digital information use for clinical care and research for patients with rheumatoid arthritis (RA) is timely and relevant.

Recent findings
The opportunities for recording and utilizing high-quality data from rheumatologists are reviewed, as well as opportunities from collecting, integrating and analysing patient-generated data to deliver a step-change in the support and management of RA.

Summary
Once greater adoption, standardization and implementation of relevant RA measures are in place within electronic health records (EHRs), patient care will improve and the ability to learn from aggregate experiences increases dramatically. Incorporating passive and patient-reported outcomes into self-management apps and integrating such data into the patient's health record will provide more responsive and better treatment results.

Keywords
health information technology, mobile health, outcome measures, rheumatoid arthritis

INTRODUCTION

Since the introduction of the World Wide Web 25 years ago, we are living in the 'Information Age' or 'Digital Age', a period of human history characterized by an economy based on information computerization [1]. Advances in technology have transformed health care, alongside other industries, through innovations such as electronic health records (EHRs), digital imaging, wireless sensors and access to online information. These changes touch the majority of our lives: for example, over 80% of Internet users seek health information online [2]. Increasing numbers of people own mobile devices from which they access the Internet. In the United States, over 95% of adults own a mobile phone [3▪▪] and over seven in 10 UK adults owns a smartphone, with older people more recently embracing smart and social technology [4]. Rheumatology and other clinical specialities need to adapt to this changing environment, embracing opportunities that emerge from better digital data and information. As rheumatoid arthritis (RA) remains a cornerstone of rheumatology practice, we review these advances in technology and their opportunities with an RA focus.

RA is a long-term condition in which symptoms including joint pain and difficulty with daily tasks vary over time and can progress to joint deformity. Treatment paradigms have changed in response to evidence from clinical trials and observational data. With the advent of biologic therapies and treat-to-target approaches seeking remission, prospects for patients are much better compared with previous decades. Nonetheless, we continue to strive to improve care and better understand treatment choices. Data are a powerful tool in advancing our knowledge, and technology has the potential to transform what data we can collect about RA and how it is presented to advance care. With careful

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KEY POINTS

- As rheumatology clinics become digitally mature, standardized RA outcome measures captured in the EHR will increase in importance for use in clinical care, quality requirements, reimbursement and local/regional/national data repositories for research.
- Although there are numerous smartphone health apps, patients with RA currently have limited options often focussed on tracking symptoms over time for self-management.
- New ways of gathering passive and self-reported data regularly from the patient, and integrating this with their rheumatology EHR, has the potential to transform management, leading to improved health, wellbeing and satisfaction by patients with RA.

consideration about what data clinicians, patients and others collect and how it is captured, its use can expand beyond clinical care to research, audit, quality improvement and more. The new era of digital epidemiology has a huge opportunity to transform our understanding of disease and treatment through more granular data and advanced analytics, resulting in improved information for medical decision-making [5].

The current article will describe opportunities for using technology to support self-management, clinical care and research in RA, as well as noting some important barriers. The two main topics that will be discussed include collecting and utilizing high-quality data from clinicians, and opportunities for collecting, integrating and analysing patient-generated data to deliver a step-change in the support and management of RA.

CLINICIAN-DERIVED DATA

The uptake of EHRs is increasing across the healthcare industry. In the United Kingdom, nearly all primary care practices are digitized, whereas a recent review suggested all hospitals should reach 'digital maturity' by 2023 [6]. The increasing use of EHRs is an important opportunity for rheumatologists to record and access better data about their patients to support improved clinical care, national audit, quality improvement programmes, research and more. As the data required for each of these purposes overlap, it is conceivable that rheumatologists might collect data once and use it to support all of these areas. The many benefits will flow more easily if data are collected in a structured and standardized way. Uptake will be enhanced if systems are useable and indeed useful in supporting rheumatologists to care for their patients in the best possible way. Careful thought thus needs to go into the design and implementation of such systems, but there are already examples of best practice from which we can learn in RA, such as the DANBIO register (Table 1).

Although DANBIO gives one illustration of what is possible in the use of structured data within EHRs for clinical care and research, data are typically collected in different ways in different systems. This can make it challenging to pool data resources when conducting large population research, or to support national audit. A review of 25 European RA cohorts found heterogeneity both in *what* was collected and *how* it was collected [11]. For example, although all cohorts collected information on disease severity, the instrument to measure disease severity varied with 80% including disease activity score-28 (DAS28) and 40% Clinical Disease Activity Index. There was greater variability in the collection of other data such as physical function, fatigue, comorbidities and radiological damage [11]. In the United States, greater disparities exist with many items not being collected systematically [12] despite there being established quality care indicators [13].

A European League Against Rheumatism (EULAR) taskforce has recently agreed upon a core dataset for RA that was designed, importantly, to support both clinical care *and* research. Data items were selected which would be useful and feasible to collect in real-time clinical practice within EHRs, and which would also support high-quality observational research [14]. Similarly, the American College of Rheumatology (ACR) has task forces leading

Table 1. Structured rheumatoid arthritis data collection in DANBIO

The Danish biologics registry DANBIO is an EHR system that collects structured data on patients with RA at least once per year, including RA severity. Patients reporting their symptoms via touch screens in the clinic at each visit supplement clinician-reported data. Digital data are summarized graphically and used as a tool for shared informed decision-making between clinicians and patients, for example demonstrating how changes in medication use have correlated with disease severity through time. DANBIO also acts as a quality registry, an audit and feedback tool, and provides secondary use of data for research while fulfilling its primary purpose of supporting clinical care [7]. Examples of research outcomes include the comparative effectiveness of biologic therapies [8], long-term biologic safety [9] and evidence to support automated nudging of treatment intensification [10▪]

EHR, electronic health record; RA, rheumatoid arthritis.

recommendations on RA activity measures and physical function assessment measures to help reduce the heterogeneity in EHR vendors' systems [15].

Maximizing the use of RA EHR data, once collected, is a challenge being addressed in a number of settings. The ACR recently launched its Rheumatology Informatics System for Effectiveness (RISE) registry that passively updates its data repository with connected rheumatology EHRs. Participating clinics can view their performance on a number of quality improvement measures in comparison with others while simultaneously complying with US reporting requirements [13,16]. Research is planned within RISE, but there are important limitations when trying to analyse hundreds of clinics with different EHRs and data collected. Data quality is variable: the RISE group has noted that measurement of RA activity was more likely if a clinic had been participating for longer [17]. RISE is also developing methods to extract value from unstructured data whilst awaiting improvements in structured data collection [18]. Recognizing the limitations of what research is possible even if you have data from whole countries, a pan-Nordic rheumatology register is being piloted to link individual-patient data across national borders without physical data transfer [19].

Clinical records have supported patient management and research for decades. Their increasing digitization provides important opportunities to deliver a step-change in how we manage patients with RA effectively and safety. The digital era also has the potential to shift from the paradigm of information coming solely from clinicians, to now supplement this clinician-generated data with information that comes directly from patients.

PATIENT-GENERATED DATA

The uptake of consumer technology including smartphones, smartwatches and wearables into patients' lives generates a range of digital opportunities for clinical care and research in RA. These include the collection of patient-generated data to support both self-management through symptom tracking and to inform clinical decisions if integrated successfully into clinical workflows; the use of sensors and wearables to measure and track important outcomes such as physical activity; and digital interventions such as behaviour change nudges.

TECHNOLOGY TO SUPPORT SELF-MONITORING AND SELF-MANAGEMENT

Patients spend over 99% of their time outside of the clinical environment and therefore often need to self-manage their RA. Specific self-management methods include rest, pacing and exercise; technical aids that address occupational and daily productivity; and pain management through self-medication. A variety of linked comorbidities also require active self-management by the patient. The use of consumer technology to track symptoms has the power to improve self-management in RA.

There are currently more than 165 000 health apps available in Apple's App Store [20], many of them designed to allow patients to monitor their disease through journaling or logging behaviours and symptoms [21]. Data entry is typically self-reported information; although inclusion of other data sources such as camera images, within-device physical activity tracking and wireless linkage to other devices such as blood pressure cuffs is increasingly common. Patterns through time are often presented back graphically to the user [22]. Short-term benefits of symptom tracking across disease areas include understanding disease and symptoms, acceptance, identifying triggers and reducing anxiety [23▪▪]. The evidence base for benefits in hard clinical outcomes such as a reduction in disease severity across disease areas, however, is less convincing for self-monitoring alone. Findings in chronic obstructive pulmonary disease and heart failure are debated, and evidence is equivocal in hypertension and diabetes [24–27].

APPS FOR PATIENTS WITH RHEUMATOID ARTHRITIS

A recent search identified 19 apps dedicated to RA, although the number continues to expand [28▪]. RA apps broadly divided into those that provided calculators for rheumatologists, for example to calculate a DAS28 score, and apps that allowed patients to track symptoms. The authors sought to examine to what extent patient data collection used validated tools and scores, concluding that they 'do not uniformly collect data using validated instruments or composite disease activity measures' [28▪]. It should be noted, however, that such instruments were developed for a different primary purpose (i.e. not for regular reporting of patient-generated data), and so the use of new measures might be expected. This is particularly true if retaining participant engagement is a goal.

There is limited evidence to date about the benefits of symptom tracking in RA. In our own experience (currently unpublished), we have observed patients' self-management benefit from tracking symptoms through increased insight into changes in their disease through time, identifying triggers, informing pacing, as well as improving communication about disease with family and

friends. The use of digital interventions within a smartphone app also holds significant promise. Interventions might include providing accessible patient and carer information, for example about RA or immunosuppressive medication; behaviour change support such as physical activity guidance or medication adherence; or support for improving emotional wellbeing such as online cognitive behavioural therapy for depression or sleep disturbance [29], or peer-to-peer support through online communities [30▪].

INTEGRATING PATIENT-GENERATED DATA INTO CLINICAL PRACTICE

Assessment at clinic visits

Patient-reported outcomes are well established as being important in RA clinical care and research: the DAS28 score includes a patient global assessment [31] and the ACR/EULAR core outcome set for RA clinical trials includes a measure of fatigue [32]. The uptake of self-reported questionnaires in clinical practice, however, has been somewhat limited, in part due to their perceived usefulness by some clinicians as well as practicalities of administration and scoring [33]. Technology has the potential to simplify the administrative burden and to integrate patient-generated data into clinical workflows. In rheumatology clinics across Denmark, patients all report symptoms on touch screens prior to joining the consultation with around 90% completeness [7] (Table 1). In Sweden, patients are able to report their symptoms prior to their consultation in the waiting area or from home (see https://www.youtube.com/watch?v=Kmqzy1hqcOw). Although some clinicians may not trust patient-reported data over their own assessment, studies have demonstrated patient reports to be well correlated with clinician assessments [34,35▪].

Daily assessment and remote monitoring

Treatment decisions are made in response to patients' descriptions of their symptoms when they see a health professional, which may be every 3–6 months. An accurate picture, however, can be obscured by patients' willingness to discuss symptoms, eloquence, recall, stoicism, the influence of recent disease severity and more [36,37]. This means treatment decisions are made using information that is imperfect, in turn suggesting decision-making may be suboptimal. Remote monitoring using consumer technology could be transformative in providing a clearer picture of disease through time if it could be integrated into clinical practice. In a recent review about opportunities in RA, it was argued that remote monitoring would potentially improve disease control [38]. A 'treat to target' paradigm with a target of remission is accepted in RA [39], yet it is often not feasible for clinicians to review patients monthly as advocated in guidelines [40]. At present, though, it is rare that patient-generated data are successfully integrated into clinical systems: a consequence of multiple challenges including patient and provider concerns, technical and workflow issues and privacy and security requirements [41].

We anticipate, however, that all such challenges are surmountable in the coming years. Rheumatologists can expect to view a clear picture of how disease severity has changed since the patients' last visit within their EHR before too long. Our own experience in a pilot study of remote monitoring in RA is that such integrated remote monitoring data are both feasible and useful, holding significant promise for clinicians and patients [42▪] (see also http://www.cfe.manchester.ac.uk/research/projects/remora/). Additional future opportunities include using remote monitoring data for rationalizing appointments [43] and triggering remote consultations, making service delivery more efficient. We are involved with a pilot study, testing if a smartphone app can help detect and provide prompt follow-up of flares between clinical visits (Wang *et al.*, under review JMIR Research Protocols).

PATIENT-GENERATED DATA FOR RESEARCH

Daily data collected as part of remote monitoring has the potential to address important research questions that have been impossible to answer to date. They will allow exploration of day-to-day patterns of disease fluctuation. The effectiveness of treatment can be studied by uniquely charting the rapidity and trajectory of response rather than being limited to assessing change between two distant time points. This advance would allow doctors to preferentially prescribe treatments that have a quicker onset of action. Furthermore, daily symptoms collected in the run-up to a disease flare would allow identification of a preflare period, supporting the development and assessment of a (potentially digital) intervention to prevent, or improve the management of, the approaching flare.

PASSIVE MONITORING

Regular remote monitoring using patient-generated data has much appeal, and yet it is hard to conceive that high proportions of patients will remain

engaged in remote monitoring for many years. We have evidence that motivated patients will track symptoms on a daily basis for 6 months or more [44], but it is likely that reporting fatigue will set in at some point. There are, nonetheless, important opportunities for passive monitoring of disease severity using technology that could support long-term remote monitoring. This might include the use of physical activity monitoring, given the known relationship between increasing disease severity and reduction in movement and the inclusion of accelerometers, gyroscopes and Global Positioning Systems in smartphones and other wearable devices along with geofencing tools to detect when a patient visits the hospital [45]. Just by carrying a phone or wearing a sensor, it may be possible to infer information about RA disease severity. Passive monitoring using patterns of physical activity has been explored in neurological conditions [46] and has face validity for RA and musculoskeletal disease. Other emerging methods of monitoring disease passively include examining the 'digital exhaust fumes' of our daily lives, in which worsening disease severity may correlate with online search histories or patterns of smartphone use [47,48]. It remains uncertain how well such measures can capture disease severity, although pilot studies show evidence that some passive data collection including mobility, phone call and texting behaviour are associated with self-reported RA disease activity [49]. Furthermore, if they are to be clinically meaningful, we need to be able to convert these data into clinical insight and present in a way that is useful and acceptable to the clinical community [50].

CONCLUSION

Taken together, the benefits to self-management, clinical care and research from technology have significant opportunities for advancing health and well being at an individual and population level. The path to successful adoption and use, however, has significant challenges including influencing EHR providers to design systems to support disease-specific needs, standardizing data items across geographies with trusted extraction and reuse of health data beyond direct care, up-front investment for longer term gain, maintaining motivation for sustained engagement of data collection, equitable access to digital services and digital literacy, and ensuring interoperability and integration across multiple platforms. Nonetheless, the potential benefits are vast. We are starting to glimpse real transformations in clinical care and research. This is a future worth striving for.

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Conflicts of interest

There are no conflicts of interest.

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What is the optimal target for treat-to-target strategies in rheumatoid arthritis?

Sytske Anne Bergstra and Cornelia F. Allaart

Purpose of review
There has been a trend over time to aim for stricter treatment targets in the treatment of rheumatoid arthritis (RA). We reviewed recent literature to attempt to identify the optimal target in treat-to-target strategies in RA.

Recent findings
Achieving lower disease activity was shown to be beneficial, but few studies directly compared the effect of aiming for different treatment targets. Based on the limited available evidence, aiming for remission seems to result in more patients achieving (drug-free) remission than aiming for low disease activity (LDA), but it does not seem to result in better physical functioning. There are indications that adherence to a remission targeted protocol can be lower. In randomized trials in which LDA or remission were compared with ultrasound remission targets, treatment targeted at ultrasound remission was associated with more intensive treatment, but it did not result in better clinical or imaging outcomes.

Summary
There were no benefits of aiming for ultrasound remission in RA-patients. To decide whether remission or LDA is the best target in the treatment of RA-patients, a randomized clinical trial comparing both targets would be needed. On an individual level, cotargets such as functional ability should be considered.

Keywords
low disease activity, remission, rheumatoid arthritis, treat-to-target, ultrasound remission

INTRODUCTION

The introduction of the treat-to-target principle in clinical practice has been one of the main contributors to the drastic improvements in the treatment of rheumatoid arthritis (RA) patients. In the past 2 decades, several trials showed favourable outcomes of targeted treatment (e.g. [1–4]). In addition, several studies showed that RA patients achieved better physical functioning and achieved remission earlier and more frequently with a treat-to-target strategy compared with usual care [5,6]. In different trials, different treatment targets were used, with in general a trend over time to aim for stricter treatment targets. Although the first treat-to-target trials generally aimed at low disease activity (LDA), more recently remission and even ultrasound remission have been applied as treatment targets [1,3,7,8,9▪▪,10▪▪]. For each of these treatment targets, several definitions are used, which are often based on different composite measures, such as the disease activity score (DAS), DAS28, simple disease activity index (SDAI) or clinical disease activity index (CDAI). As some of these treatment targets are stricter than others, it could be argued that each of these definitions is different treatment targets on their own [11]. Current recommendations are to aim for clinical remission, as defined by the absence of signs and symptoms of significant inflammatory disease activity, or at least LDA, especially in patients with longer disease duration [12▪▪]. These recommendations are based on studies showing that patients in remission have better outcomes than patients in LDA and on studies showing that treat-to-target aimed at remission results in better treatment outcomes than usual care (without targeted treatment) [5,6,11, 13–15]. However, these results do not necessarily indicate that patients receiving treatment targeted at remission always achieve remission more often than patients receiving treatment targeted at LDA. Whether patients achieve remission may be a patient or disease type characteristic rather than a consequence of stricter treatment targets. Comorbidities

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KEY POINTS

- Aiming for remission seems to result in achieving remission more often than achieving LDA, but not in better physical functioning, especially not in patients with longstanding disease.
- Aiming for ultrasound remission is not associated with favourable clinical outcomes compared with LDA or remission, but it does lead to more intensive treatment.
- Rheumatologists' adherence is higher to a LDA steered treatment than to a remission steered treatment, which is important to achieve the desired target.
- To identify the best target in treat-to-target strategies, randomized clinical trials comparing LDA and remission are needed.

and comedications, as well as (fear of) side effects and costs, may put a limit to further treatment intensification. Moreover, it is possible that the best treatment target varies among different patients. In this review, we describe literature of the past 18 months to attempt to identify the optimal treatment target in treat-to-target strategies in RA according to recent literature.

DEFINITIONS OF TREATMENT TARGETS

In general, the choice of a treatment target in RA is between 'low disease activity (LDA)' and 'remission'. Each of these targets can be defined according to different composite measures and different cut-offs (Table 1). As for each target, each of these different composite measures or cut-offs are intended to measure the same construct, ideally they would all strongly agree with each other and result in the same treatment consequences. Although CDAI and SDAI LDA and remission are reported to strongly agree with each other, other measures had higher discordance [16]. For example, in one study, the DAS28 calculated using the erythrocyte sedimentation rate was on average 0.3 points higher than the DAS28 calculated using the c-reactive protein (CRP), with especially large differences for patients in LDA. Therefore, using the DAS28-CRP resulted in 4% more patients classified as in remission without a need for further treatment intensification [17]. However, despite differences in proportions of patients being categorized in remission, various composite indices show comparable associations with functional ability and radiologic progression [11].

RACE TO THE BOTTOM: HOW LOW SHOULD YOU GO? (EVER LOWER REMISSION TARGETS)

Instinctively, when treating a debilitating disease such as RA, aiming for remission would be expected to be favourable compared with aiming at 'merely' LDA. There has been a trend in clinical trials in setting ever more stringent treatment targets. However, no direct comparative studies have been done to determine which is the optimal treatment target. This leaves us to compare different studies, with all the problems that imposes. Several studies have been published that show excellent long-term effects of treatment targeted at LDA, with follow-up ranging from 12 months to 10 years. Treatment resulted in 57–82% of patients achieving LDA, limited radiographic damage and good physical functioning

Table 1. Overview of cut-off values for low disease activity and remission for different composite scores

Composite score	Formula	Low disease activity	Remission
DAS[a]	$0.54 \times \sqrt{\text{RAI}} + 0.065 \times \text{SJC} + 0.33 \times \ln(\text{ESR}) + 0.007 \times \text{PTGLBL}$	≤2.4	<1.6
DAS28[a]	$0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{PTGLBL}$	≤3.2	<2.6
DAS28-CRP[a]	$0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.36 \times \ln(\text{CRP}+1) + 0.014 \times \text{PTGLBL} + 0.96$	≤2.9	<2.4
SDAI	SJC + TJC + PTGLBL + DRGLBL + CRP	≤11	≤3.3
CDAI	SJC + TJC + PTGLBL + DRGLBL	≤10	≤2.8
ACR/EULAR Boolean remission	TJC, SJC, CRP mg/dl and PTGLB (0–10 scale)	–	All measures ≤1
Ultrasound remission	Various definitions including no or limited power Doppler activity and limited grey-scale ultrasound, possibly combined with clinical remission		

CDAI, clinical disease activity index; CRP, c-reactive protein; DAS, disease activity score; DRGLBL, visual analogue-scale physician assessment of global health; ESR, erythrocyte sedimentation rate; PTGLBL, visual analogue-scale patient assessment of global health; RAI, Ritchie Articular Index; SDAI, simple disease activity index; SJC, swollen joint count; TJC, tender joint count.
[a]Alternative formulas exist for the DAS(28) based on CRP, based on three components (no PTGLBL) or based on three components and CRP. These use the cut-offs of the original DAS(28).

[1,18,19]. Between 44 and 53% of patients in these LDA targeted trials in fact achieved remission and one study reported 14% of patients in drug-free remission after 10 years [1]. This suggests that besides the treatment target, patient-dependent factors determine the disease activity outcomes. More studies published the outcomes of a treat-to-target strategy aimed at remission. High percentages of patients in remission were reported (ranging between 43, 62, 73, 75% DAS28-remission after 1 year, 84% DAS28-remission after 2 years and 74% DAS-remission after 5 years) and 26% in sustained (at least 1 year) drug-free remission were reported after 5 years. Patients in remission showed hardly any radiographic damage progression [7,20–23]. Moreover, achieving remission was associated with regaining normal physical functioning [Health Assessment Questionnaire (HAQ) ≤ 0.5] [7,24]. The potential downside of aiming at remission was seen in high usage of costly biologic disease modifying anti-rheumatic drugs (bDMARDs) [7]. In a treat-to-target study in patients with established RA, the costs of 2 years of treatment with a bDMARD were between €38.880 and €79.681 and only 33% achieved DAS28-remission [25]. Some observational studies compared patients who achieved LDA with patients who achieved remission. In patients with long-standing RA, patients who achieved remission had less hospitalizations, less joint surgeries, lower mortality rates and lower healthcare costs, but patients in longstanding LDA had similar hospitalization and joint surgery rates compared with patients in longstanding remission [26▪,27,28▪]. Furthermore, patients who achieved SDAI or CDAI remission (but not DAS28-CRP remission) had better physical functioning than patients who achieved LDA [29]. However, a different study suggested that a DAS28 between 2.6 and 3.6 already predicted the achievement of normal physical functioning (HAQ < 0.5) [26▪,29]. In an observational study in newly diagnosed RA patients, no difference in functional ability or the number of orthopaedic surgeries was found between patients who achieved DAS28 remission and those who achieved DAS28 LDA [30▪]. Lastly, patients with a stricter remission target (DAS28 ≤ 1.98) had a lower risk and a shorter time to relapse (30 vs. 62%, 8 vs. 3 months) than patients in 'clinical remission' (DAS ≤ 2.6) [31▪]. Only two studies compared a treat-to-target strategy aimed at remission to a treat-to-target strategy aimed at LDA. One observational multicentre study compared data from 210 patients treated to a target of DAS28 remission and seven patients treated to a target of DAS28 LDA. After 1 year, the remission target was achieved by 56%, with median DAS28 2.38, and the LDA target by 21% with median DAS28 3.89. No data on functional ability or radiology have been presented [32]. The second study compared 5 years follow-up of two clinical trials: the BeSt study in which treatment was targeted at DAS LDA and the IMPROVED study in which it was targeted at DAS remission. Patients from both trials were selected who fulfilled the same inclusion criteria and received similar treatment. After 5 years, 61% of patients treated according to both targets were at least in DAS LDA. However, more remission targeted patients indeed reached DAS remission (18%) or drug-free remission (18%), compared with patients treated to a target of low DAS (32 and 8%, respectively). Radiographic damage progression and HAQ scores were approximately similar between both groups. Although the authors adjusted for baseline differences between both studies, frequency of follow-up visits, treatment steps tapering strategies differed between both studies, which could have influenced the results [33▪]. Also in the IMPROVED study, it was assessed whether intensifying medication to aim for remission in patients who are already in LDA leads to clinically relevant improvement in physical functioning. It was found that although a treatment intensification in patients in LDA leads to a small improvement in HAQ, this improvement was not clinically meaningful and even became smaller over time [34▪]. Thus, in general, these studies seem to confirm that patients who achieve remission have better outcomes than patients who achieve 'only' LDA, with better functional ability, less damage, fewer hospitalizations and joint surgeries. Based on the limited available evidence, aiming for remission seems to result in more patients achieving remission and possibly drug-free remission than aiming for LDA. However, if patients are already in LDA, further intensifying treatment does not result in clinically relevant functional improvement and patients who have longstanding LDA do not have worse functional ability than patients with longstanding remission.

ULTRASOUND REMISSION

Although ideally remission would be considered as the absence of disease activity, several studies have shown that subclinical synovitis, as measured by ultrasound, is often present in patients in remission or even 'deep clinical remission' (DAS28 ≤ 1.98) [31▪,35]. Subclinical synovitis was associated with disease flares and radiographic progression in newly diagnosed patients and in patients with existing RA [31▪,36]. Moreover, patients in 'ultrasound remission' had lower HAQ, DAS28 and visual analogue scale (VAS) global health than patients not in ultrasound remission [37]. Indeed, when ultrasound measures were available, 20% of final treatment decisions

were altered, especially in less experienced rheumatologists [38]. It is tempting to assume that further suppression of these signs of inflammation will result in better clinical outcomes. But again, rather than a causal relationship between ultrasound findings and clinical results, it may be intrapatient characteristics that determine that one patient will have better HAQ, DAS, VAS as well as ultrasound responses to a treatment than another patient. Two randomized clinical trials and one cohort study compared targeting ultrasound remission with targeting clinical remission or LDA. The IMPERA study compared two cohorts with in total 313 patients: one aimed at LDA (DAS28 < 3.2) and the other aimed at ultrasound remission, defined by grey-scale ultrasound less than 2 and no Power Doppler activity. After 18 months, disease activity (DAS28) and physical functioning (HAQ) were similar between the two cohorts [37]. The TaSER study randomized 111 newly diagnosed patients with RA or undifferentiated arthritis to treatment targeted at LDA (DAS28 < 3.2) or targeted at ultrasound remission (total power Doppler joint count ≤ 1). Over 18 months both groups had similar improvements in DAS and HAQ and had no differences in imaging outcomes or serious adverse event rates. Only the proportion of patients in DAS-remission (but not in ACR/EULAR Boolean remission) was 23% higher in the ultrasound-targeted patients. However, treatment intensity was higher in the ultrasound group, with more patients receiving combination DMARD therapy and treatment with bDMARD [10▪▪]. The ARCTIC trial randomized 238 DMARD naïve RA patients to a treatment arm aimed at clinical remission (DAS < 1.6 and no swollen joints) or to a treatment arm aimed at ultrasound remission (clinical remission and no power Doppler activity). After 12 and 24 months of follow-up, there were no differences in clinical remission, number of swollen joints, progression of radiographic joint damage, disease activity as measured by various composite indices, physical functioning or the number of adverse events. However, the patients in the ultrasound remission arm more often received biologics and intra-articular injections [9▪▪]. Thus, there was no clinical benefit of aiming for ultrasound remission in randomized clinical trials. However, it does lead to more intensive treatment, probably associated with higher costs.

ADHERENCE TO DIFFERENT TREATMENT TARGETS

Next to the clinical effectiveness of different treatment targets, the feasibility of using a target in daily clinical practice is essential for its influence on patient outcomes. Apart from potentially increasing costs of treatment, the feasibility of setting a treatment target in daily practice depends on rheumatologists' adherence to targeted treatment. The only study available indirectly compared adherence in two clinical trials, one aimed at DAS LDA and the other aimed at DAS remission, showed that over 5 years rheumatologists' adherence to a DAS LDA steered treatment was higher (86% over time) than to a DAS remission steered treatment (70% over time) [39▪]. This is especially relevant, as adherence has been shown to influence the achievement of remission and good physical functioning in clinical practice after 3 years [40]. Specifically, the minimally needed compliance with a treat-to-target strategy aimed at remission was found to be 81% to achieve DAS28 remission and 71% to achieve DAS28 LDA (93% for SDAI remission and 77% for SDAI LDA) [41▪]. Despite the advantages of adherence to a treat-to-target protocol, it can be imagined that nonadherence to a treatment target may be unavoidable or even beneficial. For example, patients may simply refuse a treatment adaptation, rheumatologists may not agree with how the DAS in certain patients reflects RA disease activity and in patients with longer disease duration and acceptable LDA, the risk/benefit ratio of further treatment adaptations may not be beneficial.

CONCLUSION

In this review, we aimed to identify the best target in treat-to-target strategies for the treatment of RA patients, based on recently published literature. All published articles confirmed the importance of using a treat-to-target strategy in RA patients. Furthermore, achieving lower disease activity levels was shown to be beneficial, but it remains doubtful whether *aiming* for lower treatment targets, in particular in patients who are already in LDA, results in clinically relevant improvement of achieved outcomes. Few articles directly compared the effect of aiming for different treatment targets. Based on the limited available evidence, aiming for remission seems to result in more patients achieving (drug-free) remission than aiming for LDA, despite indications that adherence to a remission targeted protocol can be lower, but it does not seem to result in better physical functioning. In randomized clinical trials in which LDA or remission targets were compared with ultrasound remission targets treatment targeted at ultrasound remission was associated with more intensive treatment, but it did not result in better clinical or imaging outcomes. This is presumably because once clinical disease activity is very low, it is difficult to substantially improve functional outcomes that are close to normal or

radiographs that show no significant damage. Therefore, it can be concluded that there are no benefits of aiming for ultrasound remission in RA patients. To decide whether remission or LDA is the best target in the treatment of RA patients, a randomized clinical trial comparing both targets would be needed. In the meantime, in daily practice both the composite score and functional ability should be taken into account when discussing with our patient whether the treatment needs to be intensified.

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Conflicts of interest

There are no conflicts of interest.

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Rheumatoid arthritis treatment in patients with a history of cancer

Anne C. Regierer and Anja Strangfeld

Purpose of review
What is the best treatment option in patients with active rheumatoid arthritis who have a history of malignant disease? Rheumatologists are increasingly faced with this question in their daily practice. As uncontrolled high disease activity is an important risk factor for further comorbidities and shortened life expectancy, the treatment has to be effective, without bearing a higher risk for cancer recurrence. What data is available today to guide treatment decisions and how robust is its evidence?

Recent findings
As patients with prior cancer are usually not included in randomized controlled trials, all data we have to elucidate this topic stems from observational cohort studies, mainly biologics registers established in several European countries. The registries investigated the risk of recurrence of cancer mainly by comparing treatments with csDMARDs and TNF inhibitors. Few results are available so far for the treatment with rituximab. However, because of their observational design, the data can only reflect current clinical practice. Because of the lack of evidence, questions such as: are biologics soon after cancer diagnosis safe, remain.

Summary
There is still insufficient data for patients with a very recent history of cancer. However, in patients with cancer being in longer remission, observational data suggest no increased risk of overall cancer recurrence when they are treated either with TNF inhibitors or rituximab.

Keywords
biologics, DMARD, malignancies, observational cohort data

INTRODUCTION

Patients with rheumatoid arthritis with a history of malignant disease are increasingly seen by rheumatologists. As long as a cancer is not in stable remission, the cancer treatment will be the main focus of attention. However, as soon as a cancer is in remission, the rheumatic disease will emerge again and should be treated adequately. Because high rheumatic disease activity is an important risk factor for the development of all kinds of comorbidities [1,2] and shorter life expectancy [3], it is crucial to start effective treatment at the earliest possible stage.

Since the introduction of tumor necrosis factor-α inhibitors (TNFi) around the year 2000, there have been concerns about the possible effects on carcinogenesis. The role of TNFα is pleiotropic and not restricted to immune cells. It can be a tumor-promoting cytokine, and it also affects tumor immunity. Its role in human carcinogenesis is not completely understood [4].

Patients with rheumatoid arthritis have increased incidence rates of specific cancers, especially lymphoma, lung cancer, and cervical cancer [5,6]. TNFi or other biologics do not seem to increase this risk further [7,8▪]. Regarding the outcome of cancer, which develops in patients with rheumatoid arthritis treated with TNFi, data from the Swedish biologics register ARTIS linked to Swedish clinical rheumatoid arthritis registers and national registers on cancer, hospitalization, and outpatient care showed that patients treated with TNFi had similar stages at cancer diagnosis and similar postcancer survival rates compared to biologics-naïve patients [9].

The question of the best rheumatoid arthritis treatment option for patients with a history of

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KEY POINTS

- Observational data suggest no increased risk of cancer recurrence for patients selected to be treated with either TNFi or RTX.
- Although increasingly used, the long-term safety of RTX after prior malignancy needs to be further elucidated.
- Altogether the insufficient evidence precludes us from giving clear recommendations for the management of patients with a history of cancer. This applies especially to patients with a very recent history of cancer.

cancer is not yet answered satisfactorily. Randomized clinical trials are an inadequate study type in this regard: their follow-up is too short and most of them exclude patients with a history of cancer. Therefore, available evidence is scarce and relies solely on observational data.

EVIDENCE FROM THE PROSPECTIVE OBSERVATIONAL COHORT STUDIES

The first results on the recurrence risk of biologic treatment in patients with rheumatoid arthritis with a history of malignant diseases were published in 2010 by the British register BSRBR [10], and by the German register RABBIT [11]. In both registers, the percentages of patients with prior malignancies were twice as high in the conventional synthetic (cs)DMARD treated groups [3.6% (BSRBR) and 3.1% (RABBIT)] as in the TNFi exposed group (1.6 and 1.8%). This indicates the channeling of patients with a possibly higher risk and mirrors the preference of rheumatologists to treat those patients with conventional synthetic rather than biologic DMARD therapies.

Both registers did not find significant differences in recurrence rates between TNFi exposed and unexposed patients. However, the BSRBR detected a recurrence rate of 25.3/1000 patient-years in TNFi and 38.3/1000 patient-years in csDMARD-treated patients resulting in an insignificantly decreased risk, in contrast to the RABBIT data with 45.5/1000 patient-years in TNFi and 31.4/1000 patient-years in csDMARD-treated patients, corresponding with a nonsignificantly elevated recurrence rate ratio of 1.4 ($P = 0.6$). Why are the results of these two registers, whose design is very similar, that diverging? Maybe it is attributable to different treatment styles of British and German rheumatologists. Whereas German rheumatologists prescribed TNFi in the majority of cases (77%) within the first 10 years after cancer diagnosis, only 42% of patients in the United Kingdom were treated with TNFi within the same period.

The BSRBR cohort was re-analyzed in 2016 [8▪]. Of 18000 patients with rheumatoid arthritis in the cohort, 425 patients were identified through linkage with the U.K. Health and Social Care Service Information Centre (HSCIC) as having had a history of cancer. Only first time biologics users were analyzed. A total of 243 were treated with TNFi, 23 with rituximab (RTX), and 159 with csDMARDs. New incident malignancies were defined as new primaries, local recurrences and metastases diagnosed after the first dose of biologic therapy or after being enclosed in the register with a csDMARD treatment.

A total of 101 new incident malignancies were identified. The rates were 33.3/1000 patient-years in the TNFi group, 24.7/1.000 patient-years in the RTX group and 53.8/1.000 patient-years in the csDMARD group. The age and sex adjusted hazard rate (HR) was 0.55 for TNFi and 0.43 for RTX, showing no significant differences compared to csDMARD. Similar to the previously published analyses from the BSRBR cohort, the data showed a patient selection based on rheumatologist preference with significantly more patients with cancer diagnosis of more than 10 years ago in the TNFi group (56.8%) compared to the RTX (17.4%) and the csDMARD (37.1%) treated group. In addition, the proportion of patients with prior lymphoproliferative malignancy was highest in the RTX group (17.4%) compared to TNFi (2.9%) and csDMARD (6.9%) treated patients. This selection mirrors the considerations in the judgment of prescribers: because RTX is used in the treatment of lymphomas, it is not considered to be tumor promoting and therefore preferably prescribed in patients with prior lymphoproliferative disease and in patients with a more recent cancer diagnosis. The results indicated that those patients selected to receive either TNFi or RTX did not have a higher risk of recurrent or new incident malignancies compared to csDMARD-treated patients [8▪].

A very recent analysis from the Danish DANBIO cohort [12] was focused on the risk for developing a second cancer in patients with rheumatoid arthritis with a history of a primary cancer, and on mortality with regard to the rheumatoid arthritis treatment. It is important to point out that recurrence (local or metastatic spread) of the primary cancer was not included in the outcome. This makes the results difficult to compare because so far all other analyses published included both outcomes, secondary primary cancer and local or distant recurrence. The authors identified 1.678 patients with rheumatoid arthritis with a history of cancer. Of these, 108 patients developed a second malignancy during follow-up. Ever-use of a biologic (b)DMARD was not associated with a higher risk of developing a second malignancy compared to never-use. During

follow-up, 342 patients died. When adjusted for the extent of the cancer, mortality was not elevated in bDMARD use compared to never-use.

META-ANALYSIS

Because of the paucity of evidence, meta-analyses of the existing data from observational studies have been published to further elucidate this context. A recent meta-analysis included nine observational studies with a total of 11679 patients with prior cancer [13▪]. Of these, 3707 patients were exposed to TNFi and compared to 7972 patients exposed to csDMARD or no immunosuppressive treatment. In the TNFi group 298 events were identified (new cancer or cancer recurrence) and in the control group 625. The pooled incidence rates were 3.2 per 100 patient-years [95% confidence interval (CI), 2.1–4.9] in the TNFi group and 3.6 per 100 patient-years (95% CI, 2.3–5.6) in the controls. These were not significantly different (Incidence rate ratio, 0.9; 95% CI, 0.59–1.37).

When analyzing different cancer entities separately (solid tumors, skin cancer, all cancers excluding skin), there was also no significant difference between TNFi exposed and controls.

Another recent meta-analysis included eight studies with patients with rheumatoid arthritis, eight studies with inflammatory bowel disease (IBD), and one study with psoriasis patients [14▪]. The analysis included 11702 patients with a prior malignancy with 1698 events of a secondary or recurrent cancer. The analysis showed no increased risk of cancer recurrence or secondary cancer in patients with a chronic immune mediated disease treated with conventional immunosuppressants or TNFi. They concluded that rates of cancer recurrence were similar among individuals receiving TNFi, other immunemodulator treatment, or no immunosuppression.

SPECIFIC CANCER TYPES

All results referred to so far were restricted to determining the overall risk of cancer. However, the recurrence risk is highly dependent on the specific cancer entity and other specific molecular characteristics of the respective malignant disease. For example, recurrence risk of hormone receptor positive breast cancer is much lower than that of small cell lung cancer [15,16]. Therefore it is important to analyze the risk of recurrence in a cancer site specific manner. However, because of the paucity of data this is only possible for the most common cancer types.

BREAST CANCER

Breast cancer is the most common cancer in females with a lifetime risk of more than 10% in western countries. Although around 30% of the newly diagnosed patients are younger than 55 years, the risk is growing with age and the mean age at diagnosis is around 60 [17]. With a proportion of 75–85% women in patients with rheumatoid arthritis, this cancer is also commonly seen in rheumatology.

The Swedish ARTIS register investigated the risk for recurrences in patients with rheumatoid arthritis with prior breast cancer treated either with TNFi or csDMARD treatment with a population-based matched cohort design [18▪▪]. To identify patients with prior breast cancer, data from the ARTIS register ($n = 11343$) were linked with the Swedish Cancer Register, which contains information on date of cancer diagnosis, and cancer histology. For each patient with rheumatoid arthritis starting a TNFi treatment with a history of breast cancer, a biologic-naive patient with rheumatoid arthritis was matched on sex, age at cancer diagnosis (±3 years), year of cancer diagnosis (±5 years), cancer stage at diagnosis (invasive vs. in situ), and county of residence.

In total, 120 TNFi-treated patients with breast cancer were matched to 120 biologics-naive patients. In both treatment groups, nine patients developed a breast cancer recurrence resulting in a recurrence rate of 15 (TNFi) and 16 (biologics-naïve) / 1000 patient-years.

Comparing TNFi-treated with biologics-naive, the HR for recurrence was 0.8 (95% CI, 0.3–2.1). After adjustment for breast cancer characteristics (e.g. nodal status, type of surgery, chemotherapy) and comorbidities, the HR was 1.1 (95% CI, 0.4–2.8). Although this result adds further evidence that TNFi is safe for patients with a history of breast cancer, it needs to be taken into account that the median time from cancer diagnosis to TNFi start was 9.4 years. Only 15% of patients started TNFi treatment within 5 years after their breast cancer diagnosis. Whether women with recently diagnosed breast cancer can be safely treated remains unclear.

A new aspect investigated in this study was physician-reasoning with regard to TNFi prescription. In 13 of the 120 patients who received TNFi, the recurrence risk was considered substantial, but TNFi was started because of high disease activity. Three recurrences occurred in this group during follow-up. Conversely, 14 of the 120 biologics-naive patients were not started on TNFi because of a perceived high risk of recurrent breast cancer, even though there was a clear indication for the TNFi treatment. In this group, one recurrence was observed during follow-up.

Another retrospective cohort study analyzing breast cancer recurrence used different cohorts derived from Medicare data [19]. The aim of this

study was to analyze the rates of breast cancer recurrence in patients with rheumatoid arthritis or IBD comparing different immune-modulating drugs, that is methotrexate, thiopurines, and TNFi. The authors performed a matched pairs analysis using factors related to the risk of breast cancer as matching criteria. The cohort consisted of 2684 women with prior breast cancer of whom a total of 107 patients experienced recurrences during 5196 patient-years. They compared users and nonusers of MTX, thiopurines, and TNFi and found no significantly different risk in breast cancer recurrence between the treatment groups. However, the definition of nonusers included prior use of the medication. For example, in the MTX-nonuser group, only 36% of 892 patients were never-users, meaning that 64% of the patients have been exposed to MTX. In the analysis of cancer as serious adverse event an ever-exposed approach is generally preferred. Therefore, the method used in the article of Mamtani *et al.* is not fully appropriate and may lead to biased results. The results for TNFi in this study are more trustworthy than for MTX because 82% of the nonuser group were never exposed. Another limitation of this analysis is the relatively short follow-up with a median follow-up ranging from 2.4 to 3.4 years. Taking into account the long latency period of a diagnosable breast cancer recurrence, this follow-up seems too short.

Taken together, evidence is growing that TNFi can be used safely in patients with a history of breast cancer. Whether a certain time interval between breast cancer diagnosis and start of TNFi treatment is important, cannot be conclusively assessed at this time.

CERVICAL DYSPLASIA/NEOPLASIA

The question of how often patients with arthritis (rheumatoid arthritis, AS, PsA) with a history of cervical dysplasia develop cervical cancer was investigated in a publication by the Danish DANBIO registry [20]. A total of 806 patients with cervical dysplasia were identified. The treatment was categorized as ever versus never bDMARD exposed. None of the patients, regardless of the treatment group, progressed to invasive cervical cancer. However, the follow-up was rather short with 3.5 (ever) and 1.5 (never) years.

A similar analysis was done in the BSRBR, with 238 RA patients with a cervical cancer in situ of whom 48/2654 patients were exposed to csDMARDs only and 190/9084 to TNFi [21]. The median follow-up was 3.9 and 5.2 years under csDMARD and TNFi treatment. During follow-up, two incident genital cancers were reported in the csDMARD group but none in the TNFi group. In conclusion, also for cervical dysplasia, there is no indication of a higher risk of progression to malignancy because of TNFi treatment.

SKIN CANCER

The risk for nonmelanoma skin cancer is increased in patients with rheumatoid arthritis compared to the general population [22,7]. However, it seems that TNFi treatment does not further exacerbate the risk of basal cell or squamous cell carcinomas [22]. Results for invasive melanoma in bio-naive patients with rheumatoid arthritis were conflicting so far [23,24]. A collaborative analysis with data from 11 biologics registers in 9 European countries did not find an increased risk for incident melanoma [25].

Less research has been done so far on the risk of recurrence of skin cancer. It was analyzed as secondary outcome in a study from the Swedish ARTIS register [26]. In this analysis, 54 TNFi treated patients and 295 patients with csDMARD treatment had a history of an invasive or in situ melanoma when they started treatment. Out of these, three (TNFi group) and ten (csDMARD treated) patients developed a new melanoma during follow-up corresponding to a nonsignificant threefold increase with an age and sex adjusted hazard ratio of 3.2 (95% CI, 0.8–13–1) for TNFi-treated patients.

In the BSRBR, 10 csDMARD-treated patients and 17 with TNFi treatment had a history of melanoma at inclusion in the study. Three of the TNFi-treated patients developed recurrences and metastatic disease whereas none of the csDMARD-treated patients did so. Two of the patients with recurrences were treated within less than 5 years after cancer diagnosis; one was in cancer remission since 7.5 years [10].

Regarding the treatment with other nonTNFi biologics, there is no systematically collected data with regard to patients with a history of melanomas. Regarding the treatment with tocilizumab, the important role of IL-6 in inhibiting the growth of early-stage melanoma should be kept in mind [27,28]. Further observation is needed.

HEAD AND NECK CANCER

Another interesting but rather small retrospective cohort study analyzed TNFi in patients with prior head and neck cancer (HNC) [29]. The authors analyzed patients with rheumatoid arthritis from the U.S. Veterans Affairs database. 180 patients had a confirmed diagnosis of rheumatoid arthritis and HNC, of whom 31 were treated with TNFi after HNC diagnosis. In the TNFi group, 16% of the patients experienced a recurrence or died from

HNC versus 30% in the csDMARD group. The authors conclude that these findings add to the evidence that TNFi may be used safely in patients with rheumatoid arthritis with HNC.

CHANNELING TO RITUXIMAB

There is a tendency to use RTX as treatment of choice for patients with a history of cancer. In the recent DANBIO analysis [12], RTX was used as first bDMARD after cancer diagnosis in 30% of the patients, reflecting this strong channeling to RTX. Also, Frisell *et al.* [30] showed that there was a strong preference of RTX, and other non TNFi bDMARDs to a lesser extent, in patients with a history of cancer.

This preference of RTX is based more on gut feeling or analogy than on strong evidence. RTX, which was developed as lymphoma treatment may be considered as well tolerated regarding tumorigenesis. However, B-cell depletion might lead to an impaired immunosurveillance of cancer and hence might theoretically promote malignancies. In a long-term outcome study after high-dose chemotherapy from the Italian lymphoma study group, RTX was an independent risk factor for the development of secondary solid tumors [31]. However, this result must be interpreted with caution because of the influence of the different drugs used in high dose polychemotherapy regimes. Despite the higher risk of a second malignancy, the overall survival in this study was significantly better in RTX-treated patients compared to the non-RTX-treated group. Certainly, the finding of a higher risk of secondary solid tumors in lymphoma patients cannot simply be transferred to patients with rheumatoid arthritis, thus from our point of view, it is necessary to gain more evidence regarding the long-term safety of RTX in patients with rheumatoid arthritis with prior malignancies.

OTHER BIOLOGIC AND TARGETED SYNTHETIC DMARDS

Long-term safety data on other non-TNFi bDMARDs like tocilizumab, and abatacept and on tsDMARDs (tofacitinib and baricitinib) are not available. Therefore, recommendations regarding their use in patients with a history of cancer cannot be made.

GUIDELINES

In regard to how to treat patients with rheumatoid arthritis with a history of cancer, it is useful to analyze the current guidelines.

In the ACR guidelines [32], the recommendations are stratified for patients with a history of skin cancer, lymphoproliferative disease, and solid cancer. Concerning both nonmelanoma skin cancer and melanoma, the guidelines conditionally recommend csDMARD over biologics or tofacitinib, however with a very low level of evidence. For previous lymphomas, a strong recommendation is made to prefer RTX over TNFi, however, there is a very low level of evidence. Combination DMARD or abatacept or tocilizumab is conditionally recommended over TNFi, again with a very low level of evidence. No publication to base this recommendation on was cited. For patients with a history of solid cancer, no specific recommendations are made.

However, from our point of view the cited literature in the recommendations does not justify these statements. The reference for the recommendation stating that RTX should be preferred over TNFi is a study without any data on RTX [10]. Only the most recent publication from this cohort (published six years after the cited reference) reports results on RTX [8▪]. Furthermore, the recommendation that a combination of DMARDs is preferable over TNFi is contrary to data from a recent meta-analysis [14▪], which included 16 studies with 11702 patients (RA, inflammatory bowel disease, psoriasis) and 31258 patient-years of follow-up after a prior cancer diagnosis. The results showed a nonsignificant but numerically higher rate of cancer recurrence among patients receiving a combination of immunosuppression (54.5/1000 patient-years) compared to patients receiving TNFi (33.8/1000 patient years) or no immunosuppression (37.5/1000 patient years).

In the recommendations of the French society for rheumatology for managing rheumatoid arthritis from 2014 [33], RTX is recommended as a good choice for patients with a history of cancer within the past 5 years.

Neither the EULAR 2016 guidelines [34] nor the NICE guideline (2009, update 2017) specify recommendations for patients with a history of a malignancy. The German guideline (2012; AWMF 060–004) has a one-sentence statement pointing out that RTX has a unique position in the treatment of patients with a history of malignancies.

Although the authors of some guidelines try to take into account the specific clinical situation, there is not enough evidence to generally recommend one specific treatment strategy.

INTERVAL

Because of the higher priority of the cancer treatment compared to comorbidities like rheumatoid arthritis, a certain time interval between the diagnosis of the cancer and (re-)initiating rheumatoid

arthritis treatment is obvious. It is neither clear whether the length of this interval is important in respect to the safety of the rheumatoid arthritis treatment nor do we know which length of treatment intermission is recommendable. Not only the recurrence risks of malignancies differ between cancer types, but also the time in which these recurrences are most probable. For example, the recurrence risk in small cell lung cancer is very high within the first 2 years after diagnosis and is getting low after more than five years; whereas in breast cancer the risk is on a much lower level but remains almost stable for decades after diagnosis [15,16]. Therefore a generalizable recommendation for a safe time interval is not possible.

The evidence from observational studies regarding patients with a very recent history of cancer is scarce, as most studies mirror the reluctance of rheumatologists to prescribe TNFi early after cancer diagnosis. The median interval between cancer incidence and treatment start in the BSRBR cohort was, for example, 7.9 years (IQR: 3.0–13.3) in csDMARD and 11.5 years (IQR: 5.8–17.6) in TNFi treatments. Only patients receiving RTX after cancer diagnosis were treated earlier with 5.4 (IQR: 3.0–9.2) years after diagnosis [8▪]. Recent data from the RABBIT cohort, published only in abstract form [35], showed a similar difference between time to TNFi start (median of 7 years) and time until start with RTX (median 3 years). In the ARTIS cohort, a median time of 9.4 years until treatment start with TNFi was observed. Only 14% of patients were treated within the first 5 years after cancer diagnosis.

CONCLUSION

In conclusion, we have to state that the best therapeutic management of patients with rheumatoid arthritis with a history of cancer is still unknown. Further analyses of the prospective cohort studies are warranted, hopefully including more data on the non-TNFi bDMARDs. Although evidence of the best rheumatoid arthritis treatment is not sufficient yet, we should keep in mind that high disease activity of rheumatoid arthritis has a detrimental effect on numerous outcomes of patients with rheumatoid arthritis, including other comorbidities, quality of life, and mortality. Therefore, an efficacious treatment of the rheumatoid arthritis is of great importance. There is a growing body of evidence, that TNFi treatment does not increase the risk of cancer recurrence, at least regarding the overall risk, after breast cancer, and if the treatment is started after a certain time interval. The available data on RTX also indicates a good safety profile in patients with rheumatoid arthritis with prior malignancies who are treated with RTX, although the numbers of patients treated are still low. For all other bDMARDs there is no data.

Close communication between the rheumatologist, oncologist, and patient is necessary to find the best treatment option for each individual patient. Patients should be informed comprehensively and may then be willing to accept a small residual uncertainty in order to get an effective treatment for their rheumatoid arthritis.

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Conflicts of interest

A.R. has received speaker honoraria in the last 3 years from Celgene, and Janssen-Cilag outside the submitted work. A.R. is one of the PIs of the RABBIT-SpA register, which is supported by a joint, unconditional grant from AbbVie, Celgene, Janssen-Cilag, MSD, Novartis, Pfizer, and UCB. A.S. has received speaker honoraria in the last 3 years from AbbVie, BMS, MSD, Pfizer, Roche, and UCB outside the submitted work. She is one of the PIs of the German Biologics Register RABBIT which is supported by a joint, unconditional grant from AbbVie, Bristol-Myers Squibb, Hexal, Lilly, MSD, Pfizer, Roche, and UCB.

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How does abatacept really work in rheumatoid arthritis?

Michael Bonelli and Clemens Scheinecker

Purpose of review
The purpose of this review is to summarize the current knowledge concerning the mechanisms of action of Abatacept in patients with rheumatoid arthritis.

Recent findings
Abatacept (CTLA-4Ig) represents a soluble, recombinant, fully humanized fusion protein, comprising the extracellular domain of CTLA-4 and the Fc portion of IgG1. Abatacept binds to the costimulatory molecules CD80 and CD86 on antigen-presenting cells (APC), thereby blocking interaction with CD28 on T cells. In humans, Abatacept treatment was shown to be effective in patients with various autoinflammatory diseases including rheumatoid arthritis. Although the prevention of T-cell activation by interfering with signaling via CD28 still represents the main mechanism of action Abatacept acts on additional cell populations including regulatory T cells (Treg), monocytes/macrophages, osteoclasts, and B cells.

Summary
Effects of Abatacept on other cell populations besides T cells have to be taken into account and might represent a valuable contribution to the therapeutic success.

Keywords
abatacept, costimulation, CTLA-4Ig, rheumatoid arthritis

INTRODUCTION

The requirement of naïve T cells to receive two signals to become activated was first proposed by Lafferty and Cunningham [1]. Signal one stems from the engagement of the antigen-specific T-cell receptor (TCR) with peptide antigens that are presented by major histocompatibility complex class II (MHC II) molecules on the surface of antigen-presenting cells (APC). This initial event leads to the upregulation of the costimulatory molecules CD80 (B7-1) and CD86 (B7-2) on APCs, which provides signal two via binding to CD28 molecules on T cells [2,3]. CD28 is the founding member of a subfamily of costimulatory molecules that are characterized by an extracellular variable immunoglobulin-like domain. In humans, CD28 is constitutively expressed on roughly 80% of human $CD4^+$ T cells and 50% of $CD8^+$ T cells. CD28 expression has also been identified on other cell lineages as well, including bone marrow stromal cells, plasma cells, neutrophils, and eosinophils. The functional importance of CD28 on these cells, however, is not completely understood. CD28 signaling increases the level of T-cell proliferation and cytokine production and it promotes T-cell survival. CD28 signaling also results in the upregulation of antiapoptotic proteins such as Bcl-XL [4] and enhances the expression of CD40 ligand (CD40L) and adhesion molecules that are required for cell trafficking such as the very late antigen-4 (VLA-4) [5–7].

At the same time while becoming activated, T cells start to express endogenous cytotoxic T-lymphocyte antigen-4 (CTLA-4) on the cell surface. CTLA-4 binds to B7 molecules on APC with a 10- to 20-fold greater affinity as compared to CD28 and delivers antiproliferative signals to T cells that downregulate the CD28 mediated T-cell activation [8–12]. CTLA-4-deficient mice develop a profound lymphoproliferative disease with immune mediated damage to multiple organs [9,13].

This central role of costimulation in T-cell function makes it a promising target for drugs to modulate

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KEY POINTS

- Abatacept represents an effective treatment of rheumatoid arthritis.
- Abatacept blocks the activation of effector T cells by interfering with signaling via CD28.
- Abatacept acts on additional cell populations including Treg, monocytes/macrophages, osteoclasts, and B cells.

the function of T cells. First studies using a soluble CD28 protein to block costimulation, however, were ineffective due to a low affinity of CD28 for its ligands.

Abatacept (CTLA-4Ig), in contrast, represents a soluble, recombinant, fully humanized fusion protein, comprising the extracellular domain of CTLA-4 and the Fc portion of IgG1 which has been modified to reduce the Fc region capacity to induce antibody-dependent cellular cytotoxicity (ADCC) and dependent complement-dependent cytotoxicity (CDC). Abatacept is the first biological compound that primarily aims to modulate T-cell activation in chronic inflammatory diseases such as rheumatoid arthritis. This effect is thought to be mediated by binding of abatacept to the costimulatory molecules CD80 and CD86 on APC, thereby blocking interaction with CD28 on T cells. In this manner autoreactive $CD4^+$ T cells receive signal one in the absence of signal two which leads to a state of T-cell anergy or unresponsiveness. Experimentally, abatacept treatment was found to be effective in various murine models of T-cell-driven inflammatory diseases. As for example abatacept has been successfully used to inhibit the level of disease severity in the collagen type II-induced arthritis (CIA) model. Treatment with Abacept at the time of disease induction for CIA was found to inhibit disease development and was associated with lack of lymphocyte expansion within the draining lymph nodes [14]. In humans, abatacept treatment was shown to be effective in patients with various diseases including rheumatoid arthritis, juvenile idiopathic arthritis, renal allograft rejection and type I diabetes. Mixed results have been reported in patients with spondylarthropathies and lupus nephritis. Abatacept was found to be ineffective or even deleterious in the treatment of patients with asthma, inflammatory bowel diseases or liver transplant rejection (reviewed in [15▪▪]).

THE EFFECT ON ABATACEPT ON EFFECTOR T CELLS

The proposed mechanism of abatacept function is to decrease T-cell responses by competing for B7 ligand (CD80/CD86) access to CD28 and limiting CD28 signaling that is required for T-cell activation [16].

In addition to APC, costimulatory molecules can also be expressed on T cells, in particular on CD4 T-cell clones, CD8 T-cell clones, and natural killer cell clones upon activation [17–19]. Although initially the expression of CD80 molecules was reported on activated T cells [17,18], also the expression of CD86 molecules was subsequently described [20].

Therefore, under conditions that stimulate T-cell activation, such as in chronic inflammation, both CD80 and CD86 costimulatory molecules can be expressed on T cell. One might therefore speculate that CD80 or CD86 molecules need to back-signal into the T cells in order to facilitate suppression. Considering the constitutive expression of CTLA-4 molecules on Tregs, this further supports the possibility of direct interactions between Tregs and pathogenic T cells mediated by CD28/CTLA-4 and CD80/CD86. Thus, the expression of CD80 or CD86 on T cells could be important for the control of pathogenic T cell by Treg [21].

Whether or not a putative interaction of CTLA-4Ig with costimulatory molecules on T cells affects phenotypic and/or functional characteristics of T cells, which might contribute or interfere with the therapeutic effect of CTLA-4Ig, has not been analysed in detail.

Our own experiments revealed that abatacept treatment in RA patients significantly increases proportions of $CD4^+$ T cells although no significant changes were observed for proportions of $CD4^+$ $CD62L^+$ naïve and $CD4^+CD45RO^+$ memory T cells. We observed a significant reduction in the expression of T-cell activation markers CD69 and CD71 and, interestingly, also the percentage of cells expressing the Fas receptor CD95, which is required for Fas-induced apoptosis, was decreased upon treatment.

It has previously been shown that CTLA-4 signalling inhibits the expression of CD95 and CD95 ligand (L) on T cells and enhances the expression of the antiapoptotic molecule Bcl-2. Thereby CTLA-4 promotes the survival of antigen-specific T helper cells by maintaining the resistance of these cells against CD95/CD95L (FAS/FAS ligand) induced apoptosis [22].

In line with this we detected a dose-dependent decrease of apoptotic cells in the presence of CTLA-4Ig, suggesting that increased proportions of $CD4^+$ T cells after CTLA-4Ig treatment can be explained by the downregulation of CD95 expression and a reduction of apoptosis in T cells.

THE EFFECT OF ABATACEPT ON REGULATORY T CELLS

Regulatory T cells (Treg) play an important role in the maintenance of peripheral immunological

self-tolerance because they specialize in the suppression of effector T-cell proliferation and thus can actively downregulate the activation and/or proliferation of self-reactive T cells. This has led to the hypothesis that either quantitative and/or qualitative deficiencies of Treg might be responsible for a situation where the sum of auto-reactive effector T-cell responses overwhelms the capacity of a weakened Treg compartment and triggers the outbreak of overt autoimmune disease.

CTLA-4 and CD28 are regarded as modifiers of Treg function, which can either enhance (via CTLA-4) or inhibit (via CD28) Treg suppression. In contrast to naive T cells, Treg express both CD28 and CTLA-4 constitutively suggesting that Treg might be more sensitive to differences in patterns of CD80 and CD86 expression on APC [23].

In addition also Treg cells can acquire CD80 and CD86 molecules from APC as well in a CTLA4-independent manner. Therefore, costimulatory molecules expressed on Treg might also server as a binding partner for abatacept.

In animal models, abatacept treatment leads to decreased Treg cell numbers as a result of a blockade of CD28 signals required for Treg homeostasis.

In humans, the role of CTLA-4Ig treatment on T-cell subsets has been investigated in different studies [24,25]. The data within these studies for Treg cell frequency are conflicting, which is partly because of different time points when Treg cell frequencies were analyzed and partly because of different patient cohorts. Picchianti *et al.* for example described normal frequencies of CD25pos-CD127low Treg but a reduced suppressive capacity of Treg that was restored upon abatacept treatment [25]. In contrast, Álvarez-Quiroga described similar levels of peripheral blood $CD4^{+}CD25$bright natural Treg cells in patients with rheumatoid arthritis as compared to healthy controls. Treg frequencies, however, were diminished upon abatacept treatment [24].

Others have reported reduced numbers of distinct Treg subsets such as CD4+CD25− LAG3+ regulatory T cells that produce high amounts of interleukin (IL)-10 and interferon (IFN)-γ, lack Foxp3 expression, and suppress B-cell antibody production in patients with rheumatoid arthritis, in particular in patients with high disease activity. Abatacept treatment significantly increased the frequency of LAG3+ Tregs in patients with rheumatoid arthritis. Moreover, naive $CD4^{+}$ T cells stimulated in the presence of abatacept were found to differentiate into $CD4^{+}$ T cells with $LAG3^{+}$ Treg-like properties [26].

Data for the effects of CTLA-4Ig on Treg cell function are also limited and conflicting. Although Alvarez-Quiroga *et al.* [24] described an enhanced suppressive capacity of Treg cells, isolated from the periphery after abatacept therapy, Pieper *et al.* could not detect an increased suppressive capacity of synovial Treg cells [27]. To our surprise our own experiments revealed a diminished suppression of T-cell proliferation *in vitro* [28▪]. In this study, we were able to show that abatacept treatment of patients with rheumatoid arthritis not only leads to increased proportions of $CD4^{+}$ T cells as described above but also of Treg cells, which display phenotypic characteristics of diminished activation. Increased proportions of T cells, including Treg cells, came with a downregulation of CD95 and a reduction in CD95-mediated apoptosis.

Functional analyses further suggested a diminished suppressive capacity of Treg cells *in vitro* at first sight. Subsequent experiments, however, revealed that the preincubation of only the responder T-cell population but not of the Treg cell population with abatacept caused a decrease of suppression, suggesting that CTLA-4Ig affects responder T cells but not Treg cells. Based on this finding we hypothesised that binding of abatacept on B7 molecules on T cells leads to a reduced susceptibility of T cells for Treg cell suppression. A direct binding of abatacept on T cells with downstream effects therefore has to be taken into account.

THE EFFECT OF ABATACEPT ON MONOCYTES/MACROPHAGES

Beside its effect on T cells, abatacept was suspected to affect other cell types as well, in particular APCs and several studies have shown that abatacept induces reverse signaling into the APC via the enzyme indoleamine 2,3-dioxygenase (IDO), although partially conflicting results have been reported so far. CD80/CD86 engagement has been suggested to activate B7 molecules and intracellular signaling events, including the recruitment of p38 mitogen-activated protein kinase and nuclear factor kappa-light-chain enhancer of activated B cell. This has been shown to induce an increase in the production of the enzyme IDO and induction of tryptophan catabolism in murine [29] and human dendritic cells [30], ultimately leading to the inhibition of T-cell proliferation. Such localized control of tryptophan catabolism in specific tissue microenvironments has been suggested to contribute to the induction and maintenance of peripheral tolerance [29]. However, no increased IDO production, in either B cells or monocyte-derived dendritic cells, upon abatacept treatment was observed by others [31,32]. Therefore, the biologic relevance of the upregulation of IDO in APCs in CTLA-4Ig-mediated immunosuppression currently remains debatable.

Our own experiments on the effect of abatacept revealed a significant increase in the percentage of $CD14^+$ monocytes in patients with rheumatoid arthritis upon abatacept treatment. Phenotypic analysis did not reveal substantial changes in the expression profile of costimulatory molecules on monocytes. However, we observed a significant reduction in the expression of several adhesion molecules that are required for the adhesion to and active migration of granulomonocytic cells through endothelial barriers. Moreover, and in line with the phenotypic analysis, the functional assessment of isolated $CD14^+$ monocytes revealed that abatacept treatment led to a reduced adhesion of monocytes to endothelial cells and a reduced capacity of monocytes to migrate through a transendothelial cell layer *in vitro* [33]. This combined effect of abatacept on adhesion and migration of monocytes might help to explain the increase in $CD14^+$ monocytes in the peripheral blood of the patients. In addition, one is tempted to speculate that the reduced migration of Monocytes might also contribute to a diminished inflammation in the synovial tissue of the joints and thereby help to ameliorate signs of clinical disease activity.

Macrophages differentiate into bone-resorbing osteoclasts at sites that are closely located to mineralized tissue such as bone. The differentiation of osteoclasts within the inflamed joint is a key step for inflammatory bone erosion and joint damage in rheumatoid arthritis. Abatacept was shown to inhibit RANKL-mediated and TNF-mediated osteoclastogenesis *in vitro* in the absence of T cells. Moreover, abatacept was also able to inhibit TNF-induced osteoclast formation in a non-T-cell dependent TNF-induced murine model of arthritis and the formation of inflammatory bone erosion *in vivo* [34]. Therefore, CTLA-4 can be regarded as an antiosteoclastogenic molecule that directly binds osteoclast precursor cells and inhibits their differentiation. This might also explain the bone-sparing effect of abatacept, which has been demonstrated in clinical studies in patients with rheumatoid arthritis.

A subsequent study from Bozec *et al.* [35] reported higher frequencies of CD14highCD155-high and of CD11bhighCD115high peripheral blood osteoclast precursors in patients with rheumatoid arthritis as compared to healthy controls. Patients with rheumatoid arthritis under abatacept treatment, however, displayed similar proportions as observed in healthy controls. In-vitro cultures further revealed a higher osteoclastogenic potential of precursor cells in patients with rheumatoid arthritis as compared to healthy controls, which was reversed by abatacept treatment. In-vitro exposure of osteoclast precursors to abatacept also reduced osteoclast marker genes such as c-Fos min, NFATc1, and C-Fms (CD115) and RANK.

THE EFFECT OF ABATACEPT ON B CELLS

Besides monocytes and macrophages, abatacept could affect other APC populations as soon as they express costimulatory molecules such as B cells.

A major role for B cells has been described for various autoimmune diseases, including rheumatoid arthritis [36]. The pathogenic role of B cells is believed to be related to their capacity to produce autoantibodies [37], to migrate to inflammatory tissues [38], to produce proinflammatory cytokines [39], to control T-cell proliferation [40,41], and to play a critical role in regulating the T-cell response to autoantigens [42]. In patients with rheumatoid arthritis, B cells have been shown to express higher levels of CD80/CD86 molecules compared to healthy controls [43], which predisposes B cells as binding partners for abatacept. In line with this, intracellular signaling events for example have been described that are induced by ligation of CD80 and CD86 in a B-cell lymphoma and in B cells, signaling via CD86 has been reported to increase immunoglobulin production [44]. In patients with rheumatoid arthritis, abatacept treatment was found to reduced $CD38^+$ and/or $CD27^+$ memory B-cell subsets. In addition, abatacept is also suspected of modulating B-cell functions directly by reducing (auto)Ab production and, indirectly, by reducing the expansion and selection of memory B cells to form plasma cells in the germinal centers by T cells [45].

Others have described a normal-sized B compartment in patients with rheumatoid arthritis but impaired B-cell proliferation in response to CpG stimulation. Abatacept therapy led to an improvement in B-cell function, in particular in patients not responding to the first anti-TNF-α agent. The authors therefore speculated that patients with rheumatoid arthritis with an inadequate response to anti-TNFα therapy are immunologically prone to benefit from an agent targeting a different pathway [25].

CONCLUSION

In conclusion, there is accumulating evidence that therapeutic interventions that interfere with costimulatory molecules not only affect the activation of effector T cells. Although the prevention of T-cell activation by interfering with signaling via CD28 might still represent the main mechanism of action of such therapeutics, we and others have shown that additional side effects of such treatments exist. As in

the case of rheumatoid arthritis abatacept treatment, while interfering with effector T-cell activation, acts on additional cell populations including Treg, monocytes/macrophages, osteoclasts and B cells.

These effects depend on the proinflammatory environment that is responsible for the expression of costimulatory molecules on cell populations beside effector T cells.

The extent as to which such side effects contribute to the overall therapeutic efficacy are not entirely clear so far. Nevertheless, they have to be taken into account and might represent a valuable contribution to the therapeutic success.

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Conflicts of interest

There are no conflicts of interest.

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

- ■ of special interest
- ■■ of outstanding interest

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