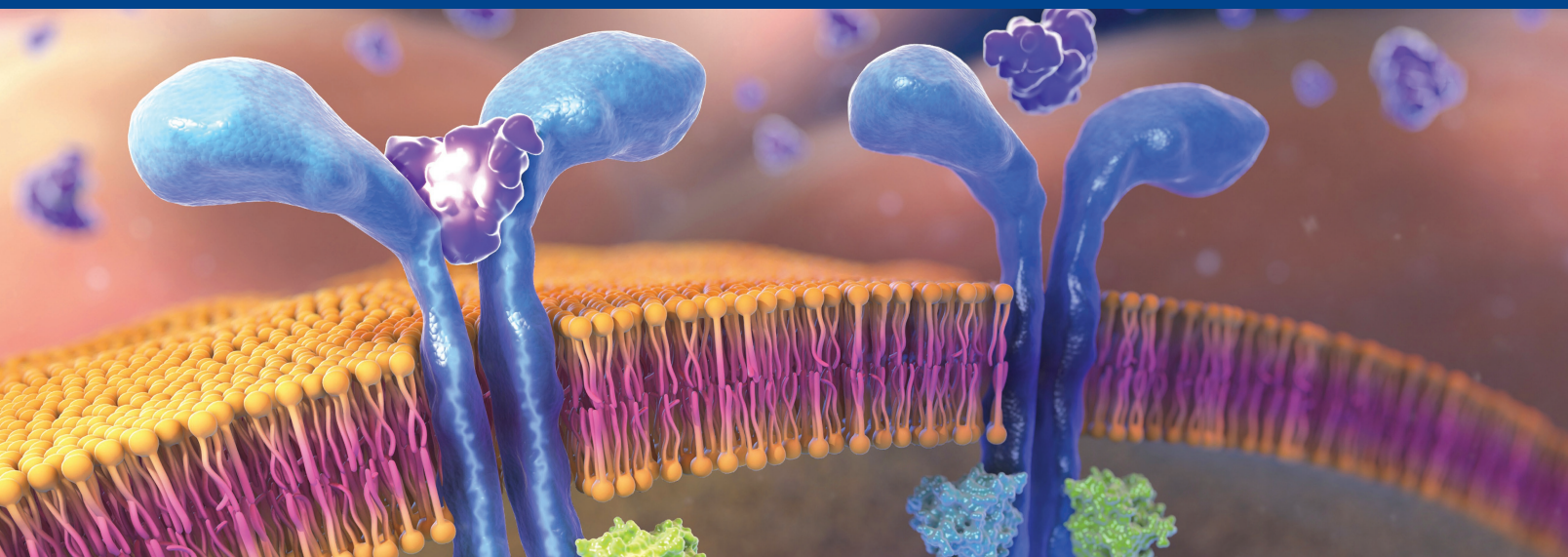


Clinical Practice Snapshot: Incorporating Janus Kinase Inhibitors Into the Management of Rheumatoid Arthritis



A Brief History of RA Therapies

Where Are We Failing Our Patients With RA?

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The Role of Janus Kinase in RA Pathogenesis

The Use of JAK Inhibitors in RA: Overall Efficacy

The Use of JAK Inhibitors in RA: Safety

What Do the Guidelines Say About JAK Inhibitors?

Conclusion

CME/CE Post-Test and Evaluation Form

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Jointly provided by



Global Academy for
Medical Education



Supported by an
educational grant from

Pfizer Inc.

Original Release Date: **October 2017**

Expiration Date: **October 31, 2018**

Estimated Time to Complete Activity: **1.0 hour**

Method of Participation

Participants should read the CME/CE information, review the activity in its entirety, and complete the online post-test and evaluation. Upon completing this activity as designed and achieving a passing score on the post-test, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail or you may print it out at that time.

Target Audience

This interactive, online activity is intended for rheumatologists, internal medicine physicians with a secondary specialty in rheumatology, physician assistants (PAs), nurse practitioners (NPs), and nurses in rheumatology, and other clinicians who treat patients with rheumatic diseases.

Learning Objectives

After completing this activity, participants should be better able to:

- Design optimal treatment strategies for patients with rheumatoid arthritis (RA) to improve remission rates and/or minimize levels of disease
- Recognize the role that Janus kinase (JAK) plays in the pathogenesis of RA and the corresponding impact of JAK inhibition in the management of RA
- Discuss treatment options for RA, including the use of JAK inhibitors, as reflected in current practice guidelines

Physician Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Global Education Group and Global Academy for Medical Education. Global Education Group is accredited by the ACCME to provide continuing medical education for physicians.

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This educational activity for 1.0 contact hour is provided by Global Education Group. Nurses should claim only the credit commensurate with the extent of their participation in the activity.

Program Overview

Current guidelines for the management of rheumatoid arthritis (RA) address the concern that many patients fail to respond, or lose response, to first-line therapy with disease-modifying antirheumatic drugs (DMARDs). Lack of understanding about the optimal use of available RA therapies—including combination therapy or switching to other drugs within a class or in a different class—means that many patients may fail to achieve remission (the ideal goal) or minimal levels of disease activity. Clinicians who are unaware of current practice guidelines may not be providing optimal management for their patients with RA. In addition, clinicians should be aware of data concerning the safety and efficacy of newly available drugs so as to ensure selection of optimal therapies for patients with RA. Knowledge of agents that have novel mechanisms of action, including Janus kinase inhibitors, can improve clinicians' confidence when switching therapies in patients who have suboptimal response despite appropriate use of DMARD therapies.

Joint Providership Statement

This activity is jointly provided by Global Education Group and Global Academy for Medical Education.

Term of Offering

This activity was released on October 1, 2017, and is valid for 1 year. Requests for credit must be made no later than October 31, 2018.

Global Education Group Contact Information

For information about the accreditation of this activity, please contact Global Education Group at 303-395-1782 or inquire@globaleducation-group.com.

Instructions for Obtaining Credit

In order to receive credit, participants must complete the online evaluation and post-test at the end of this activity. Participants must also score at least a 65% on the post-test. Statements of credit will be issued upon completion of the evaluation and post-test.

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Name of Faculty or Presenter: Roy Fleischmann, MD, MACR

Reported Financial Relationship: *Consultant:* AbbVie, Lilly, Pfizer.

Grant/Research Support: AbbVie, Lilly, Pfizer.

Name of Faculty or Presenter: Iain B. McInnes, FRCP, PhD, FRSE, FMedSci

Reported Financial Relationship: *Consultant:* AbbVie; Galapagos Pharma; Lilly; Pfizer. *Grant/Research Support:* Bristol-Myers Squibb; Janssen; Pfizer; UCB.

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Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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A CME/CE-CERTIFIED SUPPLEMENT TO

Rheumatology News®

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This continuing education supplement was developed from interviews with the faculty. It is the second activity in the two-part curriculum, *From Science to Practice: Understanding the Role of Janus Kinase in RA Pathogenesis to Appropriately Incorporate JAK Inhibition in RA Management*. The supplement content was derived from the key teaching points from the previous online activity, which may be found at: www.globalacademycme.com/specialties/rheumatology.

The faculty acknowledge the editorial assistance of Global Academy for Medical Education, LLC, and Scott Kober, medical writer, in the development of this supplement.

Neither the editors of *Rheumatology News* nor the Editorial Advisory Board nor the reporting staff contributed to its content. The ideas and opinions expressed are those of the faculty and do not necessarily reflect the views of the supporters, Global Academy for Medical Education, Global Education Group, or the Publisher.

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**Global Academy for
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This supplement explores the current shortfalls in the care of patients with rheumatoid arthritis (RA), the similarities and differences between small molecules and biologics, the role of Janus kinase (JAK) inhibition in RA pathogenesis, and the current and potential future role of JAK inhibitors in the treatment of RA.

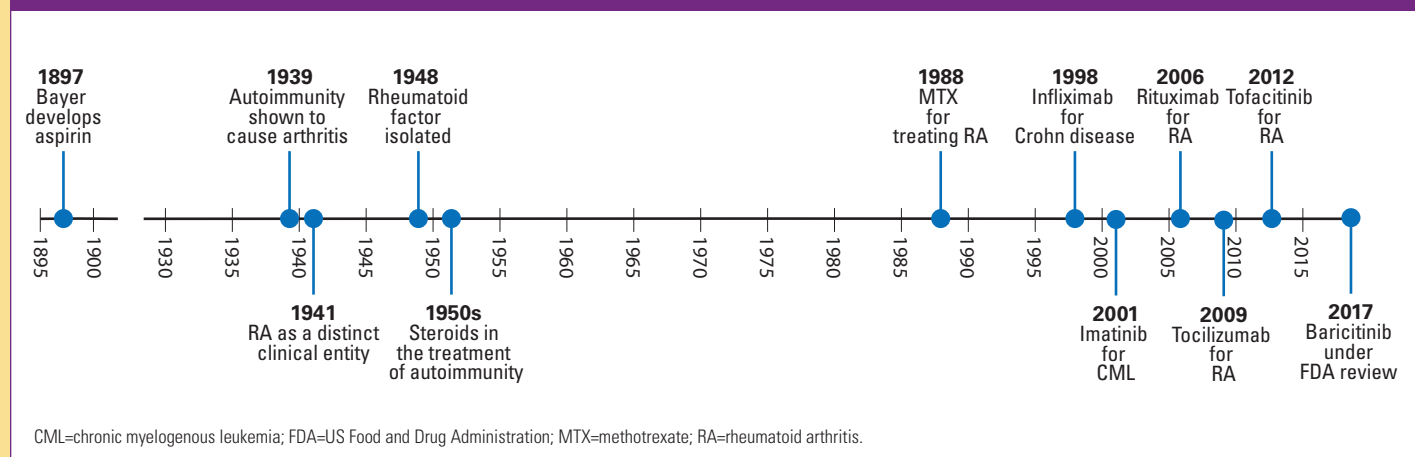
A Brief History of RA Therapies

In 1998, the US Food and Drug Administration (FDA) approved infliximab for the treatment of Crohn disease, marking the dawn of the biologic era in inflammatory diseases (Figure 1).¹ A few months later, etanercept became the first tumor necrosis factor (TNF) inhibitor to be approved by the FDA for the treatment of RA. As the rheumatology community gained a more thorough understanding of the role of cytokines and immune system cells in RA, additional biologics were introduced that targeted TNF, interleukin (IL) 1 and 6, and T- and B-cell function.¹

In parallel with the development of biologics in RA, cancer researchers developed a new type of agent that blocked intercellular tyrosine kinases. The first small-molecule tyrosine kinase inhibitor (TKI) to be FDA approved was imatinib, introduced in 2001 for patients with chronic myelogenous leukemia. Additional TKIs for treating solid-tumor cancers soon followed.

As our understanding of the role of tyrosine kinases in the development and progression of autoimmune disease grew, research into new strategies for the treatment of RA shifted in the direction of unique small molecules that could target these pathways. In 2012, tofacitinib, a JAK inhibitor, became the first small-molecule kinase inhibitor to be approved by the FDA for the treatment of RA. A second JAK inhibitor, baricitinib, is approved for use in the European Union for the treatment of RA and was submitted to the FDA for potential approval in 2016. In April 2017, however, the FDA issued a complete response letter asking baricitinib's manufacturer for more safety data, as well as additional information on the most appropriate doses of the drug to be used in patients with RA. In August 2017, baricitinib's manufacturer announced that it would add additional data to its resubmission for potential FDA approval in early 2018.

Figure 1. Timeline of RA Research and Therapy¹



Where Are We Failing Our Patients With RA?

Without question, the rheumatology community has made remarkable strides in halting the functional loss and associated damage of RA, thanks primarily to the use of biologic therapy along with refined treatment strategies. Nonetheless, as the bar keeps being raised, and both providers and patients expect to achieve clinical remission in many cases, further improvements are needed.

Up to 35% of patients with RA do not respond adequately to biologic therapy; less than one-third of established patients with RA

achieve clinical remission by American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) remission criteria.² Although the use of biologic disease-modifying antirheumatic drugs (DMARDs) in combination with methotrexate (MTX) is clearly superior to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in alleviating symptoms of RA, many patients continue to experience unacceptable levels of pain despite the use of these newer agents.² Physical and sexual functioning, as well as levels of fatigue, also persist at an unsatisfactory level in many patients with RA despite aggressive therapy.^{2,3}

Treat-to-target guidelines, updated in 2014, were intended to help narrow these treatment gaps by providing rheumatologists and patients with clear strategies to help achieve optimal outcomes—either remission or, in cases of patients with active disease, low disease activity.⁴ Unfortunately, the adoption of these guidelines in real-world scenarios has lagged for several reasons⁵:

- 1. Many patients with RA do not receive a csDMARD, let alone a biologic DMARD (bDMARD).** Population-based studies have shown that $\geq 35\%$ of Medicare recipients diagnosed with RA do not fill a prescription for a csDMARD.⁶ Although it is possible that some of these patients have very mild RA (and thus may not require csDMARD therapy) or have contraindications to csDMARD therapy, there are many appropriate candidates for csDMARD therapy who receive a prescription but opt not to fill it.
- 2. Many patients with RA do not have easy access to a rheumatologist.** A 2013 workforce study by the ACR showed that 83% of urban areas in the United States with between 10,000 and 50,000 residents have no rheumatologist; the median distance to the nearest rheumatologist in those regions is 159 miles.⁷ Consequently, many patients with RA are being managed by non-rheumatologists, who may not feel comfortable prescribing csDMARDs, much less bDMARDs.
- 3. Many clinicians may not adequately educate their patients about the value of a treat-to-target strategy.** In a study from the National Data Bank for Rheumatic Diseases, 77% of patients with RA indicated they were satisfied with their medications, yet 71% of these satisfied respondents still had at least moderate functional limitation as determined by their Health Assessment Questionnaire (HAQ) score.⁸ Unless patients with RA understand that feeling “just OK” is not acceptable, they may not push their clinicians to help them reach a targeted goal of remission or low disease activity.
- 4. Use of a treat-to-target strategy requires frequent patient visits and utilization of composite RA disease activity measures that typically include joint examinations.** This can present challenges related both to geography (for patients who cannot regularly access their rheumatologist’s office) and time (for busy rheumatologists or their staff who cannot assess joints at every patient visit).
- 5. Delays in obtaining and/or accessing medication can prevent timely escalation of treatment as RA progresses, extending the time needed to reach treatment goals.** Delays for authorization of more aggressive therapies in patients with RA are common in the United States, which means that patients are unable to switch therapies as frequently as is suggested in the treat-to-target guidelines.⁵

There are, of course, other barriers to achieving optimal outcomes for patients with RA. One medication-related barrier involves the development of detectable anti-drug antibodies (ADAs) to some current bDMARDs. Neutralizing ADAs can reduce drug response rates by 68%, decreasing the likelihood of clinical response and increasing the risk that patients will discontinue using bDMARDs.⁹ The development of ADAs may also increase the risk of developing a hypersensitivity reaction.¹⁰ Although biomarker tests to measure ADA levels are not commonly performed outside of clinical trials, they may in the future become more common to help tailor therapeutic regimens.

For these reasons and others, it is paramount that rheumatologists develop new strategies with new agents to meet the needs of patients with RA.

Rheumatology Practice Snapshot

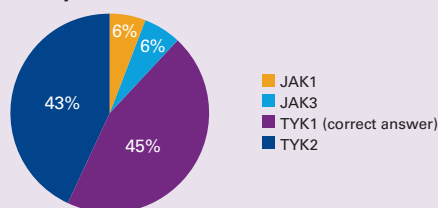
In May 2017, the first activity in this educational series began educating clinicians about the role of Janus kinase (JAK) inhibition in the treatment of RA. This 30-minute online Video Lecture activity, which can be found at www.globalacademycme.com/specialties/rheumatology, involved an in-depth review by Roy Fleischmann, MD, on the science and emerging clinical data driving the use of JAK inhibitors in RA. It is available for 0.75 *AMA PRA Category 1 Credits*™ until May 2018.

As of October 2, 2017, nearly 200 clinicians had accessed this activity, with data collected from 119 learners. Data from this activity were used, in part, to shape the focus of this educational supplement. Learner gaps in knowledge and competence were assessed, and specific deficiencies received extra emphasis in this activity. Please take a moment to review the data of your peers and consider how they compare to your knowledge levels and opinions.

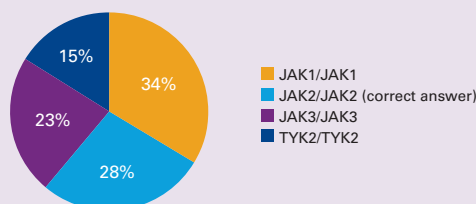
Clinicians have a poor understanding of the role of Janus kinase in the pathogenesis of RA

Several questions within the online program gauged learners’ knowledge of important nuances related to the mechanism of action and overall level of activity of JAK inhibitors. On an activity pre-test, approximately half of all respondents were unable to correctly exclude TYK1 as a member of the JAK family. In a follow-up question, only 28% of learners correctly identified JAK2/JAK2 as the lone homodimer among the JAK family combinations. And finally, only 37% of learners correctly identified the approximate percentage of individual cytokine targets blocked by JAK inhibitors.

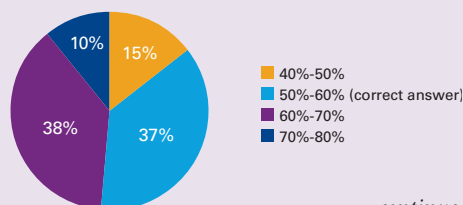
Which of the following is not considered to be within the JAK family? (n=119)



Which is the only homodimer among the JAK family combinations? (n=119)



JAK inhibitors block approximately what percentage of individual cytokine targets? (n=71)



continued on page 12

Comparing Small Molecules and Biologics

Traditional csDMARDs such as MTX and new targeted synthetic kinase inhibitors (tsDMARDs) such as tofacitinib are both technically small-molecule therapeutics. Both are oral agents. However, there are some fundamental differences. Perhaps most important, traditional csDMARDs were approved because of general efficacy in patients with RA even though a thorough understanding of their mechanisms of action or their therapeutic targets was unknown. Indeed, even today, how and why MTX works in patients with RA is not entirely clear, although research is ongoing that may solve that riddle.¹¹

In contrast, the newer small-molecule tsDMARDs were developed to target specific molecules that are thought to be important in the inflammatory process and thus have well-understood mechanisms of action.

There are several key differences between today's bDMARDs used to treat RA and the new small-molecule JAK inhibitor tsDMARDs (Table 1). These differences include the following:

Chemical Composition and Weight

Biologic agents are large, complex proteins, generally >1 kDa in size, that target a specific mediator in the inflammatory cascade. JAK inhibitors are much smaller organic molecules, <700 Da in size. This gives them the ability to penetrate cells and alter intracellular signaling.

Administration

Biologic agents are given parenterally, either by injection or infusion. JAK inhibitors are oral agents.

Because of their significantly shorter half-life, oral JAK inhibitors need to be taken either once or twice a day. With the exception of anakinra, a daily injectable that today is used infrequently in patients with RA, biologics are given on a more extended schedule, ranging from weekly injections to biannual infusions.

The route and frequency of drug administration should not be under-emphasized as a factor in patient adherence to treatment regimens. Studies of anti-TNF-based regimens have shown that 27% to 41% of patients will have significant adherence issues within 6 to 12 months of initiating anti-TNF therapy, for example, by failing to fill prescriptions

for injectable agents or by not showing up for infusion appointments.¹² Although these adherence issues are not solely attributable to the route and frequency of anti-TNF drug administration, they may well be a factor in many instances.

Rates of adherence to oral JAK inhibitors are currently unknown—and may indeed turn out to be similar or poorer—but such statistics emphasize the importance of educating and supporting patients to ensure that they begin and continue treatment as prescribed.

A recent sensitivity analysis looking at the rates of drug discontinuation among patients who did not respond to traditional csDMARDs found no significant differences between patients treated with tofacitinib versus those treated with a bDMARD.¹³

Therapeutic Target

bDMARDs act as antibodies that block extracellular targets such as cell surface receptors or circulating cytokines. They are highly selective in their targets, which means they have narrow and generally predictable clinical consequences. JAK inhibitors target intracellular signaling pathways and have broad anti-JAK activity. This mechanism has advantages and disadvantages.

On the plus side, by blocking multiple members of the JAK family, JAK inhibitors offer wide protection against proinflammatory cytokines. On the downside, there is greater potential for off-target adverse effects as well as possible immune suppression arising from unwanted on-target effects.¹⁴ Non-JAK small molecules previously tested in RA, such as mitogen-activated protein kinase (MAPK) inhibitors and phosphodiesterase 4 (PDE4) inhibitors, primarily failed because of intolerable side effects or insufficient efficacy. As an example, one PDE4 inhibitor—apremilast, which has been approved for the treatment of psoriatic arthritis—was not found to be efficacious in patients with RA.¹⁵

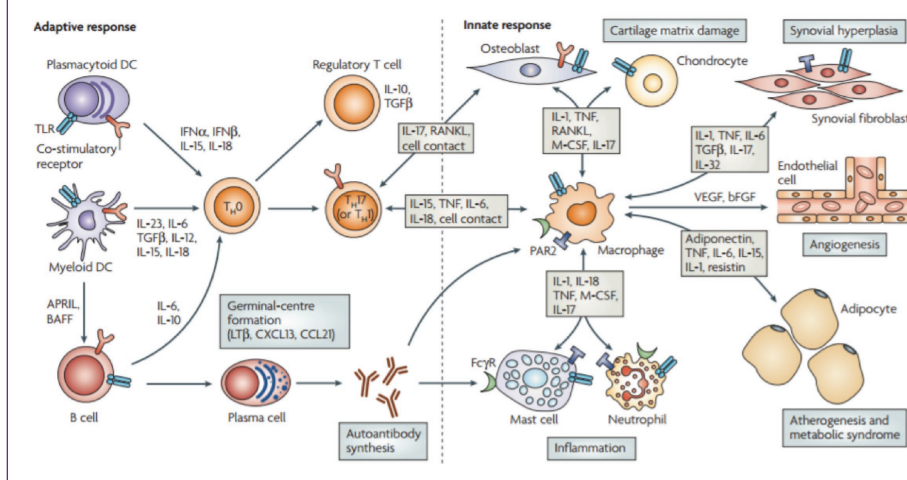
In Vivo Half-Life

The chemical and pharmacodynamic half-life of JAK inhibitors is significantly less than that of biologic agents.¹⁴ This can be beneficial in cases in which the drug needs to be cleared quickly from the body should adverse events develop.

Table 1. Comparing Biologics to JAK Inhibitors		
	Biologics	JAK Inhibitors
Chemical composition	Protein	Organic small molecule
Structure	Known sequence, variable 3-dimensional structure and glycosylation	Well-defined structure
Molecular weight	>1 kDa	<700 Da
Administration	Parenteral	Oral
Target	Extracellular	Intracellular
Mechanism of action	Blocking, depletion	Enzyme inhibition
Specificity	High	Low/variable
Stability	Protease- and heat-sensitive	Mostly stable
In vivo half-life	Longer	Shorter
Degradation	Catabolism	Metabolism
Manufacturing costs	High	Low/variable
Generic agents	Biosimilars (not a true generic)	Identical chemical copies

JAK=Janus kinase.

Figure 2. The Complex Pathophysiology of RA



APRIL=a proliferation-inducing ligand; BAFF=B-cell activating factor; bFGF=basic fibroblast growth factor; CCL21=C-C motif chemokine ligand 21; CXCL13=C-X-C motif chemokine ligand 13; DC=dendritic cell; FcγR=Fc gamma receptor; IFN=interferon; IL=interleukin; LTβ=lymphotxin beta; M-CSF=macrophage colony-stimulating factor; PAR2=protease-activated receptor 2; RA=rheumatoid arthritis; RANKL=receptor activator of nuclear factor kappa B ligand; TGFβ=transforming growth factor beta; T_H=T helper cell; TLR=toll-like receptor; TNF=tumor necrosis factor; VEGF=vascular endothelial growth factor.

The pathophysiology of RA involves the interaction of numerous cell types and multiple mediators of inflammation. Considering this complexity, treatments can target a variety of pathways to try to halt inflammation. Pathways such as IL-6, IL-1, and TNF are among the targets of current therapy. Reprinted by permission from Macmillan Publishers Ltd. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol*. 2007;7:429-442. Copyright © 2007.

Overall Efficacy and Safety: Conventional and Biologic DMARDs

In most patients with either early or established RA, csDMARDs such as MTX are typically initiated as first-line agents.¹⁶ The efficacy of many conventional csDMARDs has been demonstrated across numerous clinical trials and is typically seen whether these agents are used as monotherapy or in combination. (Hydroxychloroquine [HCQ], which is efficacious primarily in combination with a second drug, is an exception.¹⁶) Approximately 30% of patients will achieve excellent disease control with the use of csDMARDs alone, with correlating improvements in their disease activity as measured by validated tools such as the HAQ or the Clinical Disease Activity Index (CDAI).¹⁶ Often a decrease in radiographic progression is noted over time.

Side effects of csDMARDs are well known and generally treatable. They include serious infection, neutropenia, and elevated liver enzymes. Again, HCQ is an outlier; anemia is its lone notable side effect.

With the exception of anakinra, all of the bDMARDs demonstrate roughly equivalent efficacy. MTX or another conventional csDMARD is typically added to bDMARD regimens to improve overall efficacy.

Studies have shown that approximately 60% to 70% of patients who start treatment with a bDMARD plus MTX will achieve an ACR50 response, compared with approximately 40% who start treatment with MTX alone.¹⁷ For patients with an inadequate response to initial MTX monotherapy, the addition of a bDMARD will help achieve an ACR50 response in 50% to 56% of cases.¹⁸

Although these numbers are impressive compared to the success of a generation ago, it still leaves approximately 30% to 35% of patients who will not have an adequate response to bDMARDs and who may respond to alternative approaches.

The safety profile of bDMARDs is well established. Biologics cause an approximately 30% increase in the risk of serious infection compared with csDMARDs due to suppression of key mediators of immune system function, although this increased risk is dose-dependent.^{3,19}

Although all bDMARDs increase the risk of infection to some degree, there are specific types of infections that clinicians should be mindful of when prescribing specific agents. Anti-TNFs, for instance, increase the risk of mycobacterial or deep fungal infections, whereas rituximab

is specifically tied to an increased risk of progressive multifocal leukoencephalopathy, a rare and typically fatal opportunistic infection.¹⁹

Both anti-TNF and non-anti-TNF bDMARDs, as well as MTX, appear to have a protective cardiovascular (CV) effect,^{20,21} which is particularly valuable for patients with RA, who are naturally at higher risk for CV morbidity and mortality compared with the general population, due to the presence of their inflammatory disease.²²

The Role of Janus Kinase in RA Pathogenesis

The pathophysiology of RA is complex, involving the interaction of numerous cell types and multiple mediators of inflammation (Figure 2). Current treatment options target some of the cytokines thought to be involved in the development of RA, such as TNF, IL-1, and IL-6.

In addition to these cytokines, there are also a variety of receptor superfamilies that mediate cytokine signaling and are thought to play a role in the development of RA. Examples include the JAK pathway, the MAPK pathway, the signal transducer and activator of transcription (STAT) pathway, the nuclear factor κB pathway, and the PDE4 pathway.

The precise role of these pathways and the ways in which they regulate cytokine-receptor-mediated functions is not entirely understood. Recent drug development efforts have looked at ways to manipulate some of these pathways. Early efforts have had fleeting success—as noted earlier, small molecules developed to inhibit the MAPK and PDE4 pathways have not demonstrated appropriate efficacy and safety in patients with RA.

To date, only JAK inhibitors have demonstrated appropriate levels of safety and efficacy among the small-molecule therapeutics. One JAK-inhibiting agent, tofacitinib, has been FDA approved in the United States; a second, baricitinib, has completed multiple phase III trials but as of the date of this publication has not yet been FDA approved. Other JAK inhibitors are in the development pipeline.

How JAK Works

The JAK family consists of four proteins—JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2. These proteins work in specific combinations to transmit extracellular cytokine signals from cell surface receptors to activate various STATs.²³

Applying Our Current Evidence Base to Real-Life Clinical Care

Case 1

Theresa is a 46-year-old local politician. Approximately 10 months ago she developed fatigue as well as pain and swelling of the small joints of both hands and forefeet. Theresa is divorced with two teenaged girls and is not planning any further additions to her family. She has a family history of skin cancer, psoriasis, and early onset cardiovascular (CV) disease (her father died of a stroke at age 55 years).

A lifelong nonsmoker, Theresa estimated that she has “around” 14 alcoholic drinks per week, usually on the weekends. She has historically struggled to keep a healthy weight; her participation in a diet club has helped her reduce her body mass index (BMI) from 32 kg/m² to her current level of 29 kg/m².

Theresa’s initial laboratory results showed a C-reactive protein (CRP) level of 4 mg/L and erythrocyte sedimentation rate (ESR) of 45 mm/h. Her rheumatoid factor was 35 IU/mL, and her anti-cyclic citrullinated peptide (anti-CCP) was 160 u/mL. Based on our workup and laboratory results, Theresa was diagnosed with RA.

Theresa’s baseline Disease Activity Score (28-joint count)–ESR (DAS28-ESR) was 5.2. Plain x-rays revealed erosions confined to her left wrist. Serologic testing showed that Theresa is hepatitis B surface antigen positive, polymerase chain reaction (PCR) negative, and hepatitis C surface antigen negative.

Theresa was started on a regimen of MTX 15 mg/week. At her initial follow-up appointment 3 months later, Theresa reported little noticeable change in her symptoms. She still had regular morning stiffness and complained that she was unable to help at a recent charity fundraiser at her daughter’s school due to pain in her wrist. Theresa’s DAS28-ESR score was only modestly reduced from baseline, at 4.7.

We decided to increase the MTX to 20 mg per week and add sulfasalazine and

hydroxychloroquine (HCQ) to her regimen. Three months later, Theresa’s DAS28-ESR score remains at 4.7, and her complaints persist. Although she is tolerating her medication regimen well, she is unhappy with the impact the disease is having on her daily function.

What would be your primary considerations as the next step in care? What are the pros and cons of each option?

Given the failure of conventional DMARDs to treat Theresa’s symptoms adequately, the next step should involve the introduction of a biologic agent. The choice of agent is typically made on the basis of local practice guidelines, national regulatory body approvals, and a shared decision between the physician and the patient.

In this case, use of a TNF inhibitor, IL-6 inhibitor, or costimulation blocker in addition to MTX would all be compatible with ACR and EULAR guidelines.^{16,24} The evidence base supports the benefits of a biologic agent for most patients who do not respond to csDMARD therapy.^{16,24} Safety data sets from national registries enrolling thousands of patients have reassured the rheumatology community about the utility and feasibility of biologic agents.^{16,24}

The introduction of JAK inhibitors has increased our options for situations such as Theresa’s. Although the evidence base for efficacy and safety of this new class of agents will take time to mature, the data that have emerged to date seem reassuring in general.^{16,24}

Although two head-to-head trials comparing a bDMARD, adalimumab, to these newer small molecules have been completed (further details on these trials are included later in this supplement),^{25,26} the picture is still somewhat murky when selecting the initial agent for our patients with RA after failure of one or more csDMARDs. Patient preference, comorbidities (eg, prior infection risk, diabetes,

CV disease, demyelinating disease), local health care costs, and patient access to medication will all influence the decision. Any therapeutic decision should also be informed by a detailed consideration of a patient’s comorbid risks and by the patient’s preferences regarding use of parenteral versus oral therapeutics.

Are any findings from Theresa’s family history and laboratory workup relevant to your decision?

Theresa’s lack of response to a regimen of three csDMARDs might raise our suspicion of the initial diagnosis of RA, especially considering her history of psoriasis. However, her anti-CCP positivity and an RA-compatible erosion in her wrist make a diagnosis of psoriatic arthritis unlikely. In addition, judicious use of imaging such as ultrasound may be helpful to confirm that the synovitis observed in her wrist is indeed located in the joint. This is likely. However, noting her high profile and stressful occupation, and her role as a single mother to two teenagers, it is always useful to consider the patient in a holistic manner and ensure that other factors—such as depression and stress—are not also complicating the clinical picture.

Is there value in simply adjusting the dosage of MTX to see what effect doing so would have on Theresa’s condition?

Dose adjustment of csDMARDs together with local injections of corticosteroids will commonly be used to adjust therapy in the early stages of disease. Although it is possible that maximizing Theresa’s dose of MTX and sulfasalazine while also adding low-dose glucocorticoids would be helpful, given her continued high disease activity and demonstration of erosive disease following the failure of multiple interventions, switching to an agent with another mechanism of action could be a more appropriate choice.

An individual JAK protein cannot carry a signal on its own; it must pair with either one or two other members of the JAK family. The only homodimer among the JAK proteins is JAK2; all other proteins pair with other proteins within the JAK family. The JAK3 protein is also unique in that it is only expressed in hematopoietic cells and pairs only with JAK1.²³

Each JAK dimer or trimer mediates function for different cytokines. For instance, the JAK1/JAK3 dimer mediates signals for the gamma chain cytokine family, which includes IL-2, -4, -7, -9, -15, and -21. The JAK1/JAK2 dimer mediates interferon gamma function. The JAK1/JAK2/TYK2 trimer affects IL-6.²³

Each JAK combination may also mediate different effects on biologic function. For example, the JAK1/JAK3 dimer is thought to impact the growth and maturation of lymphoid cells, differentiation and homeostasis of T cells and natural killer cells, B-cell class switching, and inflammation. The JAK2 homodimer, meanwhile, facilitates signaling mediated by erythropoietin, granulocyte-macrophage colony-stimulating factor, and other factors vital to erythropoiesis, myelopoiesis, and platelet production. The effects of other combinations are shown in **Figure 3**.²³

The one commonality among the JAK combinations—with the exception of the JAK2 homodimer—is that they each affect pathways involved with inflammation. This is the primary reason they are thought to hold promise for patients with RA and continue to be researched. **Table 2** includes a list of current JAK inhibitors under investigation, as well as their stage of development, in different indications.²³

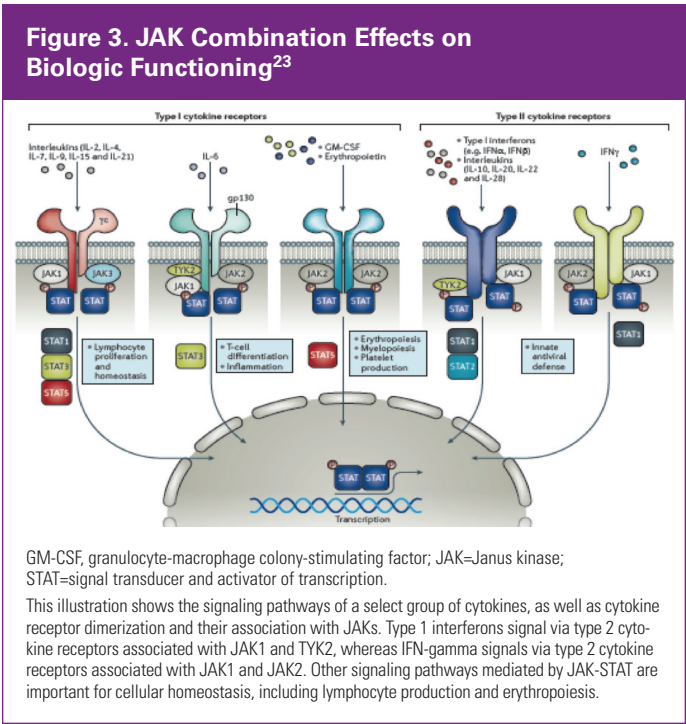


Table 2. JAK Inhibitors in Clinical Development ^a			
Compound	Target	Indication	Stage of Development
Baricitinib	JAK1, JAK2	RA	Phase III
		Psoriasis	Phase II
		Diabetic nephropathy	Phase II
		Systemic lupus erythematosus	Phase II
		Atopic dermatitis	Phase II
Decernotinib	JAK3	RA	Phase III
Filgotinib	JAK1	RA	Phase III
		Crohn disease	Phase III
		Ulcerative colitis	Phase III
Momelotinib	JAK1, JAK2	Myelofibrosis	Phase III
Pacritinib	JAK2	Myelofibrosis	Phase II
Peficitinib	JAK1, JAK3	RA	Phase III
		Psoriasis	Phase II
Ruxolitinib	JAK1, JAK2	Myelofibrosis	Approved by FDA
		Psoriasis	Phase I
Tofacitinib	JAK1, JAK3	RA	Approved by FDA
		Psoriatic arthritis	Phase III
		Psoriasis	Phase III
		Ulcerative colitis	Phase III
		Juvenile idiopathic arthritis	Phase I
Upadacitinib	JAK1	RA	Phase III
		Crohn disease	Phase II
		Ulcerative colitis	Phase II
		Atopic dermatitis	Phase II

FDA=US Food and Drug Administration; JAK=Janus kinase; RA=rheumatoid arthritis.
^aAs of October 2017.

The Use of JAK Inhibitors in RA: Overall Efficacy

As noted earlier, tofacitinib is currently the only JAK inhibitor FDA approved for use in the United States. Although baricitinib is approved for use in Europe and Japan, its manufacturer received a complete response letter from the FDA in April 2017 asking for additional clinical data to determine the most appropriate doses of the drug. The FDA also stated that additional data are necessary to further characterize safety concerns across treatment arms in clinical trials. In August 2017, baricitinib’s manufacturer announced that it would be resubmitting the drug for FDA approval by the end of January 2018.

Tofacitinib, approved by the FDA in 2012 for the treatment of RA, primarily inhibits JAK1 and JAK3 although, like the majority of other JAK inhibitors, it also has lesser activity against other JAKs, most notably JAK2. Baricitinib is primarily a JAK1/JAK2 inhibitor.

In this section, we’ll take a closer look at these two JAK inhibitors, which have been studied thoroughly in late-stage trials, review their efficacy and safety data, and explore the guidance provided by expert committees regarding their use.

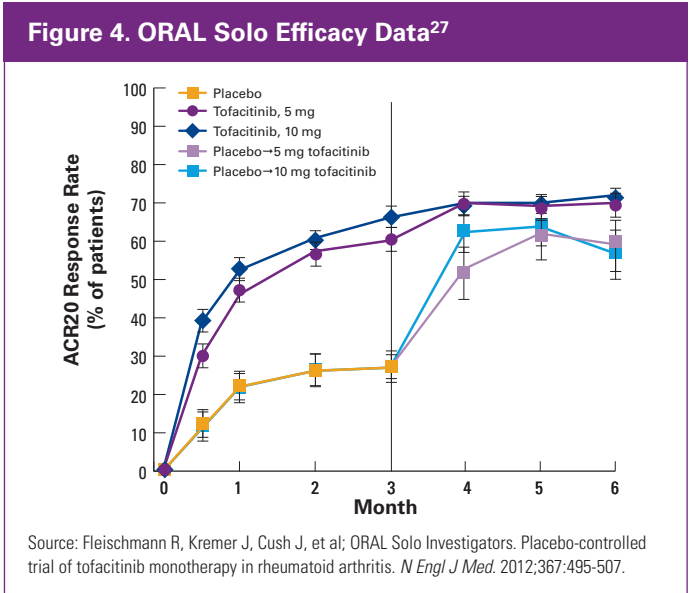
Tofacitinib

Multiple phase III trials of tofacitinib have been completed utilizing the drug in various populations and at different doses (Table 3).^{25,27-31}

The first of these trials—the ORAL Solo trial—enrolled 611 patients with active RA who failed previous treatment with at least one other DMARD, either a csDMARD or a bDMARD. Patients were randomly assigned to one of four groups²⁷: tofacitinib 5 mg or 10 mg twice daily for 6 months; or placebo for 3 months followed by tofacitinib 5 mg or 10 mg twice daily for 3 months.

After 3 months, patients in both tofacitinib groups were significantly more likely to achieve ACR20, 50, and 70 responses compared with the placebo groups. At 6 months, patients who transitioned from placebo to tofacitinib achieved a similar response compared with the response at 3 months among those who were initially treated with tofacitinib (Figure 4).²⁷

It should be noted, however, that there were no differences in the proportion of patients who achieved DAS28-ESR remission at 3 months in any of the treatment groups, which underscores the challenge of getting patients who fail prior therapies to reach clinical remission quickly.



A second phase III trial, the ORAL Standard study, enrolled 717 patients with active RA who had an inadequate response to MTX.²⁵ In this trial, patients were randomized into five treatment groups for 12 months, all with background MTX: tofacitinib 5 mg or 10 mg twice daily; adalimumab 40 mg by subcutaneous injection once every 2 weeks; or placebo for 3 or 6 months followed by tofacitinib 5 mg or 10 mg twice daily for 3 months.

Although adalimumab was included as a comparator arm, it is important to note that this trial was not powered to compare the efficacy of tofacitinib and adalimumab.

Results showed that patients treated with either tofacitinib or adalimumab were significantly more likely than those treated with placebo to achieve an ACR20 response at 6 months. They were also significantly more likely to experience improvement in HAQ Disability Index (HAQ-DI) scores and achieve clinical remission.

An open-label extension study of ORAL Standard called ORAL Sequel showed that use of tofacitinib after adalimumab was safe and effective.³²

Tofacitinib has also been studied in other patient populations, as in the ORAL Start trial, which looked at tofacitinib as an alternative to MTX in treatment-naïve patients with RA.²⁸ This trial randomized patients to one of three treatment groups, all as monotherapy: tofacitinib 5 mg or 10 mg daily; or MTX titrated to a dose of 20 mg over 8 weeks.

Table 3. Phase III Trials of Tofacitinib ^{25,27-31}		
Trial	Patient Population Studied	Treatment Arms
ORAL Solo ²⁷	Incomplete response to ≥1 RA medications, including conventional DMARDs or biologic agents	Tofacitinib vs placebo monotherapy
ORAL Standard ²⁵	Incomplete response to MTX	Tofacitinib vs adalimumab vs placebo, each with background MTX ^a
ORAL Start ²⁸	MTX naïve	Tofacitinib vs MTX monotherapy
ORAL Sync ²⁹	Incomplete response to ≥1 RA medications, including conventional DMARDS or biologic agents	Tofacitinib vs placebo monotherapy, with stable background DMARD therapy
ORAL Scan ³⁰	Incomplete response to MTX	Tofacitinib vs placebo monotherapy with stable background MTX
ORAL Step ³¹	Inadequate response to TNF inhibitors	Tofacitinib vs placebo, all with MTX

DMARD=disease-modifying antirheumatic drug; MTX=methotrexate; RA=rheumatoid arthritis.
^aTrial was not powered to compare efficacy of tofacitinib vs adalimumab.

Applying Our Current Evidence Base to Real-Life Clinical Care

Case 2

Martin is an unmarried tax accountant referred to us from his community rheumatologist. He has had symptoms for approximately 2 years, including multiple painful and swollen joints, a regularly recurring fever, and general fatigue. His type 2 diabetes, diagnosed 6 years ago, is currently well managed on oral metformin.

At initial presentation, Martin, then 47 years old, had a rheumatoid factor of 36 IU/mL, an anti-CCP of 140 u/mL, and an ESR of 30 mm/h. He was diagnosed with RA. His baseline DAS28-ESR score was 5.0.

Martin was started on MTX, and the dosage was titrated to 20 mg/week. After 4 months, his response to MTX monotherapy was inadequate, and adalimumab 40 mg every 2 weeks was added to his regimen. Three months later, his DAS28-ESR score was improved to 4.5 (moderate disease activity) and adalimumab frequency was increased to weekly administration. At Martin's subsequent follow-up 3 months later, his DAS28-ESR score had decreased only slightly to 4.4. He was switched to rituximab and received 2 cycles of therapy. His lowest DAS28-ESR during this period was 4.3.

He is now back in your office 12 months after his first rituximab infusion. His DAS28-ESR is up to 4.9. He asks if more can be done to help him.

What would be your next step in treatment?

Options for a patient who has failed two bDMARDs include use of a further bDMARD with a different mechanism of action, such as tocilizumab or abatacept, or the small-molecule JAK inhibitor tofacitinib. (As noted earlier, in Europe and Japan, another JAK inhibitor, baricitinib, is an approved option.)

You decide to start Martin on subcutaneous tocilizumab injections. Four weeks

after his initial injection, Martin's DAS28-ESR is down to 3.0. However, he continues to describe fatigue and joint pain and tenderness. His CRP is undetectable.

How would you proceed?

Based on his complaints, it is difficult to assess whether this is a patient whose RA disease activity has truly improved despite the improvement in DAS28-ESR score. It is important to recognize that CRP levels often fall as a marker of IL-6 receptor blockade, which could account for most, if not all, of the quantitative improvement we see with Martin. In addition to a physical exam and assessment of his CDAI (which does not utilize acute phase reactants), the use of power Doppler ultrasound or magnetic resonance imaging could be useful in this case to assess the true current articular inflammatory burden.³³ Additionally, it would be wise to assess the current status of his diabetes to make sure his disease is under control. In cases like this, coordination with the diabetes management team is strongly suggested.

Ultrasound imaging confirms that Martin has ongoing synovitis in his metacarpophalangeal (MCP) joints, so you consider a further change in treatment, weighing whether to introduce abatacept or a JAK inhibitor. You then receive a call from Martin's diabetologist telling you that his total cholesterol has increased approximately 15% in the last 3 months, raising concern about his CV risk.

What is the likely explanation for this latest set of findings? How would they affect your decision regarding subsequent therapeutic options?

Although the ultrasound findings support a move to another immune-modifying agent, Martin's lipid level profile may complicate the decision.

The value of a JAK inhibitor is that such drugs influence numerous cytokine and immune receptor signal pathways and

may consequently offer broader immune mediation than a targeted, costimulatory blockade biologic. However, clinical trials of these agents have shown that, in some patients, JAK inhibitors and IL-6 receptor blockers such as tocilizumab elevate total cholesterol and low-density lipoprotein (LDL) cholesterol levels by approximately 15%.³⁴

The increase in lipid levels resulting from use of IL-6 receptor blockers is associated primarily with changes in large LDL and reflects an altered cholesterol metabolism rather than a true rise in atherogenic lipid mediators. IL-6 receptor blockade may, in fact, increase the atheroprotective properties of high-density lipoprotein (HDL) by increasing paraoxonase and reducing serum amyloid A components in HDL composition.³⁴ Moreover, a recent large clinical observational study suggested no difference in major adverse cardiac events (MACE) among patients with RA treated with tocilizumab versus etanercept.³⁵

A suggested general approach is to treat an elevated lipid level only if it raises a patient with RA into an "at-risk" 10-year predictive MACE classification. It may also be appropriate to adjust the calculated MACE risk upward by a factor of 1.5 in patients with elevated lipid levels, analogous to the presence of diabetes (which would have already occurred with Martin, but is worth remembering in patients without diabetes).

Based on our clinical findings and the recent literature, we vaccinated Martin against herpes zoster prior to the initiation of therapy with tofacitinib, 5 mg twice daily. At 3 months, he demonstrated a reduction in DAS28-ESR score to 2.8. In consultation with his diabetologist, Martin—who is reluctant to add more medications to his regimen—agreed to make further lifestyle changes to better control his dyslipidemia and his blood glucose levels.

Rheumatology Practice Snapshot

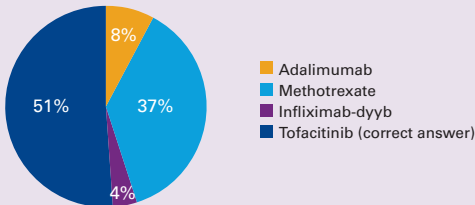
Clinicians do not completely understand the nomenclature that differentiates a csDMARD from a tsDMARD

While both methotrexate (MTX) and tofacitinib (a JAK inhibitor) are small-molecule therapeutics, only tofacitinib is a *targeted* synthetic DMARD. How and why MTX works remains unclear, while tofacitinib was established specifically to attack a specific pathway related to inflammation, the Janus kinase pathway. On an intra-activity question, 37% of respondents incorrectly selected MTX as an example of a tsDMARD.

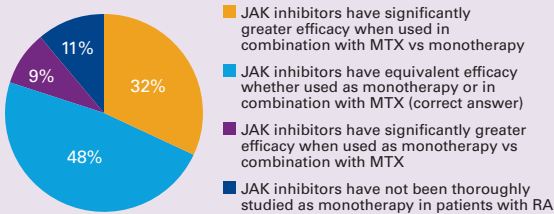
Clinicians need reminders about data from clinical trials of JAK inhibitors focused on monotherapy vs combination therapy

In clinical trials, JAK inhibitors have demonstrated nearly equivalent efficacy whether used as monotherapy or in combination with MTX. On an activity pre-test, more than half of all respondents incorrectly concluded that monotherapy results were either better, worse, or not thoroughly studied in clinical trials.

Which of the following is an example of a targeted synthetic DMARD? (n=83)



Which of the following has been demonstrated in clinical trials of JAK inhibitor? (n=119)



After 6 months, patients in both tofacitinib arms were significantly more likely to achieve ACR70 responses compared with MTX and to achieve a greater reduction in the progression of structural joint damage. These improvements were maintained over 2 years.

A follow-up report showed that improvements in patient-reported outcomes such as function and health-related quality of life (HRQoL) with tofacitinib monotherapy persisted over 2 years.³⁶

Three other trials (ORAL Sync; ORAL Scan; ORAL Step) also reported significantly greater improvements in various outcomes with tofacitinib compared with placebo (see Table 3).²⁹⁻³¹

Baricitinib

The phase III program for baricitinib evaluated safety and efficacy in different patient populations (Table 4).^{26,37,39,40}

The RA-BEACON trial enrolled 527 patients with moderate to severe RA who had not responded to one or more bDMARDs or who experienced intolerable side effects. Patients were randomly assigned to one of three groups, all on background csDMARDs³⁷: baricitinib 2 mg or 4 mg daily, or placebo.

At 3 months, patients in both baricitinib groups were significantly more likely to achieve an ACR20 response, have ≥0.3-point improvement in HAQ-DI score, and achieve either clinical remission or low disease activity compared to placebo (Figure 5).³⁷ Treatment benefits were most pronounced in patients treated with the higher dose of baricitinib.

The RA-BEAM trial was designed as a head-to-head comparison of baricitinib versus adalimumab in patients with an inadequate response to MTX.²⁶ The trial enrolled 1,307 patients who were randomized to one of three groups, all in addition to background MTX: baricitinib 4 mg daily, adalimumab 40 mg every 2 weeks, or placebo.

The results showed that patients treated with baricitinib or adalimumab were significantly more likely to achieve ACR20, 50, and 70 responses compared with placebo at week 12, as well as to reach DAS28-CRP remission. Perhaps most important, patients treated with baricitinib were significantly more likely to achieve ACR20, 50, and 70 responses, as well as achieve more significant DAS28-CRP improvement, than were those treated with adalimumab. As this was a non-inferiority trial, baricitinib was not only shown to be non-inferior to adalimumab, but also superior in helping patients achieve an ACR20 response at month 3.

In the long-term extension of this trial, patients were switched from adalimumab to baricitinib without the need for a washout period.³⁸

RA-BUILD, a European phase III trial, enrolled 684 patients who had had an incomplete response to one or more traditional DMARDs but who were naïve to bDMARDs.³⁹ Patients were randomly assigned to one of three treatment arms with background csDMARDs: baricitinib 2 mg or 4 mg daily, or placebo.

Table 4. Phase III Trials of Baricitinib ^{26,37,39,40}		
Trial	Patient Population Studied	Treatment Arms
RA-BEACON ³⁷	Incomplete response or intolerance to ≥1 biologic agents	Baricitinib vs placebo, each with background csDMARD
RA-BEAM ²⁶	Incomplete response to MTX	Baricitinib vs adalimumab, each with background MTX
RA-BUILD ³⁹	Incomplete response to conventional DMARDs	Baricitinib vs placebo, each with background csDMARD
RA-BEGIN ⁴⁰	bDMARD- and csDMARD-naïve	MTX monotherapy vs baricitinib with or without MTX

bDMARD=biologic disease-modifying antirheumatic drug; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DMARD=disease-modifying antirheumatic drug; MTX=methotrexate.

Results showed that both baricitinib arms led to a significantly greater likelihood of achieving an ACR20 response at week 12. Additional objectives, such as improvements in DAS28, Simplified Disease Activity Index (SDAI) remission, HAQ-DI, and morning joint stiffness, also all significantly favored baricitinib. As with other trials, the results in the 4-mg baricitinib group were superior to those seen in the 2-mg group.

The RA-BEGIN phase III trial enrolled 588 patients randomized (4:3:4) to MTX monotherapy (once weekly), baricitinib monotherapy (4 mg once daily), or combination baricitinib and MTX for 52 weeks.⁴⁰ Baricitinib monotherapy was superior to MTX monotherapy at week 24 with a higher ACR20 response rate (77% vs 62%; $P \leq 0.01$). Similar results were seen with combination therapy.

Several other JAK inhibitors are currently being studied in clinical trials (Table 2). In the phase II DARWIN 1 and DARWIN 2 trials, filgotinib—a selective JAK1 inhibitor—demonstrated efficacy both in combination with MTX and as monotherapy.^{41,42} Phase III studies are ongoing. A second selective JAK1 inhibitor—upadacitinib (ABT-494)—also showed promising activity in the BALANCE I and BALANCE II trials among patients with moderate to severe RA and an inadequate prior response to MTX or anti-TNF therapy.⁴³ Peficitinib, a JAK1/JAK3 inhibitor, is also being evaluated in phase III trials.⁴⁴

The Use of JAK Inhibitors in RA: Safety

Due to their broad activity targeting multiple cytokines, concerns have been raised about the potential off-target effects of JAK inhibitors. And with their general newness in the RA treatment armamentarium—especially compared to bDMARDs—it is important to review and understand safety concerns associated with JAK inhibitors.

In general, many of these concerns appear to be similar in nature and frequency to those associated with bDMARDs used to treat RA: serious infection, neutropenia, anemia, and elevated liver enzymes.²³ There are, however, some specific safety issues with JAK inhibitors that should be discussed.

Perhaps most notably, patients treated with JAK inhibitors appear to have a higher incidence of herpes zoster infection than do those treated with bDMARDs. Clinical trials showed an approximately 1.5- to 2-fold greater risk of herpes zoster infection in patients treated with either tofacitinib or baricitinib compared to rates typically observed in patients with RA.²³

The 2015 ACR guideline for the treatment of RA recommends that all patients 50 years and older receive the herpes zoster vaccine before initiating any therapy.¹⁶ The attenuated live herpes vaccine is contraindicated in patients currently taking a bDMARD or JAK inhibitor, which can make this a tricky balancing act in patients on therapy who have not already received the herpes zoster vaccine.

A few more important notes related to safety of JAK inhibitors²³:

- Short-term hematologic changes have been noted in trials of tofacitinib, including decreases in neutrophil and lymphocyte counts and increases in hemoglobin levels. These counts tended to revert to near-normal levels by 24 months. However, if severe, they require a dose reduction or discontinuation.
- The impact of JAK inhibitors on CV risk, at present, remains unknown.
- In patients with moderate to severe renal impairment, and in those with abnormal liver function, the maximum dose of tofacitinib should be 5 mg daily.

What Do the Guidelines Say About JAK Inhibitors?

In the 2015 guideline for the treatment of RA, the ACR generally indicated a preference for using anti-TNFs over tofacitinib, particularly in patients with early RA. This preference, the authors wrote, is due to the fact that “there are potential longer-term safety concerns related to tofacitinib that need more study, partly related to the shorter experience using tofacitinib.”¹⁶

EULAR’s guidelines for the treatment of RA, published in June 2017, offer a similar perspective, indicating that although both biologics and JAK inhibitors can be considered after failure of traditional DMARDs, “current practice would be to start a bDMARD.”²⁴ Again, this recommendation was based on the larger amounts of available data supporting biologic therapies versus JAK inhibitors and not on data showing that bDMARDs were safer or more efficacious. The EULAR guidelines also suggested that JAK inhibitors should be used in combination with MTX, while noting that there is evidence showing that these agents can be efficacious and safe when used as monotherapy.²⁴

As more experience is gained with JAK inhibitors and as longer-term data become available, these recommendations will be updated and revisited.

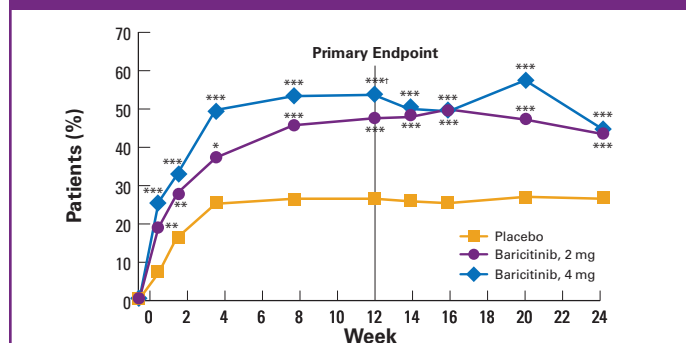
Conclusion

In patients with RA who are treatment-naïve, the current standard of care as reflected in treatment guidelines remains MTX, an inexpensive drug that works in approximately 40% of patients with RA. For those patients who do not respond adequately to MTX after 3 months, alternative options, typically involving the addition of a bDMARD or tsDMARD, should be explored.

Treatment recommendations for patients with RA have rapidly evolved in the last decade. As a greater push for earlier and more aggressive intervention has taken hold, patients are being driven toward goals of remission or, in those who cannot achieve remission, low disease activity.

JAK inhibitors remain the “new kids on the block” for many rheumatologists, and concerns about safety were reflected in both the 2015 ACR and 2017 EULAR treatment guidelines. Nonetheless, a growing body of clinical evidence has shown that JAK inhibitors have at least equivalent efficacy to bDMARDs, with a slightly higher incidence of herpes zoster infection. JAK inhibitors have shown nearly equivalent efficacy when used both as monotherapy and in combination with MTX, and are available in oral formulations, which may be attractive to some patients.

Figure 5. RA-BEACON Efficacy Data³⁷



DAS28-CRP=Disease Activity Score (28-joint count)—C-reactive protein; HAQ-DI=Health Assessment Questionnaire Disability Index.

* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, all for baricitinib vs placebo.

[†] $P \leq 0.001$ for comparisons between baricitinib at the 4-mg dose and placebo for the endpoints of the ACR20 response at week 12 and the changes from baseline in the DAS28-CRP and the HAQ-DI score at week 12.

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Clinical Practice Snapshot: Incorporating Janus Kinase Inhibitors Into the Management of Rheumatoid Arthritis Post-Test

FOR REVIEW PURPOSES ONLY.
MUST BE COMPLETED ONLINE.

Original Release Date: **October 2017** • Expiration Date: **October 31, 2018** • Estimated Time to Complete Activity: **1.0 hour**
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POST-TEST CME/CE QUESTIONS

- According to treat-to-target guidelines, which of the following should be the primary target of therapy for most patients with rheumatoid arthritis (RA)?**
 - Clinical remission
 - Low disease activity
 - Stable disease activity
 - None of the above; goals must be individualized for every patient
- Which of the following statements about Janus kinase (JAK) inhibitors is true?**
 - JAK inhibitors are significantly less effective in combination with methotrexate (MTX) than as monotherapy.
 - JAK inhibitors have a longer half-life than biologic disease-modifying antirheumatic drugs (DMARDs).
 - JAK inhibitors are most effective in patients who have received a prior tumor necrosis factor (TNF) inhibitor.
 - The rate of herpes zoster infection is higher in patients treated with JAK inhibitors compared to biologic DMARDs.
- Approximately what percentage of patients with RA do not achieve an adequate response to biologic therapy?**
 - 20%-25%
 - 30%-35%
 - 40%-45%
 - 50%-55%
- Which of the following was among the conclusions of the phase III RA-BEAM trial that was used to support the initial submission of baricitinib for US Food and Drug Administration (FDA) approval?**
 - Baricitinib was superior to adalimumab + MTX regarding improvement in patients' Disease Activity Score (28-joint count)–C-reactive protein (DAS28-CRP) at 12 weeks.
 - Baricitinib was superior to adalimumab + MTX regarding improvement in patients' American College of Rheumatology 20%, 50%, and 70% improvement criteria (ACR20/50/70) response rates at 12 weeks.
 - Baricitinib was superior to adalimumab + MTX regarding changes in radiographic progression at 24 weeks.
 - Baricitinib was equivalent to adalimumab + MTX across all study measures at all key time points.
- Which of the following is included among the commonly cited reasons for the lack of uptake of treat-to-target guidelines in real-world clinical practice?**
 - Many of today's practicing rheumatologists are not appropriately keeping up with changes to their field and are therefore unaware of the treat-to-target guidelines.
 - The treat-to-target guidelines were drafted mainly by a contingent of European rheumatologists and are not applicable in the United States.
 - Scheduling frequent patient visits with regular joint assessments, a necessity within the treat-to-target guidelines, has proven to be challenging due both to geography and time.
 - Patients are not interested in making frequent medication changes as long as their disease remains stable.
- Because they target intracellular signaling pathways and have broad anti-JAK activity, which of the following is true of JAK inhibitors?**
 - Off-target adverse effects are generally more predictable with JAK inhibitors than with biologic DMARDs.
 - Immune suppression is less likely with JAK inhibitors than with biologic DMARDs.
 - JAK inhibitors offer wide protection against anti-inflammatory cytokines.
 - JAK inhibitors offer wide protection against proinflammatory cytokines.
- The JAK3 protein is unique in that it is only expressed in hematopoietic cells and pairs only with which other member of the JAK family?**
 - JAK1
 - JAK2
 - TYK1
 - TYK2
- All JAK combinations affect pathways involved with inflammation with the exception of which of the following?**
 - JAK1/JAK2
 - JAK1/JAK3
 - JAK2/JAK2
 - JAK1/JAK2/TYK2
- Tofacitinib primarily inhibits which two JAK pathways?**
 - JAK1 and JAK2
 - JAK1 and JAK3
 - JAK2 and TYK2
 - JAK3 and TYK2
- The current ACR RA treatment guidelines offer which of the following recommendations regarding the use of tofacitinib?**
 - Anti-TNFs are generally preferred over tofacitinib, particularly in patients with early RA.
 - Tofacitinib should only be used after failure of at least one anti-TNF and a second non-TNF biologic DMARD.
 - Tofacitinib should only be used in combination with MTX.
 - There is not enough current evidence to recommend the use of tofacitinib in any patient with RA, regardless of disease duration or severity.

Clinical Practice Snapshot: Incorporating Janus Kinase Inhibitors Into the Management of Rheumatoid Arthritis Evaluation Form

FOR REVIEW PURPOSES ONLY.
MUST BE COMPLETED ONLINE.

Original Release Date: **October 2017** • Expiration Date: **October 31, 2018** • Estimated Time to Complete Activity: **1.0 hour**

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: <https://tinyurl.com/JAKSuppl17>.

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Please indicate your profession/background:

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Student ☐ Resident/Fellow Researcher
☐ Administrator ☐ Other; specify _____

LEARNING OBJECTIVES: Having completed this activity, you are better able to:	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Design optimal treatment strategies for patients with rheumatoid arthritis (RA) to improve remission rates and/or minimize levels of disease	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Recognize the role that Janus kinase (JAK) plays in the pathogenesis of RA and the corresponding impact of JAK inhibition in the management of RA	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Discuss treatment options for RA, including the use of JAK inhibitors, as reflected in current practice guidelines	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)

- ☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Implement a change in my practice/workplace and seek additional information on this topic.
☐ Do nothing differently. Current practice/job responsibilities reflect activity recommendations.
☐ Do nothing differently. Content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you plan to change your practice/professional responsibilities, may we contact you in 2 months to see how you are progressing?

☐ Yes ☐ No ☐ I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc).

OVERALL EVALUATION	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
The information presented increased my awareness/understanding of the subject.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will influence how I practice/do my job.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will help me improve patient care/my job performance.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The program was educationally sound and scientifically balanced.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Overall, the program met my expectations.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I would recommend this program to my colleagues.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Roy Fleischmann, MD, MACR –Demonstrated current knowledge of the topic. –Was organized in the written materials.	☐ 5 ☐ 5	☐ 4 ☐ 4	☐ 3 ☐ 3	☐ 2 ☐ 2	☐ 1 ☐ 1
Iain B. McInnes, FRCP, PhD, FRSE, FMedSci –Demonstrated current knowledge of the topic. –Was organized in the written materials.	☐ 5 ☐ 5	☐ 4 ☐ 4	☐ 3 ☐ 3	☐ 2 ☐ 2	☐ 1 ☐ 1

What issue(s) are you experiencing in your practice/regarding your professional responsibilities that could be addressed in future programming?

Please provide additional comments pertaining to this activity and any suggestions for improvement.