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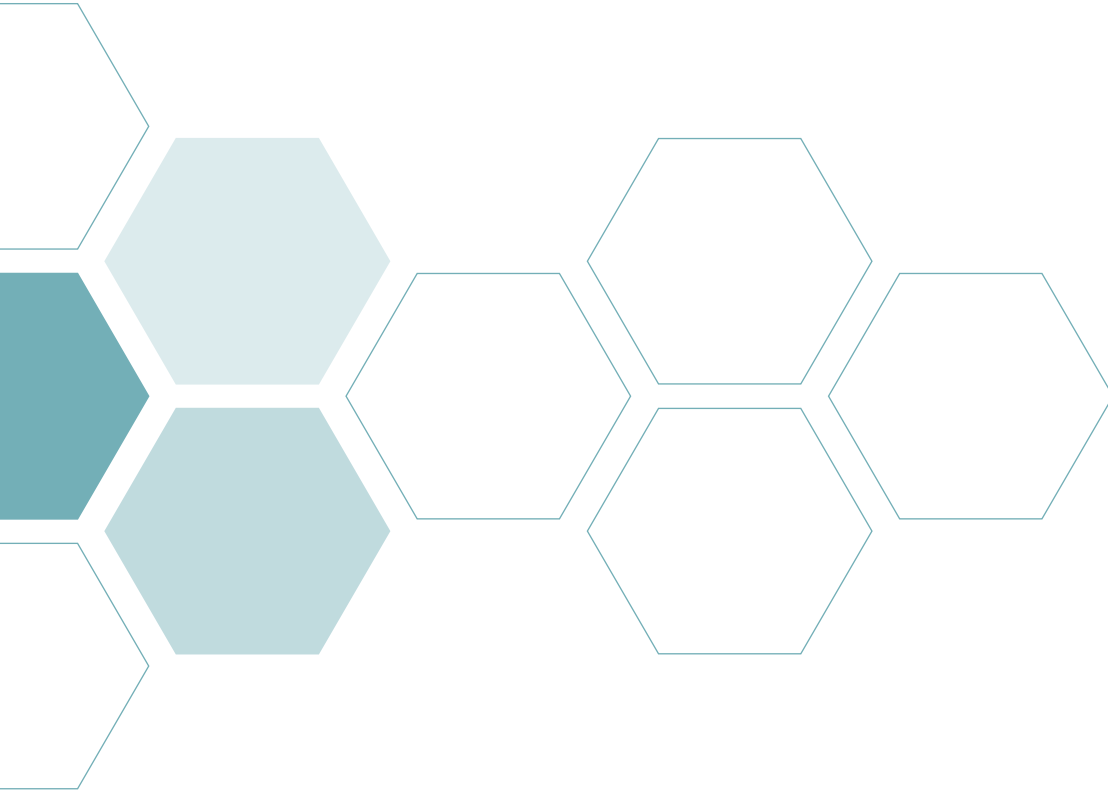
New Horizons in the Treatment and Management of Rheumatoid Arthritis: How Janus Kinase (JAK) Inhibitors are Changing the Treatment Paradigm

New Horizons in the Treatment and Management of Rheumatoid Arthritis: How Janus Kinase (JAK) Inhibitors are Changing the Treatment Paradigm

Instructions for CME/CNE: Activity is valid from April 25, 2017 to April 30, 2019.
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Dr. Owens is President of Gary Owens Associates.

Learning Objectives:
1. Review the mechanisms of action, efficacy and safety of new and emerging janus kinase (JAK) inhibitors in the management of Rheumatoid Arthritis (RA) for achieving treatment goals.
2. Describe the role of the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway in the pathogenesis of RA.
3. Analyze recent clinical trial data of emerging JAK inhibitors in patients with rheumatoid arthritis.
4. Tailor treatment regimens for moderate-to-severely active RA based on repeated assessment of disease activity, functional status, treatment response, and other patient-specific risks.
5. Identify strategies to monitor and manage adverse events associated with emerging JAK inhibitors in order to improve patient adherence.
6. Explain the pharmacokinetic and pharmacodynamic differences across the JAK inhibitors in patients with RA.
7. Discuss the role of medical directors and payers in the management of patients with RA.

Faculty Disclosure:
Dr. Calabrese serves as a consultant to AbbVie, Crescendo, GlaxoSmithKline, Janssen, Pfizer, Regeneron and UCB. He also is on the speaker's bureau for AbbVie, Bristol-Myers Squibb, Genentech, Janssen and UCB.
Dr. Curtis receives grant/research support from and serves as a consultant to AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Janssen, Lilly, Myriad Genetics, Pfizer, Roche/Genentech, and UCB Pharmaceuticals.
Dr. Kamen has no real or perceived financial relationships to disclose.
Dr. Owens serves as a consultant AbbVie, Biogen, Novartis and Roche.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacquelyn Smith, RN, BSN, MA, CMCN; Katie Eads and Will Williams have no real or perceived financial relationships to disclose.

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New Horizons in the Treatment and Management of Rheumatoid Arthritis:
How Janus Kinase (JAK) Inhibitors are Changing the Treatment Paradigm

Post-Test Questions

1. Which of the following best describes the rate of joint damage in rheumatoid arthritis (RA)?
   a. All patients have a steady increase in joint damage.
   b. The majority of damage occurs in the first few years of disease.
   c. Joint damage progressively accelerates after first year of disease.
   d. Joint damage only occurs in the first year of disease.

2. Use of tumor necrosis factor (TNF) inhibiting disease modifying anti-rheumatic drugs (DMARDs) has led to a 25 percent reduction in premature mortality risk from RA.
   a. True   b. False

3. Which of the following is NOT a known environmental trigger of the process leading to RA in genetically susceptible individuals?
   a. Peridontitis   b. Smoking   c. Life stressors   d. Obesity

4. Which of the following is an accurate statement about cytokines and the development of RA?
   a. Cytokines are minor drivers of autoimmune diseases
   b. In RA there is overproduction of pro-inflammatory factors.
   c. Cytokines regulate recruitment, retention and activation of immune cells.
   d. Tumor necrosis factor (TNF) is the main cytokine leading to joint damage.

5. Which of the following is the goal of RA treatment?
   a. 75 percent decrease in symptoms.
   b. Complete disease remission.
   c. Normalization of markers of systemic inflammation.
   d. No joint damage

6. Which of the following is an ACCURATE statement about JAK inhibitors?
   a. JAK inhibitors lower transforming growth factor (TGF-β) and TNF.
   b. They work extra-cellularly.
   c. Various interleukins (2, 4, 6, 7, 12, 15, 21, 23) and interferon are affected by JAK inhibition.
   d. These agents cause immunogenic effects through the production of autoantibodies.

7. Which of the following oral DMARDs has been shown to be more effective than methotrexate in DMARD naïve patients?
   a. Azathioprine   b. Lefluomide   c. Cyclosporine   d. Tofacitinib.

8. Which of the following is an adverse effect of concern with JAK inhibitors?
   a. Herpes zoster
   b. Progressive multifocal leukoencephalopathy
   c. Steven's Johnson syndrome
   d. Tendon rupture

9. The onset of effect and maximum effect for the investigational JAK inhibitor, baricitinib, occurs at:
   a. 1 week/8 weeks   b. 2 weeks/16 weeks
   c. 6 weeks/24 weeks   d. 8 weeks/24 weeks

10. Which of the following is an indication for JAK inhibitors that is supported by clinical trials but not yet recommended in the American College of Rheumatology (ACR) RA management guidelines?
    a. Initial therapy in early RA with mild disease activity.
    b. Switch therapy in case of inadequate response to methotrexate.
    c. Initial therapy in early RA with moderate to severe disease activity.
    d. Initial therapy in combination with methotrexate and a TNF inhibitor for moderate to severe disease activity.

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent   3 - Good   2 - Fair   1 - Poor)

1. Based on the content presented I am better able to:

   Review the mechanisms of action, efficacy and safety of new and emerging janus kinase (JAK) inhibitors in the management of Rheumatoid Arthritis (RA) for achieving treatment goals.

   4   3   2   1

   Describe the role of the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway in the pathogenesis of RA.

   4   3   2   1

   Analyze recent clinical trial data of emerging JAK inhibitors in patients with rheumatoid arthritis.

   4   3   2   1

   Tailor treatment regimens for moderate-to-severely active RA based on repeated assessment of disease activity, functional status, treatment response, and other patient-specific risks.

   4   3   2   1

   Identify strategies to monitor and manage adverse events associated with emerging JAK inhibitors in order to improve patient adherence.

   4   3   2   1

   Explain the pharmacokinetic and pharmacodynamic differences across the JAK inhibitors in patients with RA.

   4   3   2   1

   Discuss the role of medical directors and payers in the management of patients with RA.

   4   3   2   1

2. The activity met my expectations.   4   3   2   1

3. The activity and presenters were free of bias. 4   3   2   1

4. The activity was applicable to my position.   4   3   2   1

5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

   4   3   2   1

6. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4   3   2   1

7. What other topics interest you? _____

8. My goal of participating in this activity was: _____

   _____

9. Did the content of the activity help in meeting your above goal?

   ☐ Yes   ☐ No

10. Due to the content of this activity, I will change my practice patterns by:

    ☐ Identifying opportunities to improve treatment options for patients.
    ☐ Providing guidelines and resources on new therapies to providers.
    ☐ My practice patterns will not change.
    ☐ Other (specify): _____

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.

    ☐ Management and leadership skills
    ☐ Business and/or financial expertise to manage the medical loss ratio.
    ☐ Exchange ideas and network with colleagues to improve patient outcomes.
    ☐ Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
    ☐ Clear knowledge of practice of medicine, especially common disease.
    ☐ Stay updated on clinical conditions.

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JOURNAL of MANAGED CARE MEDICINE

The Official Journal of the
NATIONAL ASSOCIATION OF MANAGED CARE PHYSICIANS MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 20, No. 2, 2017

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Leonard H. Calabrese, DO; Jeffrey Curtis, MD, MS, MPH;
Diane L. Kamen, MD, MSCR; Gary M. Owens, MD

RHEUMATOID ARTHRITIS (RA) IS A SYStemic autoimmune disease whose main characteristic is persistent joint inflammation that results in joint damage and loss of function. It is a chronic and progressive disease of unknown etiology that affects about 1 percent of the population with a female predominance of 3:1.[1] The age of RA onset is usually between 30 and 50 years. It results in over nine million physician visits and 250,000 hospitalizations per year.

A major consequence of RA is joint damage with the majority occurring within the first few years of disease onset. The rate of damage progression is significantly more rapid in the first year than in the second and third years, but the early rapid rate of joint damage does not occur in all patients. A goal of research is to identify predictive factors for the subgroup of patients who are more likely to have erosive joint damage.

Extra-articular manifestations of RA also occur in some patients and are usually a marker for severe active disease. Organs involved include the skin, eye, heart, lung, kidney, nervous system, and gastrointestinal tract. Risk factors for developing extra-articular RA include positive rheumatoid factor (RF, autoantibodies that bind to Fc fragment of IgG and form an immune complex), certain genetic markers (HLA DR4+), male gender, and concomitant subcutaneous nodules, scleritis, vasculitis, and Felty's syndrome.

RA has a significant impact on both overall health and quality of life. Because of chronic systemic inflammation, it results in increased morbidity and premature mortality. Those with RA have a five-fold increased cardiovascular event rate compared with the general population.[2] The mortality rate is 1.5 to 1.6 times higher in RA patients compared with the general population.[3] Before the advent of targeted therapies, RA shortened life span by 3 to 18 years. The introduction of tumor necrosis factor (TNF) inhibitors has reduced premature death, myocardial infarctions, hospitalizations, and hip and knee replacements.[4,5] There has been a 25 percent reduction in premature mortality risk with TNF inhibitor biologic use.[6]

RA has a significant impact on quality of life because of pain and joint deformity. Many patients are unable to work within 10 years of disease onset. In the pre-biologic era, 50 percent of patients were disabled within 10 years, whereas in 2008 about 35 percent were disabled with biologic therapy.[7,8] As therapy continues to better target the underlying pathology of RA and clinicians more aggressively treat the disease, additional improvements in morbidity and mortality should be seen.

The diagnostic criteria for RA require synovitis in at least one joint, absence of alternative diagnosis that better explains the synovitis, and a total score of six or more on several criteria [number of joints affected, RF and anti-cyclic citrullinated peptide (ACCP) positivity, acute phase reactant levels {erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and duration of symptoms).[9] RF is sensitive for RA (80%), particularly in established disease, but not specific. ACCP is specific for RA (88-96%) and predictive of future joint damage. Typical radiologic findings in RA include juxta-articular osteopenia, joint space narrowing, and progressive erosions. Newer imaging modalities like ultrasound and MRI are more sensitive but specificity is still unclear. Hopefully, patients would be diagnosed before joint damage on X-ray is seen, but this does not always occur.

A combination of genetic predisposition and environmental triggers are thought to lead to development of RA.[10] Periodontitis, smoking, life stressors, and certain bacteria are known environmental triggers in genetically susceptible individuals. Prior to the development of symptoms, autoantibodies can be measured; these may be detected up to 10 years before the development of disease. At some point, there is a transition from a silent autoimmunity to symptomatic disease. How to identify those people likely to develop RA and how to alter the progression to symptomatic disease is unknown at this time. Once the patient with autoantibodies has symptoms, this is the articular phase of the disease where systemic and joint localized inflammation begin to cause damage.

Cytokines are major drivers of autoimmune diseases including the development of RA. Cytokines are structurally distinct factors binding to receptors that belong to seven distinct families. Cytokines regulate recruitment, retention, and activation of immune cells. In RA, there is an imbalance between pro-inflammatory [tumor necrosis factor alpha (TNF–alpha), interleukin-1 (IL-1), and others] and anti-inflammatory factors [soluble TNF receptor, IL-10, IL-1 receptor antagonist] leading to tissue inflammation and joint damage.[11] Overall, there is a vicious cycle of upregulated cytokine production promoting cell growth, cell proliferation, and more inflammation.

Treatment

The treatment of RA has evolved significantly in recent years. Traditionally, treatment involved suppressing inflammation with nonspecific agents like corticosteroids. These suppress cytokine function across the entire immune system but have widespread unwanted adverse effects such as type 2 diabetes, osteoporosis, and infection. Over the years, RA has also been treated with other nonspecific immune suppressants, including injectable and oral gold, hydroxychloroquine, sulfasalazine, azathioprine, and D-penicillamine. All but corticosteroids are disease-modifying antirheumatic drugs (DMARDs) which reduce joint damage. Many of these agents are still used for mild disease. Exhibit 1 lists the FDA approved DMARDs.

The modern era of treating RA began in the 1980s with the use of methotrexate (MTX), which is still the cornerstone of RA treatment. Control of the disease is possible in about one-third of patients with MTX alone. The introduction of targeted biologic therapies in the 1990s began the treatment revolution of more narrowly targeting pathologic cytokines rather than general immunosuppression which is continuing today. Those that target single cytokines such as tumor necrosis factor alpha (TNF-α) inhibitors work within the extracellular space targeting cell surface receptors. While single cytokine targeting has been effective, not all patients respond. This is because there are many different cytokines involved in the pathogenesis. This challenge suggests alternatives to single cytokine inhibition should be considered.

The American College of Rheumatology (ACR) publishes treatment guidelines for RA.[12] The goal

Exhibit 2: Treat-to-Target Approach versus Standard of Care[15-17]
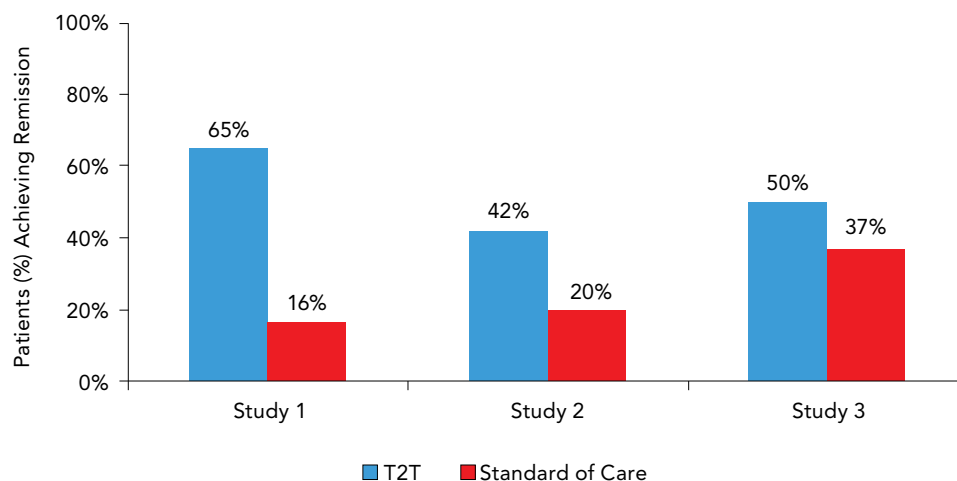
of therapy is disease remission or, at the very least, very low disease activity. This is a paradigm shift from controlling symptoms to controlling the disease process with the abrogation of inflammation. Remission is defined as complete absence of clinical signs and symptoms of synovitis, elimination of silent synovial inflammation, and normalization of markers of systemic inflammation such as ESR and CRP.[13]

Some important changes in the 2015 update of the ACR guidelines are a strong recommendation about achieving remission with treat-to-target, emphasis on vaccination of the immunomodulated patient, a recommendation for considering the addition of low-dose glucocorticoid for patients with moderate to high disease activity, recommendation for short-term glucocorticoid use for RA flares, and more recommended treatment options for those with moderate to severe disease. Tofacitinib, an agent discussed later, was added to the treatment algorithms in this update.

The concept of treat-to-target (T2T) was put forth in the 2012 update of the ACR guidelines and continued in the 2015 update. T2T has become the treatment paradigm in RA; composite measures are used to score disease activity and therapy is adapted until the targeted disease activity state (remission or very low disease activity) is attained. Key elements of T2T are monitoring disease activity every one to three months until the goal is reached; then every three to six months and adjusting therapy regularly until the goal is achieved.[13,14] As shown in Exhibit 2,

an aggressive T2T approach results in a much higher percentage of patients who achieve disease remission compared with standard care.[15-17] It should be noted that even with aggressive therapy not everyone is able to achieve remission.

For DMARD naïve RA patients, those with low disease activity are initially started on MTX monotherapy unless contraindicated. If MTX is not sufficient to control disease, treatment can be a combination of conventional synthetics csDMARDs, TNF inhibitor with or without MTX, non-TNF-inhibitor biologic with or without MTX, or tofacitinib plus MTX.[13] The guidelines recommend the use of biologic DMARDs (bDMARDs) over tofacitinib, but this is a conditional recommendation based on low evidence.[13] Exhibit 3 illustrates some characteristics of the biologic DMARDs (bDMARDs). The bDMARDs have limitations in that not everyone responds and they must be given by injection.

For DMARD naïve RA patients with moderate to severe disease activity, the ACR guidelines strongly recommend combination therapy over monotherapy. Combination therapy can again be a combination of csDMARDs, TNF inhibitor with or without MTX, non-TNF-inhibitor biologic with or without MTX, or tofacitinib plus MTX.[13]

Targeted Synthetic DMARDs
Targeted synthetic DMARDs (tsDMARDs), oral small molecules that inhibit intracellular signaling of cytokines and growth factors, are the up-and-coming agents in RA treatment. These agents are

	Etanercept (Enbrel)	Infliximab (Remicade)	Certolizumab (Cimzia)	Adalimumab (Humira)	Toclizumab (Actemra)	Abatacept (Orencia)	Rituximab (Rituxan)
Target	TNF	TNF	TNF	TNF	IL-6 Inhibitor	T-Cell Modulation	B-Cell
Half Life	3 - 5 Days	8 - 10 Days	14 Days	10 - 20 Days	8 - 14 Days	13 - 16 Days	19 Days
Construct	Human	Chimeric	Fab-Pegylated	Human	Humanized (Mouse)	Human	Chimeric
Dosing	Once Biweekly-weekly	Once every 4 - 8 weeks	Once every 4 weeks	Once every 1 - 2 weeks	Once every 4 - 6 weeks	Once Monthly	Twice every 6 - 12 months
Route	SQ	IV	SQ	SQ	IV	IV	IV

Exhibit 3: Characteristics of Biologic DMARDs

TNF = tumor necrosis factor
IL = interleukin
SQ = subcutaneous
IV = intravenous

chemically more related to traditional medications like methotrexate than to bDMARDs but act like bDMARDs in their suppression of cytokines. Some call them small molecule biologics, but they are not monoclonal antibodies like the biologics.

The benefit of small molecules is increased biologic activity across multiple pathways but with that wide activity there is a risk of increased toxicity from perturbation of the integrated immune response. These agents have the advantage of being given orally. The first of the tsDMARDs to be approved was a Janus kinase (JAK) inhibitor, tofacitinib (Xeljanz®) in 2012.

Role of the JAK/STAT Pathway in the Pathogenesis of RA
Janus kinase (JAK) is an intracellular tyrosine kinase which influences immune cell function and hematopoiesis by transmitting signals from cytokine-growth factor receptor interactions.

JAK phosphorylates and activates signal transducers and activators of transcription (STATs) which modulate intracellular gene expression.[18] There are four known JAK enzymes: JAK1, JAK2, JAK3 and TYK2. JAK-dependent cytokines have been implicated in the pathogenesis of a number of inflammatory and autoimmune diseases, suggesting that JAK inhibitors may be useful for the treatment of a broad range of inflammatory conditions beyond RA.

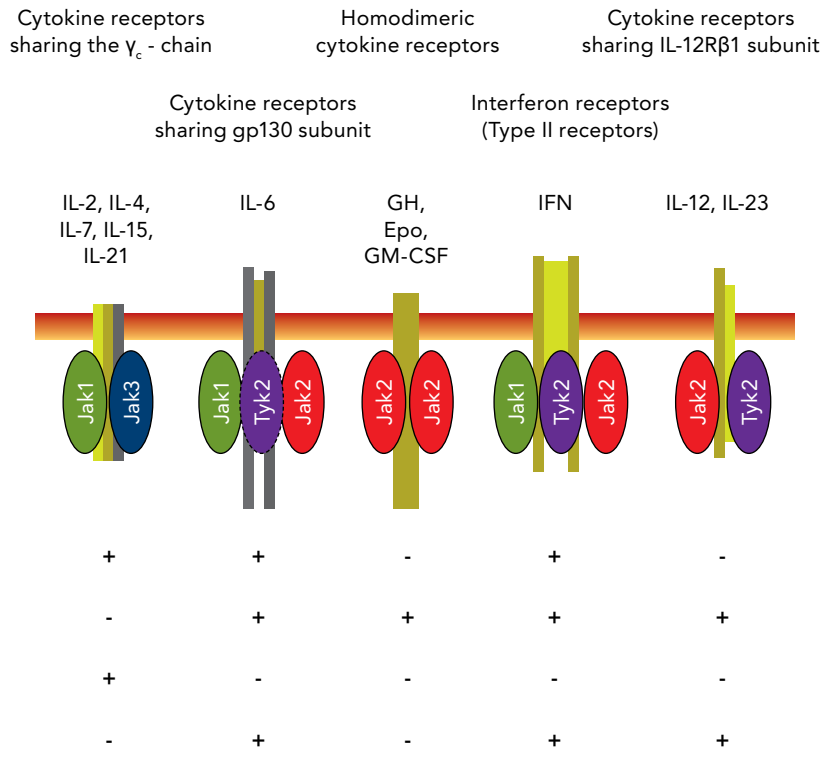As shown in Exhibit 4, targeting cytokine signaling pathways using JAK inhibitors, alters a wide range of cytokines including various interleukins (IL-2, IL-4, IL-6, IL-7, IL-12, IL-15, IL-21, IL-23) and interferon.[19] All of these cytokines are involved in the pathogenesis of RA and activate other cytokines. In addition to cytokines implicated in RA, JAK inhibitors affect colony stimulating factor, erythropoietin, prolactin and growth hormone.[20] The particular cytokines affected varies by which version of JAK is inhibited. The selectivity of a JAK inhibitor may impact the development of adverse effects. Other pathogenic cytokines in RA including IL-1, IL-17, IL-18, transforming growth factor beta (TGF-β), and TNF are not affected by JAK inhibition.

JAK Inhibitors
JAK inhibitors, also known as jakinibs, work uniquely by inhibiting several intracellular pathways thought to be important in the pathogenesis of RA. Tofacitinib (Xeljanz®) blocks JAK1 and JAK3 much more than JAK2 and has little effect on TYK2. In addition to affecting interleukins discussed previously, tofacitinib also blocks T helper cell one (TH1) and seventeen (TH17), and decreases natural killer (NK) cells. Overall, it prevents transmission of extracellular information into the cell nucleus, influencing DNA transcription.

Tofacitinib is indicated for the treatment of adult patients with moderate to severe active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combi-

Exhibit 4: Targeting Cytokine Signaling Pathways Using JAK Inhibitors[19]

Cytokine receptors sharing the γ_c - chain
Homodimeric cytokine receptors
Cytokine receptors sharing IL-12Rβ1 subunit

Cytokine receptors sharing gp130 subunit
Interferon receptors (Type II receptors)

	IL-2, IL-4, IL-7, IL-15, IL-21	IL-6	GH, Epo, GM-CSF	IFN	IL-12, IL-23
	Jak1 / Jak3	Jak1 / Tyk2 / Jak2	Jak2 / Jak2	Jak1 / Tyk2 / Jak2	Jak2 / Tyk2
Jak1 inhibitor	+	+	-	+	-
Jak2 inhibitor	-	+	+	+	+
Jak3 inhibitor	+	-	-	-	-
Tyk2 inhibitor	-	+	-	+	+

IL = interleukin
IFN = interferon
GH = growth hormone
Epo = erythropoietin
GM-CSF = granulocyte macrophage colony stimulating factor

nation with MTX or other csDMARDs. Trials have shown tofacitinib to be effective at halting structural damage and to be superior to MTX clinically, functionally, and radiographically.[21,22] It is the first oral DMARD to be shown to be better than MTX. Tofacitinib is effective in multiple populations, including DMARD naïve, MTX, csDMARD and TNF inhibitor inadequate response. Exhibit 5 summarizes the clinical evidence with this agent.[21-26] Onset of response occurs within two weeks and efficacy has been maintained for up to five years in open label extensions of trials. Thus, rapid and durable response is another advantage of JAK inhibitors.
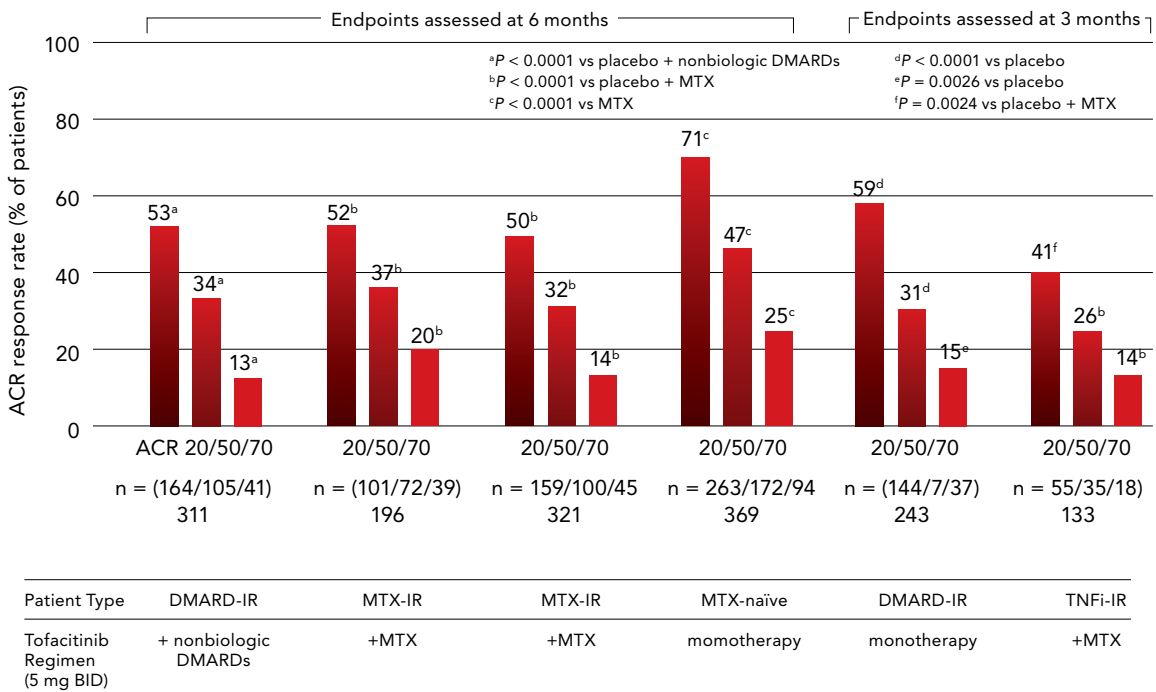
Tofacitinib is given as a 5 mg oral dose twice daily or as a single 11 mg extended release tablet daily (Xeljanz XR®). Oral dosing makes this agent much easier to use than the injectable bDMARDs. Dosing does need to be adjusted to 5 mg daily for moderate and severe renal or moderate liver impairment. Tofacitinib therapy is not recommended for those with severe liver impairment.

This agent does have some significant drug inter-actions. In combination with potent inhibitors of cytochrome P450 3A4 (CYP3A4) such as ketoconazole, the recommended dose of tofacitinib is 5 mg once daily.[27] When one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole), the dose should be 5 mg once daily. Potent CYP inducers such as rifampin may result in loss of or reduced clinical response.

The most common adverse events with tofacitinib in clinical trials were infections.[27] The overall frequency of infections was 2 percent greater in tofacitinib 5 mg twice a day groups compared with placebo. The most commonly reported infections were upper respiratory tract, nasopharyngitis, and urinary tract (4%, 3%, and 2% of patients, respectively). Serious adverse events occurred in 15.4 percent of those treated with tofacitinib. Serious bacterial, viral, or opportunistic infections occurred in 4.5 percent. The most common serious infections reported with tofacitinib included pneumonia, cellulitis, herpes zoster, urinary tract infection, and diverticulitis.

Exhibit 5: Tofacitinib Clinical Evidence Summary[21-26]

Endpoints assessed at 6 months | Endpoints assessed at 3 months

ACR response rate (% of patients)

[a]P < 0.0001 vs placebo + nonbiologic DMARDs
[b]P < 0.0001 vs placebo + MTX
[c]P < 0.0001 vs MTX
[d]P < 0.0001 vs placebo
[e]P = 0.0026 vs placebo
[f]P = 0.0024 vs placebo + MTX

	ACR 20/50/70	20/50/70	20/50/70	20/50/70	20/50/70	20/50/70
Values	53[a] 34[a] 13[a]	52[b] 37[b] 20[b]	50[b] 32[b] 14[b]	71[c] 47[c] 25[c]	59[d] 31[d] 15[e]	41[f] 26[b] 14[b]
n =	(164/105/41) 311	(101/72/39) 196	159/100/45 321	263/172/94 369	(144/7/37) 243	55/35/18 133
Patient Type	DMARD-IR	MTX-IR	MTX-IR	MTX-naïve	DMARD-IR	TNFi-IR
Tofacitinib Regimen (5 mg BID)	+ nonbiologic DMARDs	+MTX	+MTX	momotherapy	monotherapy	+MTX

In the premarketing trials, there were 11 gastrointestinal (GI) perforations of which six were associated with diverticulitis. Risk factors for GI perforation include older age, oral steroids use (> 7.5 mg/day of prednisone), and history of diverticulitis and other GI conditions (but not diverticulosis).[28] This is a rare adverse effect, but the rate does appear to be higher with tofacitinib than other agents used to for RA, except tocilizumab (Actemra®).

Tofacitinib should not be used in patients with an active, serious infection, including localized infections. Additionally, viral reactivation can occur. Patients should be screened for hepatitis B and C viral infection and tuberculosis in accordance with clinical guidelines before starting tofacitinib.

There is an increased risk of herpes zoster with tofacitinib use which is highest when it is used in combination with MTX.[29] Patients should be immunized with the live zoster vaccine prior to tofacitinib, but not while on bDMARDs. Patients who have been vaccinated can still develop a herpes zoster outbreak, but the rate is lower than that seen in those who are not vaccinated. Vaccination is especially important because incident herpes zoster is associated with as much as a twofold increased risk of stroke in the subsequent 90 days afterwards in those with autoimmune diseases.[30] If an outbreak occurs, prompt antiviral therapy is associated with a lower incidence of subsequent stroke.[30]

Laboratory changes with tofacitinib include increased liver function tests (AST, ALT), low-density lipoprotein cholesterol (LDL-C), and creatinine and decreased hemoglobin, neutrophils, and lymphocytes.[27] These laboratory changes tend to stabilize over time. In the clinical trial program of tofacitinib-treated patients, lung cancer, breast cancer, lymphoma, and gastric cancer were among the most common malignancies reported.[31]

It is important to note that the risk of malignancies such as lymphomas, lung cancer, and nonmelanoma skin cancers is greater in patients with RA compared with the general population. The incidence of all malignancies (excluding nonmelanoma skin cancers) was similar in tofacitinib users compared with the general population. Overall, the rates and types of malignancies observed in the tofacitinib clinical program remained stable over time with increasing tofacitinib exposure and are similar to what is expected in the RA population and not different from other DMARDs.

The FDA approved tofacitinib with a Risk Evaluation and Mitigation Strategy (REMS) which consists of a medication guide advising patients about important safety information and a communication plan to inform health care providers about the serious risks associated with tofacitinib.

Investigational JAK Inhibitors
There are numerous additional JAK inhibitors under investigation for RA which all have different selectivity.[32] These include baricitinib (JAK1/JAK2 inhibitor submitted to FDA), filgotinib (JAK1 inhibitor in Phase III trials), ABT 494 (JAK1 inhibitor, Phase II), and peficitinib (pan-JAK inhibitor, Phase II). Other indications being studied for JAK inhibition include psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, lupus, spondyloarthropathies, and others.

Baricitinib (Olumiant®) is the closest investigational JAK inhibitor to market. A NDA was submitted in January 2016, and the FDA review of this agent was extended in January 2017 to allow time for additional data review.[33] This is an oral, reversible inhibitor of JAK1 and JAK2 which is given once daily. It was approved in February 2017 in the European Union as monotherapy or in combination with methotrexate, for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs.[34]

Four pivotal phase III clinical trials of baricitinib in patients with moderate to severe active rheumatoid arthritis have been done. [35-38] Two of the four studies included pre-specified comparisons to MTX and adalimumab. The clinical trial program includes a wide range of patients including those who are MTX-naïve and inadequate responders to MTX, csDMARDs, and bDMARDs. Long-term extension studies are planned. In a trial of baricitinib, MTX, or baricitinib plus MTX in patients with early RA who had received limited or no treatment with DMARDs, in MTX naïve patients 4 mg daily of baricitinib monotherapy was equivalent to combination therapy and superior to MTX monotherapy clinically.[38] Although baricitinib was more clinically effective as monotherapy and reduced radiologic progression in this trial, the effect on radiographic progression of the combination with MTX only was statistically significant compared to MTX monotherapy. [38]

In a trial in MTX nonresponders, superior clinical responses with baricitinib were seen compared with adalimumab and a slightly more rapid response and same inhibition of radiographic progression was found.[37] In TNF inadequate responders, clinical responses to baricitinib were consistent with previous biologic therapy. [36]

The adverse effects of baricitinib shown in trials are similar to those seen with tofacitinib. Compared with adalimumab, there were more cases of leukopenia, elevated liver function tests, creatinine phosphokinase, lipids and creatinine, herpes zoster infection, and no reduction in NK cells.[36]

In the trials, benefits in efficacy with baricitinib were seen as early as two weeks after starting therapy. Maximum effect is seen in 16 weeks compared with 20 to 24 weeks with bDMARDS.[38] Early scores of disease activity may be used to predict response to baricitinib. Using data from two trials, investigators demonstrated that a lack of early clinical response, as indicated by a failure to achieve a decrease in DAS28 greater than 0.6 or CDAI greater than 6 after four weeks of treatment, was associated with lower attainment of low disease activity or remission at 12 or 24 weeks.[39] Larger decreases in DAS28 or CDAI at week 4 were associated with improved clinical responses. This potential ability to identify patients very early who are not likely to achieve significant clinical targets might be useful in tailoring therapy to individual patients.[40]

Where Do JAK inhibitors Fit in the Emerging RA Treatment Paradigm?
The place of JAK inhibitors in RA therapy is evolving. Although TNF inhibitors have been the first-line choice for therapy in moderate to severe disease, one-third of patients with RA show inadequate response. Switching to a therapy with a different mechanism of action is more effective after TNF inhibitor failure than switching to another TNF inhibitor. A 52-week multicenter, pragmatic, open-label, randomized clinical trial compared a second TNF inhibitor to non-TNF biologics in those with initial TNF inhibitor failure.[41] Patients treated with a non-TNF biologic had lower disease activity scores at 12, 24, and 52 weeks than those who received another TNF agent. In this trial, 69 percent of patients achieved an effective clinical response with a non-TNF biologic versus 52 percent of patients who took a second TNF inhibitor.[41] Another trial found that response and remission outcomes were consistently inferior for the second and third TNF inhibitor versus the first.[42] For patients with RA and an insufficient response to anti-TNF therapy, a non-TNF agent appears to be more effective than a second TNF. If managed care currently has a policy that patients must try multiple anti-TNF agents before moving to non-anti-TNF agents, this policy should be reconsidered.

Tofacitinib is an option for those with TNF inhibitor failure. In a meta-analysis of five randomized, placebo-controlled trials in RA patients who failed TNF inhibition, the efficacy of tofacitinib in combination with methotrexate was comparable with abatacept, golimumab, rituximab, and tocilizumab combined with csDMARDs.[43] Withdrawal rates due to all causes and adverse effects were comparable

between treatments, but tofacitinib had a lower rate of withdrawals due to lack of efficacy. Based on the available evidence, tofacitinib is an efficacious option for TNF inhibitor inadequate response and an alternative to a second TNF inhibitor or non-TNF bDMARD. This is reflected in the ACR treatment algorithm recommendations.[13]

For those patients who initially respond to a TNF inhibitor, long-term persistence is low. The rates are 72 percent at one year with the first TNF inhibitor but only 57 percent by the end of two years.[42] Rates are even lower with the second or third TNF inhibitor, possibly because of lack of efficacy (60% at 12 months, 42% at 24 months). Data from 60 months of open-label tofacitinib use in 4,102 patients found that 20.8 percent discontinued within 60 months and 79.2 percent continued therapy.[44] Thus, long-term persistence is as good as if not better with JAK inhibitors.

A JAK inhibitor may also be cost effective. In one analysis of claims data, tofacitinib was more commonly used as monotherapy and yielded at least comparable persistence and adherence with lower adjusted mean RA-related total costs versus adalimumab, etanercept, and abatacept over 12 months.[45]

Approximately one-third of patients are ineligible or intolerant of MTX. JAK inhibitors would seem ideal in this population as initial monotherapy because JAK inhibitors have been shown to be more effective than MTX in early disease (less than 6 months). The current ACR RA management guidelines do not currently include JAK inhibitors for use in early DMARD naïve RA. Exhibit 6 shows some possible areas for JAK inhibitor use.[32] Tofacitinib is currently approved for after another DMARD failure but, there are studies for using it and baricitinib in DMARD naïve patients. Moving the JAK inhibitors up in the ACR algorithm for early disease will likely occur as additional data are accumulated.

Overall, the JAK inhibitors have at least comparable efficacy to the bDMARDs with rapid onset of action. These agents, unlike the monoclonal antibody bDMARDs, do not cause anti-drug antibodies. No studies have yet compared the JAK inhibitors to tocilizumab, abatacept, or rituximab. JAK inhibitors have a similar adverse effect profile and lab monitoring akin to tocilizumab, other biologics, and MTX. Herpes zoster incidence is a key differentiating safety issue from other RA therapies. Barriers to the use of JAK inhibitors include long-term safety unknowns and clinical inertia.

Strategies to Monitor and Manage Adverse Effects and Adherence Associated with JAK Inhibitors
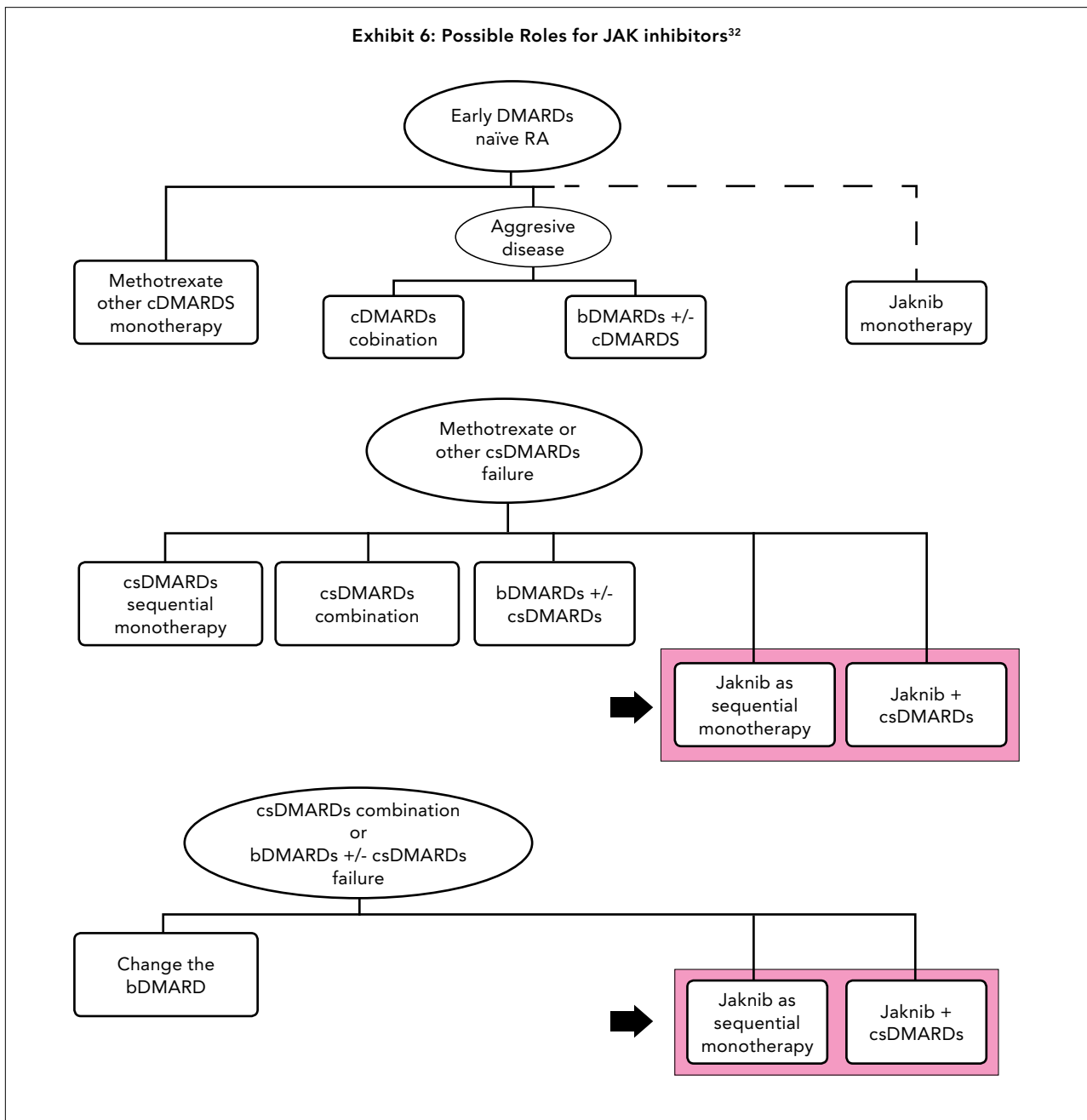One important way to reduce serious infections with JAK inhibitors and other DMARDs is appro-priate vaccination. As discussed previously related to JAK inhibitors and zoster vaccine, it is important that patients receiving any type of DMARD therapy receive appropriate vaccines before and during therapy. The ACR recommended vaccines based on a patient's given regimen are presented in Exhibit 7.[13] Clinicians should consult the published recommendations for further details.

Another way to identify and manage adverse effects is to have strong provider-patient communication. This communication is especially important to help patients remain on DMARDs long term to optimize care. Clinicians should clarify the patient's goal(s) of care and document past and current disease state, damage, and prognosis. It is important for clinicians to quantify expected risks and benefits of recommended treatment(s), but it helps to present the information in a positive manner. For example, a patient can be told that about 5 percent of patients on tofacitinib will have a zoster outbreak in one year of taking this medicine. But, a patient is much more likely to not fear the medication if they are told that 95 percent of patients will not have an outbreak. Pictograms are an easy way to explain risks and benefits. Patients also must understand that they may need to try several medications to find the regimen that works and combination therapy may be required.

Identifying outcomes and adverse effects so they can be managed can be done with a standardized approach at each patient visit. One example of a point of care data collection system is the READY© system. Patient reported outcome data is electronically collected using a tablet computer. Surveys presented to the patient are adapted based on which condition(s) the patient has. READY© also has an application which uses pictograms to explain risks and benefits of therapy. Another method is a patient global questionnaire (examples are available at www.ArthritisPower.com and www.pcornet.org). There are numerous online and application based tools for patients and physicians to track symptoms and joint impact of RA. An example of a clinician tool for tracking health assessments, RA and non RA medications, and symptoms is RheumPRO.

In presenting treatment options to patients, it is important to consider nonpharmacologic factors under the patient's control that may affect outcomes. Loss aversion is one of these factors. Humans are typically risk-avoiding when it comes to a gain or benefit, especially with medications.[46] There is a premium they are willing to forgo to be guaranteed a "sure thing." Patients who are doing "ok" on a given medication may be unwilling to change medication that would provide a better chance of re-

Exhibit 6: Possible Roles for JAK inhibitors[32]

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                    ┌─────────────────┐
                    │  Early DMARDs   │
                    │   naïve RA      │
                    └────────┬────────┘
         ┌───────────────────┼─────────────────────────────┐
         │          ┌────────────────┐                      ┊
         │          │   Aggresive    │                      ┊
         │          │    disease     │                      ┊
         │          └───────┬────────┘                      ┊
┌─────────────┐     ┌───────┴──────┐                 ┌─────────────┐
│ Methotrexate│   ┌─────────┐  ┌──────────┐          │   Jaknib    │
│ other       │   │ cDMARDs │  │bDMARDs +/-│         │ monotherapy │
│ cDMARDS     │   │cobination│  │ cDMARDS  │         └─────────────┘
│ monotherapy │   └─────────┘  └──────────┘
└─────────────┘
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                    ┌──────────────────┐
                    │ Methotrexate or  │
                    │ other csDMARDs   │
                    │    failure       │
                    └────────┬─────────┘
      ┌──────────┬───────────┼────────────────┬──────────────┐
┌──────────┐ ┌──────────┐ ┌──────────┐   ┌──────────┐  ┌──────────┐
│ csDMARDs │ │ csDMARDs │ │bDMARDs +/-│  │ Jaknib as│  │ Jaknib + │
│sequential│ │combination│ │ csDMARDs │   │sequential│  │ csDMARDs │
│monotherapy│ └──────────┘ └──────────┘   │monotherapy│ └──────────┘
└──────────┘                              └──────────┘
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              ┌────────────────────────────┐
              │   csDMARDs combination     │
              │           or               │
              │   bDMARDs +/- csDMARDs     │
              │        failure             │
              └────────────┬───────────────┘
        ┌──────────────────┴──────────────────────┐
  ┌───────────┐                          ┌──────────┐  ┌──────────┐
  │ Change the│                          │ Jaknib as│  │ Jaknib + │
  │  bDMARD   │                          │sequential│  │ csDMARDs │
  └───────────┘                          │monotherapy│ └──────────┘
                                         └──────────┘
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mission. Two studies found that T2T was not implemented at one-third of RA patient visits when it was indicated and patient refusal was the most common reason for not escalating therapy.[47, 48] Potential adverse events and loss of current level of disease control, even if not optimal, deter patients from wanting to change therapy. This leads to clinical inertia and patients not in remission or at low disease activity. Clinicians can change the conversation by talking about the effects of under treated RA, including continued cardiovascular effects, serious infections, and other risks with continued disease activity.

There are several resources which can be helpful for clinicians and patients in making treatment decisions. One example is RA Med Guide©, an online patient decision aid for RA medications (www.ramedguide.com). This site provides unbiased information on the risks and benefits of the various therapies that are most important in making a decision. Patients can be directed to this site and then the clinician can follow-up to see if they have any remaining questions.

Challenges in RA Management

There are numerous challenges for clinicians and managed care related to RA treatment. These in-

Exhibit 7: Recommended Vaccinations Based on Current RA Treatment[13]

	Killed Vaccine			Recominant vaccine	Live vaccine
	Pneumococcal	Influenza (IM)	Hepatitus B	Human papilloma	Herpes zoster
Before initiating therapy					
csDMARD bDMARD tsDMARD	√	√	√	√	√
While already on therapy					
csDMARD	√	√	√	√	√
bDMARD tsDMARD	√	√	√	√	Not recommended

csDMARD = conventional disease modifying anti-rheumatic drug
b = biologic
ts = targeted synthetic

Costs of RA Treatment

The medical costs of RA are high and continue to increase with the development of expensive biologic and non-biologic agents. Several studies have been conducted over the last decade to determine the direct medical costs of RA. However, these studies have a produced a wide range of results. One study published in 2004 estimated the direct medical costs in the United States ranged from $2,298 to $13,549 per patient.[49] Data from studies between 2007 and 2012 have estimated that the per patient annual direct medical costs of RA range from $2,000 to $10,000, with estimated indirect costs ranging from $1,500 to $22,000.[50-52]

The economic burden of RA has grown substantially since the biologic therapies were first introduced in the mid to late 1990s. Most payers now report that the biologic and targeted synthetic DMARDs to treat RA (and other conditions) are among the top five drug categories by total cost and the number one specialty category.[53] In a 2015 paper, Curtis and colleagues used a claims-based al-

gorithm to estimate mean one-year biologic cost per effectively treated patient. The authors reported the following costs: etanercept ($43,935), golimumab ($49,589), adalimumab ($52,752), abatacept ($62,300), and infliximab ($101,402).[54] Because RA is a chronic disease, the drug costs continue over years. High budget impact and lack of clear clinical superiority among the various newer DMARDs alternatives makes RA an attractive target for cost-effectiveness research.[55]

It can be a challenge for smaller managed care plans to determine the total cost of RA care. It is often difficult for payers to merge medical and pharmacy data into a clear picture of total cost, especially in pharmacy benefit carve-out situations. Benefit design changes and changes of carriers can make it hard to track costs year over year. The medical claims system often does not have granular information to allow care costs to be accurately tracked.

Treatment Selection Challenges

Appropriate treatment selection is another challenge. Although the ACR treatment guidelines provide some assistance in choosing one DMARD over another, there is a lack of strong evidence to guide clinicians and managed care. Not every DMARD works

sirukumab	IL-6 monoclonal antibody
sarilumab	IL-6 receptor antibody
clazakizumab	IL-6 inhibitor
mavrilimumab	Monoclonal antibody to alpha subunit of GMCSF
vobarilizumab	Nano-antibody targeting IL-6 receptor

IL = interleukin
GM-CSF = granulocyte-macrophage colony-stimulating factor

for every RA patient and clinicians have little understanding of the cause of this variation of drug efficacy.

The growing number of biologic agents for the treatment of RA is also a challenge for management. Physicians, patients, and plan managers need better data to compare the effectiveness of the different biologics. Because there are few head–to–head studies for all the newer DMARDs, decision makers have to rely on comparing medications across studies, but this has to be done with caution.[56] Given the high cost of these agents, it is important to understand and monitor the optimal use of these agents.

As discussed previously, there is a therapeutic window of opportunity in early RA for preventing or at least limiting functional impairment, work disability, and radiographic damage.[57, 58] Aggressively treating the disease in the first two years can pay dividends down the road. Rheumatologists are trying to meet aggressive treatment approaches to achieve early remission with various combinations of DMARDs. In trying to achieve remission, treatments are going to be more frequently switched due to inadequate response or intolerance. Managed care treatment guidelines and approvals should encourage rather than retard early aggressive treatment.

Having personalized therapy for RA would be ideal because not all patients are going to have a progressive course and thus need aggressive therapy. Although there is not yet a validated method for identifying those who will have a progressive course, poor prognosis factors, including functional limitations, extra-articular disease, seropositivity, positive RF and/or anti-CCP antibodies, bone damage, and early erosive disease predict a need for the most aggressive therapy. Better methods are needed to predict which patients will benefit the most from aggressive therapy.

Monitoring Disease State Activity
Looking ahead to help managed care get the most bang for their RA treatment dollar, monitoring disease state activity will be more important. Currently, there is a heavy reliance on clinical and patient driven evaluations. There is no tool to prospectively determine which therapy will benefit which patient, and there is minimal ability to measure disease activity by labs due to non-specific markers of disease activity. Better measurements are needed. Measuring multiple biologic markers in a panel is now available and managed care will have to figure how to integrate these into care. One example is Vectra DA, which measures 12 different biologic markers and provides a single disease activity score that can be tracked over time. Measuring B-cell activity may be another method. Memory B cells secrete molecules called anticitrullinated protein antibodies (ACPAs). ACPA levels were directly proportional to the recirculating memory B cells in the blood stream.[59]

Not all clinicians use standardized outcome measures routinely in clinical practice to guide therapy. The ACR recommends the use of six measurement tools that can be used at the point of care to track disease activity.[13] Patient only tools include Patient Activity Scale (PAS) and the Routine Assessment of Patient Index Data with three measures (RAPID-3). The Clinical Disease Activity Index [Disease Activity Score with 28-joint count with ESR (DAS28-ESR) or CRP (DAS28-CRP)] is a patient and provider tool. Another tool is the Simplified Disease Activity Index (SDAI). These tools encompass different combinations of patient and provider assessments of swollen joints, patient assessments of pain or disease activity, provider assessments of swollen/tender joints, and laboratory tests. The six were selected because they are sensitive to change,

discriminate well among low, moderate and high disease activity states, have remission criteria, and are feasible to perform in clinical settings.[13]

Investigational Pipeline

The pipeline in RA is robust and new entrants may drive additional costs. In addition to more JAK inhibitors, several new classes of agents are under investigation (Exhibit 8).

Conclusion

RA is a chronic and costly disease from a payer perspective, with treatment of RA as a major driver of specialty pharmacy cost. Treatment approaches are changing and guidelines have moved toward earlier and more aggressive treatment. Early and aggressive treatment for RA is warranted to limit the long-term consequences of the disease. Overall, RA patients are much better off than in the past due to ongoing research and new therapies. Yet, current treatment often is suboptimal because of clinical inertia. JAK inhibitors belong in the rheumatologists' armamentarium and are changing the RA treatment paradigm by their unique mechanism of action, rapid onset of clinical response, and efficacy. The current place for JAK inhibitors in the RA treatment algorithm is as second-line therapy after MTX, but they will likely become first-line agents since they are more effective than MTX in DMARD naïve patients. Long-term safety with JAK inhibitors looks promising with specific monitoring and vaccinations. Clinicians are looking forward to increasing medication options for patients and advances in personalized medicine, but payers are challenged to get the most value from RA treatments. Management of the space will get even more complex in the near future.

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