Recent advances in the treatment of rheumatoid arthritis

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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. [15]. Smolen. [16▪].
SB4 (Benepali, Brenzys)	Etanercept	Approved in Europe, Current US clinical trial	ClinicalTrials.gov:NCT01895309 *Ann* [19].
ABP501	Adalilumab	Current US clinical trial	ClinicalTrials.gov:NCT01970475 *Ann* [20].
GP2013	Rituximab	Current US clinical trial	ClinicalTrials.gov:NCT01274182 *Ann* [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; 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

None.

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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.