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Rheumatoid Arthritis (Y Yazici, Section Editor)

Updates in the Treatment of Rheumatoid Arthritis

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Abstract

Purpose of review The treatment of rheumatoid arthritis (RA) is rapidly evolving; there is extensive literature to keep up with each year. The purpose of this review is to summarize the current general approach to rheumatoid arthritis treatment, with an emphasis on recent advances (since 2017).
Recent findings There have been three new medications approved for use in RA in the USA (not including biosimilars), new data made available on safety of more established medications, and new RA treatment guidelines published in that time period. Two of the approved medications are JAK inhibitors; indeed, JAK inhibitors are the biggest news in RA management in recent years.
Summary Despite these advances, the general treatment strategy—when to start treatment, what medications should be tried first and in refractory cases, treatment goal, and how and when to discontinue medications—remains largely unchanged.

Introduction

During recent years, we have seen new medications being added to the rheumatoid arthritis (RA) treatment armamentarium, but there have not been any significant changes in overarching treatment strategy. There are three classes of disease-modifying antirheumatic drugs (DMARDs) available: conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DAMRDs (tsDMARDs). We will first review updated guidelines and outline the general treatment strategy before moving into a discussion of specific therapies.

Guidelines

The last American College of Rheumatology (ACR) guidelines were published in 2015; an update is anticipated in 2020 [1, 2]. The European League Against

Rheumatism (EULAR) published updated guidelines in 2019 [3••]. Most of their recommendations remained unchanged. They added a new "overarching principle" of RA management: patients may require multiple drugs with different mechanisms of action in order to reach therapeutic goals. Of the 12 specific EULAR recommendations, only 3 were changed. In patients who are refractory to csDMARDs with poor prognostic factors, bDMARDs and tsDMARDs are now considered equivalent options (in the past, bDMARDs were favored over tsDMARDs). In patients refractory to tumor necrosis factor inhibitors (TNFis), slight preference was given to trying a medication with another mechanism of action (MOA) rather than another TNFi. Finally, in patients in persistent remission on a tsDMARD, taper can be considered (in the past, only bDMARDs were included in this statement).

General treatment strategy

The major points to consider are as follows: when to start treatment, what treatment to start with, what treatment to use in refractory patients, what the treatment target should be, and if/when to withdraw or taper therapy. As previously mentioned, there have not been significant changes on any of these fronts in the preceding few years. While a full review of treatment strategy is beyond the scope of this article, we will summarize the major points. Treatment with DMARDs should be started at the time of diagnosis: multiple trials have shown that earlier treatment leads to better outcomes [4]. Both the ACR and EULAR guidelines recommend starting with methotrexate monotherapy in most patients, regardless of level of disease activity at diagnosis [2, 3••]. TsDMARDs have been shown to be superior to methotrexate in treatment-naïve patients, but cost/insurance reimbursement is a significant barrier to their use as an initial treatment strategy [5]. This may change when generic tsDMARDs become available. In general, monotherapy with an aggressive step-up strategy is supported over initial combination therapy, although this is subject to debate. There is no clear answer on which therapy to choose in methotrexate inadequate responders (MTX-IRs). Options in patients who can tolerate methotrexate include combination therapy with other csDMARDs, addition of a bDMARD, or addition of a tsDMARD. In patients with MTX intolerance, IL-6 inhibitors and JAK inhibitors have demonstrated efficacy as monotherapy. Finally, current data support tapering DMARD therapy, including bDMARD therapy, in patients in remission over discontinuing therapy.

Use of imaging to guide therapy

Trials of the use of imaging to guide treatment in RA have largely been negative. One trial compared MRI-guided to a conventional treat-to-target strategy in RA patients in clinical remission and found that using MRI did not result in improved maintenance of clinical remission or a decrease in radiographic progression [6]. In another trial, ultrasound was used to try to predict who would flare in a group of RA patients discontinuing DMARD therapy; ultrasound did not add significant value to existing clinical predictors [7].

Diet and lifestyle

Diet and lifestyle changes are not featured prominently in the RA treatment algorithm. Exercise and occupational/physical therapy can improve function and symptoms in patients with RA [8, 9]. Increasing physical activity has been shown to reduce pain and fatigue [10, 11]. The only dietary intervention that may have disease-modifying effect is fish oil at high doses (greater than 3 g daily) [12]. RA patients are at increased risk of osteoporosis and cardiovascular events, so diet and lifestyle modifications (along with pharmacotherapy) targeted to reduce these risks should be recommended.

Pharmacologic treatment

There are six different effective targets for biologic or targeted synthetic treatments for RA: Janus kinase (JAK), tumor necrosis factor α (TNF α), interleukin-6

(IL-6), IL-1, CD 80/86, and CD20 (Table 1). Discussion of the conventional synthetic treatments is beyond the scope of this review, as there have not been any recent major developments. The biggest news in RA management in recent years has been the JAK inhibitors (JAKis), with new drug approvals and publication of multiple large trials. Each of the six classes will be reviewed, with emphasis on treatments with more recent advances.

Drug approvals

For USA readers, the Federal Drug Administration (FDA) approved three new medications for RA between 2017 and 2020 (sarilumab, baricitinib, upadacitinib) as well as several biosimilars (for adalimumab, rituximab, etanercept, infliximab). Relevant data is reviewed in the following sections.

Safety issues in pharmacologic treatment

The recombinant zoster vaccine is now available in the USA. While we do not have prospective direct data on its safety in the RA population, it was shown to be safe in a population of patients with hematological malignancies receiving immunosuppressive therapies [13]. The recommendation for use in the immunocompromised population is under review, but it is commonly being used in practice [14]. In one recent series, the safety profile in rheumatic disease patients was similar to that in clinical trials of the vaccine [15].

Two small trials have been published assessing the effect of temporary discontinuation of methotrexate on the efficacy of the flu vaccine [16, 17]. Based on these trials, many providers are holding methotrexate for 2 weeks after administration of the flu vaccine. The generalizability to other medications used in RA and other vaccines is unknown.

JAK inhibitors

JAKis are small molecules which may be orally administered, in contrast to biologic therapies. They inhibit tyrosine kinases that are required for signal transduction for several inflammatory cytokines, including IL-6, although it would be a mistake to think of these agents simply as oral IL-6 inhibitors. Currently approved JAKis in the USA include tofacitinib, upadicitinib, and baricitinib; upadicitinib and baricitinib are newly approved in the last few years and will be discussed in detail below. Both upadicitinib and tofacitinib are approved for csDMARD-IRs; bariticinib is approved only for bDMARD-IRs. This class of medications demonstrates superior efficacy to methotrexate as monotherapy [5, 18•]. They also have a generally faster onset of action compared to bDMARDs [19].

There are three boxed warnings in the USA that apply to the entire class for thrombosis, malignancy, and infection. As with biologics, these medications are associated with an increased risk of serious infections. Immunizations should be up to date prior to starting. With this class more than others, there is an increased risk of herpes zoster [20]. The malignancy risk is largely based on animal studies without any clear increased risk of malignancy in human trials compared to patients on other RA treatments [20]. The thrombosis warning is unique to this class of medications in RA treatment. It is based on a data involving baricitinib 4mg and tofacitinib 10mg twice daily, which are not doses that are approved in the USA for RA; there has not been increased risk demonstrated with baricitinib

Table 1. RA treatment options at a glance

Medication	Dosing route and frequency	Price per dose in dollars	Price per day in dollars	Notes
Conventional synthetic DMARDs				
Methotrexate	PO Q wk; SQ Q wk	28 (PO); 148 (SQ)	4 (PO); 21 (SQ)	Liver toxicity; hypersensitivity pneumonitis; stomatitis; GI intolerance; teratogenic
Leflunomide	PO QD	6	6	Liver toxicity; GI intolerance; teratogenic
Sulfasalazine	PO BID	<1	<1	GI intolerance; cytopenias
Hydroxychloroquine	PO QD	<1	<1	Favorable side effect profile; retinopathy with long-term use; rare myopathy; reduces risk of DM
Azathioprine	PO QD	6	6	Cytopenias; pancreatitis; GI intolerance
Biologic DMARDs				
TNF inhibitors				Contraindicated in advanced CHF, multiple sclerosis
Certolizumab	SQ Q 2 wk	5556	397	Pegolated; does not cross placenta
Etanercept	SQ Q wk	1667	238	Fusion protein; less antigenic; good option in patients that cannot take csDMARDs
Adalimumab	SQ Q 2 wk	3334	238	
Golimumab	IV Q 2 mo; SQ Q mo	9157 (IV); 6031 (SQ)	152 (IV); 201 (SQ)	
Infliximab	IV Q 2 mo	2803	47	Chimeric antibody; more antigenic; csDMARD required
IL-1 inhibitors				
Anakinra	SQ QD	186	186	Probably less effective than TNFis
IL-6 inhibitors				Avoid if history of diverticulitis; monitor lipids
Tocilizumab	IV Q mo; SQ Q 1–2 wk	2767 (IV); 1254 (SQ)	92 (IV); 90 (SQ)	
Sarilumab	SQ Q 2 wk	1831	131	
B Cell				

Table 1. (Continued)

Medication	Dosing route and frequency	Price per dose in dollars	Price per day in dollars	Notes
Rituximab	IV Q 6 mo	112,740	626	Hepatitis B reactivation; vaccines potentially less effective
CD 80/86				
Abatacept	IV Q mo; SQ Q wk	4232 (IV); 2785 (SQ)	141 (IV); 397 (SQ)	Possible lower infection risk and higher malignancy risk; slower onset than TNFis
Targeted synthetic DMARDs				
JAK inhibitors				Herpes zoster; avoid if history of diverticulitis; monitor lipids; possible thrombosis risk
Baricitinib	PO QD	91	91	JAK1/JAK2; lower dose approved in US than rest of world
Upadacitinib	PO QD	197	197	JAK1
Tofacitinib	PO QD	188	188	JAK1/JAK3

Drug pricing: average wholesale price per Medi-Span [56]; as of May 2020. If weight-based, 60kg used. Specific dosing: tocilizumab 4mg/kg; infliximab 3mg/kg; azathioprine 2.5 mg/kg; rituximab 1000mg; methotrexate 20mg; leflunomide 20mg; sulfasalazine 2g; hydroxychloroquine 200mg. *BID*, twice daily; *SQ*, subcutaneous; *PO*, oral; *IV*, intravenous; *DMARD*, disease-modifying anti-rheumatic drug; *mo*, month; *wk*, week; *QD*, daily; *DM*, diabetes; *GI*, gastrointestinal; *TNFi*, tumor necrosis factor inhibitors; *CHF*, congestive heart failure; *JAK*, Janus kinase

2mg, tofacitinib 10/11mg daily, or upadacitinib [20]. Similar to IL-6 inhibitors, these medications should be avoided in patients with a history of diverticulitis: gastrointestinal perforations have been reported. Labs should be monitored to evaluate for hematologic and hepatic toxicity as well as lipid abnormalities.

In our practice, JAKis are presented as one of the many options for add-on therapy in patients who do not respond to an adequate trial of methotrexate. We are often using other csDMARDs or bDMARDs first (because of longer-term safety data and ease of insurance approval). We move to JAKis more quickly in patients who cannot tolerate methotrexate (since they are effective as monotherapy) or in patients who are csDMARD-IRs and have a preference to avoid injections or infusions.

Upadacitinib

Upadacitinib was approved in 2019 for treatment of patients with active RA who have inadequate response to or are intolerant of methotrexate. It has a higher affinity for JAK-1 compared to tofacitinib and baricitinib. There have been multiple RCTs in recent years demonstrating efficacy in several clinical

populations of RA patients. It is effective in treatment-naïve patients [21] (only available as abstract), csDMARD-IRs [22•, 23•, 24•], and in bDMARD-IRs [25•] compared to placebo. It is more efficacious than TNFis in csDMARD-IRs [22•]. It has been studied both as monotherapy [21, 23•] and in combination with csDMARDs [22•, 24•, 25•] although we currently do not have a trial to directly compare these approaches.
The standard dose is 15mg as a daily oral dose. There are no safety issues that set it apart from other JAKis. While there has not been any increased risk of thrombosis in clinical trials, the class-wide boxed warning applies. In our practice, this medication is considered an equivalent option to tofacitinib and the selection is typically made based on insurance implications.

Baricitinib

Baricitinib is a JAK-1/2 inhibitor approved in 2018 for patients with active RA who have had an inadequate response to TNFis. It is effective in treatment-naïve patients alone or in combination with methotrexate [18•]. It is efficacious in csDMARD-IRs [26•, 27•] and in bDMARD-IRs [28] compared to placebo. It is more efficacious than TNFis in csDMARD-IRs [27•]. These trials [26•, 27•, 28] allowed but did not require background csDMARDs. Of the previously mentioned studies, only the study involving bDMARD-IRs included the 2-mg dose (in addition to the 4-mg dose) [28].
The approved dose in the USA is 2mg daily. It is only approved for use in RA patients that are refractory to biologic DMARDs, which sets it apart from the other JAKis. As previously mentioned, there has been an increased risk of thrombosis reported with the 4-mg dose. This is generally not the first JAKi we reach for because most of the trials use a dose that is not approved for use in the USA.

Tofacitinib

As the oldest JAKi, approved in 2012, data on its efficacy will not be reviewed in detail. One recent development, unique to this medication and not the entire class, is an added boxed warning/safety alert for mortality in 2019. This was based on an interim analysis of a post-marketing trial that included 5mg BID (approved dose in RA) and 10mg BID (approved for ulcerative colitis only); there was an increased occurrence of blood clots and death (including sudden cardiovascular events) in the 10mg BID group [29]. This trial is ongoing, and the full analysis is pending.

IL-6 inhibitors

IL-6 inhibitors are monoclonal antibodies that act as IL-6 receptor antagonists to limit the effects of this inflammatory cytokine. Tocilizumab was the first medication in its class; sarilumab is a more recent addition that will be reviewed in detail. A third IL-6 inhibitor, sirikumab, was studied but not approved by the FDA. Tocilizumab and sarilumab can be used either in combination with a csDMARD or as monotherapy in csDMARD-IRs. Tocilizumab is available in subcutaneous and intravenous forms; sarilumab is only available for subcutaneous administration. As with all

bDMARDs and tsDMARDs, there is an increased risk of serious infection (boxed warning). Labs need to be monitored for liver toxicity and cytopenias. These medications have uniquely pronounced effects on acute phase reactants: c-reactive protein levels and erythrocyte sedimentation rates drop dramatically, sometimes independently of the clinical response. Similar to JAKis, they can increase lipid levels, but they have not been associated with increased cardiovascular risk [30]. Also similar to JAKis, they are contraindicated in patients with a history of diverticulitis due to risk of bowel perforation. Due to the risk of hepatic toxicity, these medications should not be started in patients with baseline hepatic impairment.

The role for IL-6 inhibitors in our treatment algorithm is typically in patients who have not responded to TNFis. Similar to JAKis, they are good options for patients who do not tolerate csDMARDs, and they may be preferable to TNFis in this situation. We select one over the other based on insurance coverage or preference for infusion therapy.

Sarilumab

Sarilumab was approved in 2017 for patients with active RA who have not responded to, or cannot tolerate, methotrexate. There are currently no published data for treatment-naïve patients. It is effective in csDMARD-IRs [31, 32•] and in bDMARD-IRs [33•] compared to placebo. As monotherapy, it is more efficacious than TNFis in csDMARD-IRs [34•]. It has been studied both as monotherapy [34•] and in combination with csDMARDs [31, 32•, 33•] although we currently do not have a trial to directly compare these approaches.

The approved dose is 200mg subcutaneously every 2 weeks. There are not any safety issues outside of the class-wide concerns previously mentioned.

TNF inhibitors

TNFis are monoclonal antibodies that interfere with the action of pro-inflammatory cytokine human tumor necrosis factor alpha. They are the oldest class of bDMARD. Currently approved TNFis include adalimumab, infliximab, certolizumab, golimumab, and etanercept. There have not been any recent additions to this class of medications. They are all approved for active RA (not just in csDMARD-IRs). Infliximab and golimumab are only approved in combination with a csDMARD; the others can be used alone or in combination. There is no evidence that one TNFi is more efficacious than others. Infliximab is available in intravenous form only, golimumab has both intravenous and subcutaneous options, and the rest are available as subcutaneous injections. They vary in frequency of dosing. Certolizumab pegol is unique because it does not cross the placenta and may be a good choice for women of childbearing age/pregnant women (although there is no evidence for toxicity of TNFis in pregnancy, and all are widely used in this situation). Etanercept appears to be less antigenic than the rest and may be a good choice for those who do not tolerate concomitant methotrexate therapy to reduce antigenicity. Infliximab is more antigenic and should almost always be used with a csDMARD.

As with other biologics, there is an increased risk of serious infection (boxed warning) including reactivation of tuberculosis and hepatitis. The concern

about malignancy risk, including lymphoma (boxed warning), has been mitigated substantially by several large longitudinal registry studies; risk for skin cancer remains a concern [35, 36]. They are contraindicated in patients with multiple sclerosis or advanced congestive heart failure. TNFi use has been associated with development of autoantibodies and more rarely with development of autoimmune diseases, including psoriasis.

We present addition of TNFis as an option, along with addition of other csDMARDs, for patients who have not responded to methotrexate. There is currently no evidence that one approach is superior to the other. The decision is often made based on patient preference and comorbidities as well as financial considerations.

CD 80/86

Abatacept is a unique biologic agent that targets T-cell co-stimulation. It is available as an injection and intravenously. It can be used as monotherapy or in combination with csDMARDs; our practice is to use it with methotrexate, as it is generally more effective when used this way. It has similar efficacy compared to TNFis [37].

The risk of serious infections is similar to or slightly less than TNFis [38]; in contrast to other biologics, there is no boxed warning regarding serious infections. There is also no boxed warning regarding malignancy risk. There was concern about increased risk of chronic obstructive pulmonary disease (COPD) exacerbations compared to placebo in an early trial; however, this has not been borne out in more recent registry studies [39, 40].

We reach for abatacept in patients who are refractory to TNFis and are able to take concomitant csDMARDs. It is often not the first non-TNFi class we try, but may be a good option in patients in whom infections are a concern.

CD 20

Rituximab is a monoclonal antibody directed at CD20. It is only available as an infusion. It should be used in combination with a csDMARD unless contraindicated. In an early trial, the duration of response was substantially less when given without concomitant MTX [41]. It works better in patients who are RF/CCP positive [42]. It may be a good option in RA patients with ILD (low-quality evidence) [43, 44] and with vasculitis (low-quality evidence; largely extrapolated from trials in other systemic vasculitides) [45, 46].

Compared to other biologics, there is a higher risk of hepatitis B reactivation (boxed warning), and concomitant antiviral therapy is recommended for patients who are core antibody positive as well as those who are antigen positive. There are also boxed warnings for severe mucocutaneous reactions, infusion reactions, and progressive multifocal leukoencephalopathy. Vaccinations are less effective in patients taking rituximab compared to other biologics [47]. Labs need to be monitored for cytopenias and for hypogammaglobulinemia. Both neutropenia and low immunoglobulin G are risk factors for serious infections in patients treated with rituximab [48].

Rituximab is a good option for patients in whom treatment compliance is an issue or that have extra-articular manifestations such as ILD and vasculitis.

IL-1 inhibitors

The IL-1 inhibitors are of limited use in the practical management of RA. Anakinra is the only IL-1 inhibitor approved in the USA for treatment of RA and it is a daily injection. While there have not been head to head trials comparing this medication to other biologics, the response rate seen in clinical trials appeared to be less than with other agents [49].

Biosimilars

There are currently biosimilars available in the USA for adalimumab, etanercept, infliximab, and rituximab. They account for a very small proportion of biologic expenditures in the USA (Fig. 1). Based on 2017–2018 data, biosimilar prescriptions consisted of no more than 3.5% of all TNFi prescriptions [50]. The 2017 market share in the USA for infliximab biosimilars was 2.4% [51]. By contrast, the company that produces an infliximab biosimilar announced that its product captured 56% of the infliximab market in Europe in 2018 [52]. There are likely a number of factors contributing to this difference in utilization [53]. There are more and earlier biosimilar approvals in Europe. In the USA, there has been delayed market entry for many biosimilars due to ongoing litigation. The key driver has been market differences in payor incentives for their use as well. In contrast to the fragmented insurance market in the USA, nationalized health systems in Europe and other areas drive medication choices, and the decisions made by these systems are quite cost-sensitive. Drivers of cost in the USA, both to the insurer and the patient, are much more complicated, and cost savings with biosimilars as an alternative to reference biologics have not been as great as anticipated.

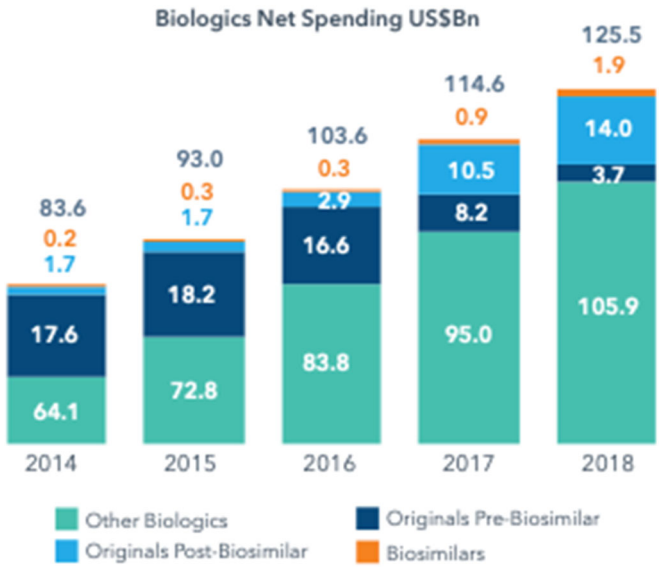

Fig. 1. Net spending in the USA on biologics (US$Bn). Bn, billion. Source: IQVIA National Sales Perspectives, IQVIA Institute, Jan 2019 [55].

Looking to the future

Twenty to 30% of RA patients remain refractory to all current treatment options [3••], which necessitates a continued focus on new treatment strategies. There are agents currently being studied that target granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, multiple JAK subsets, IL-2, and fractalkine [54]. Methods to predict individual therapeutic response to medications are needed in order to improve on current strategies that require several months to cycle through medications with different MOA until finding one that works. Treatment algorithms may change once the JAKis come off patent and become available as more affordable generics, given their superior efficacy compared to other oral DMARDs. We will also likely see more research on strategies to taper DMARDs. Can particular biomarkers or imaging findings predict which patients will flare if they taper or discontinue their medication? We also anticipate more studies on the potential treatment of "preclinical" RA in order to prevent the advent of clinical disease. We may also see an increase in biosimilar use in the USA, as has occurred in other regions.

Declarations

Ethics Approval and Consent to Participate
This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest
Eric Ruderman reports personal fees from Abbvie, personal fees from Amgen, personal fees from BMS, personal fees from Gilead, personal fees from Janssen, personal fees from Lilly, personal fees from Novartis, and personal fees from Pfizer, outside the submitted work.
Sarah Fantus declares that she has no conflict of interest.

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- • Of importance
- •• Of major importance

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