

# JAK Inhibitors for Rheumatoid Arthritis

HISTORICAL PERSPECTIVES  
AND POSTMARKETING  
CLINICAL REPORTS



BY GREGORY M. WEISS, M.D.

**A**utoimmunity is well known to result from a complex pathogenesis rooted in the body's aberrant reactions to internal and external elements. Over the last several decades, many advances have been made in both our understanding of the pathogenic pathways behind autoimmune disease and treatment options leading to earlier diagnosis and more effective control of a myriad of inflammatory conditions. One such crucial pathway involves the production of cytokines and their effects down stream dictating signal transduction and transcription of genetic information leading to the production of inflammatory mediators.

Cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6) utilize the Janus kinase/signal transduction and activation of transcription (JAK-STAT) signaling pathway and are implicated in rheumatoid arthritis, psoriasis and inflammatory bowel disease.

While previous biologic therapies have targeted specific cytokines, the interplay of multiple cytokines in the inflammatory process has limited their effectiveness in some rheumatologic conditions over time.<sup>1</sup> Evidence from the pediatric literature confirms the shortcomings realized for biologic disease-modifying anti-rheumatic drugs (DMARDs) in children with juvenile idiopathic arthritis.<sup>2</sup> Understanding the importance of JAK and STAT signaling in the homeostasis of the immune system has

led to the development of Janus kinase inhibitors (JAK) as a therapeutic strategy with research beginning in the 1990s.

JAK inhibitors target JAK type I, II and III cytokine receptor pathways which operate independently of traditional biologics targeting only TNF $\alpha$ , making them of potential use in patients who do not respond to other therapies.<sup>3</sup> Current JAK inhibitors act by competitively blocking the adenosine triphosphate-binding (ATP) site in the JH1 domain through non-covalent interactions. By targeting transcription pathways downstream, JAK inhibitors can affect many cytokines rather than just one, leading to greater control over inflammation.

The Food and Drug Administration (FDA) has approved two JAK inhibitors for rheumatoid arthritis.

Baricitinib (Olumiant, Lilly) was approved in June 2018 for the treatment of moderate-to-severe rheumatoid arthritis in patients with inadequate response to one or more tumor necrosis factor inhibitors. Tofacitinib was approved in 2012 for the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response or intolerance to methotrexate. In 2016, tofacitinib citrate—a once-daily oral version—was approved for rheumatoid arthritis. Then, in 2017, both tofacitinib and tofacitinib citrate were approved for psoriatic arthritis. More recently, in 2018, tofacitinib was approved to treat patients with moderate to severe ulcerative colitis.

## **TOFACITINIB**

Tofacitinib was the first JAK inhibitor ap-

proved for autoimmune conditions. Tofacitinib primarily inhibits JAK3 and JAK1 and is highly specific in its targeting. Phase II and III trials have shown that tofacitinib was efficacious in rheumatoid arthritis patients who had previously failed DMARDs both as monotherapy and in combination with methotrexate.<sup>3</sup> Phase I, II and III trials showed significant efficacy using oral tofacitinib in patients with moderate-to-severe plaque psoriasis and ulcerative colitis.<sup>1</sup>

In a recent study looking at the safety and efficacy of tofacitinib for psoriatic arthritis, it was found to be well tolerated and efficacious in combination with methotrexate in adult patients with active psoriatic arthritis who had failed DMARD therapy.<sup>4</sup> The Oral Rheumatoid Arthritis (ORAL) trial, a large randomized and blinded study, determined

that tofacitinib alone or in combination with methotrexate, was not inferior to adalimumab in combination with methotrexate in the treatment of rheumatoid arthritis in patients not respond to methotrexate monotherapy.<sup>5</sup>

In an editorial reviewing the ORAL trial, three main points were highlighted with regards to tofacitinib in rheumatoid arthritis: Its efficacy and toxicity are comparable to injectable biologics like adalimumab; its onset of action is equally rapid, and, most patients are able to remain on tofacitinib therapy for 12 months.<sup>6</sup>

## **BARICITINIB**

Baricitinib targets JAK1 and JAK2 pathways selectively unlike tofacitinib, which is non-selective for JAK enzymes.<sup>7</sup> Baricitinib is approved for and found to be effective in

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highly active rheumatoid arthritis patients who have been resistant to DMARDs and biologics.<sup>1,7</sup> Efficacy of baricitinib was found to be superior to DMARDs and biologics in higher doses up to 8 mg once daily.<sup>3</sup>

Extensive phase II and III trials were undertaken looking at baricitinib in rheumatoid arthritis between 2009 and 2012. All results confirmed its high efficiency and limited incidence of side effects that include a decrease in hemoglobin and an increase in LDL, HDL, creatinine and creatine phosphokinase.<sup>8</sup> Recently, baricitinib was found to maintain low disease activity or remission in rheumatoid arthritis patients even with tapering the dose in most cases.<sup>9</sup> Evidence also exists that baricitinib may be useful in psoriasis and atypical neutrophilic dermatosis.<sup>1</sup>

While 4 mg daily was shown to provide better outcomes in rheumatoid arthritis, only the 2 mg dose was approved by the FDA due to increased risk for thromboembolism at the higher dose.<sup>7</sup> Like tofacitinib, baricitinib is generally safe, although an increase in herpes zoster infections over the general population was found.<sup>10,11</sup> Some concern with regards to patients being able to mount a proper immune response to vaccination, led to a study that showed less than robust responses to the tetanus vaccine, but no attenuation of effect from baricitinib on the pneumococcal-13 vaccine response.<sup>12</sup>

### POSTMARKETING STUDIES

A postmarketing safety study published earlier this year in *Arthritis and Rheumatology*, highlighted risks associated with high dosing of tofacitinib. The study examined risks for patients prescribed at the approved 5 mg or 10 mg (the clinical trial dosage) twice daily in combination with methotrexate or TNF inhibitor. An elevated risk for blood clots in the lungs and a higher risk of mortality were identified for patients on the high dose.

In February of this year, the FDA issued a statement saying that physicians should follow the dosing recommendations on the prescribing label.

In January 2019, van der Heijde D, Strand V, et al., reported in *Arthritis and Rheumatology* (doi: 10.1002/art.40803) that, for rheumatoid arthritis patients on a combination of tofacitinib (at 5 mg or 10 mg) and methotrexate, clinical and radiographic improvements were reported at 12 and 24 months.

Also, earlier this year, Taylor PC, Weinblatt ME, et al. reported in *Arthritis and Rheumatology* (doi: 10.1002/art.40841) that an analysis of 3,492 patients (7,860 patient-years of exposure) treated with baricitinib, found no association between baricitinib and major adverse cardiovascular events, arterial thrombotic events, or congestive heart failure. However, six cases of deep vein thrombosis/pulmonary embolism were reported for patients prescribed 4 mg baricitinib.

In April of this year, Christina Charles Schoeman, et al., reported in *Arthritis and Rheumatology* (<https://doi.org/10.1002/art.40911>) that, after 24 weeks of tofacitinib of at least 1 mg, rheumatoid arthritis patients experienced increased HDL-c, but not an increase in LDL-c or total cholesterol—which appeared to reduce their risk of myocardial infarction, stroke or cardiovascular death.

In one study (*Arthritis and Rheumatology*, December 2018, doi: 10.1002/art.40798) that compared the risk of venous thromboembolism in rheumatoid arthritis receiving tofacitinib with those on TNF therapy, researchers

**CONDITION**  
Rheumatoid arthritis

**TREATMENT**  
JAK inhibitors tofacitinib and baricitinib are the first oral small molecules for rheumatoid arthritis

**THERE ARE FOUR KNOWN JAK INHIBITORS**  
JAK 1, 2, 3 and TYK2

**SPECIFIC JAK INHIBITORS:**

- Tofacitinib
- Baricitinib
- Ruxolitinib
- Filgotinib
- Peficitinib

found no statistically significant risk of venous thromboembolism among 34,074 patients on tofacitinib and 17,086 on tofacitinib.

### NEW DIRECTION

Other JAK inhibitors are in clinical trials, including those designed as once-daily oral dosing instead of injections. With effectiveness proven in rheumatoid arthritis and psoriatic arthritis, researchers are looking to expand the indications for JAK inhibitors with applications ranging from systemic lupus erythematosus (SLE) to myositis, scleroderma and primary Sjogren's syndrome.<sup>1</sup>

A recent case report showed off-label use of tofacitinib to be effective in treating severe refractory juvenile idiopathic arthritis in a 13-year-old patient.<sup>13</sup> Trials continue in psoriasis, IBD and transplantation while JAK inhibitors for SLE remain in the pre-clinical stage.<sup>3</sup> STAT inhibition represents yet another avenue for future development, however, altering transcription has proven very difficult with no drugs in trials to date.<sup>3</sup>

Another direction JAK inhibitors may take is toward greater selectivity. Approved JAK inhibitors block multiple kinases. In the future, selectivity for specific JAK inhibitors may more specifically target a particular rheumatologic pathology and minimize related side effects.<sup>3</sup> Decernotinib is a next-generation JAK inhibitor with high selectivity for JAK3 and has shown promise in animal models of autoimmune disease.<sup>1</sup> Decernotinib is now in clinical trials for the treatment of rheumatoid arthritis.

Filgotinib (GLPG0634) has 30-fold selectivity towards JAK1 and is showing promise in preliminary human trials as a treatment for rheumatoid arthritis and Crohn's disease.<sup>1</sup> Peficitinib (ASP015K) inhibits JAK1, JAK2, JAK3 and TYK2, has a good safety profile, and appears to be effective in rheumatoid arthritis and psoriatic arthritis in early clinical trials.<sup>1</sup>

Solcitinib (GSK2586184) and INCB039110 are selective JAK1 inhibitors. Trials with Solcitinib in SLE patients were

terminated due to severe, reversible liver function abnormalities, while INCB039110 has shown promise in rheumatoid arthritis and psoriatic arthritis trials.<sup>1</sup>

ABT494 is a next generation JAK inhibitors with 74-fold selectivity for JAK1 over JAK2 and, after very promising phase II evidence, is now in phase III trials for treatment of rheumatoid arthritis after inadequate response to methotrexate.<sup>1</sup>

In addition to looking for new more selective JAK inhibitors, dosing strategies need further investigation in order to find the appropriate induction and maintenance regimens. Like other anti-rheumatic treatments, biomarkers will need to be identified so that appropriate patients can be selected for treatment with JAK inhibitor drugs and efficacy can be monitored during therapy.

The future of targeted autoimmune therapy is exciting with rheumatologists poised on the cutting edge of JAK research and development. These drugs are novel in structure and function representing the first small orally bioavailable molecules capable of blocking a multitude of cytokines implicated in autoimmunity downstream of their receptors. With proper investigation, JAK inhibitors could revolutionize the treatment of many rheumatologic conditions, dramatically improving the quality of life experienced by patients affected by these chronic and debilitating disorders.

### ABOUT THE AUTHOR

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# The safety of JAK inhibitors

**SERIOUS INFECTIONS ARE LOW, BUT HERPES ZOSTER SURPASSES EXPECTATIONS**

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**R**heumatoid arthritis patients with herpes zoster infections who are on JAK inhibitors have a low overall risk of serious infections, shows a systematic review and meta-analysis published in the April 14 issue of *Rheumatology*.

Biologic therapies have revolutionized the treatment of rheumatoid arthritis by selectively targeting key inflammatory factors which, if effective, can lead to remission.

While not all patients respond, and some realize diminishing gains over time, Janus kinase (JAK) inhibitors have emerged as important drugs that target small molecules down stream of cytokine production and influence the functional outcomes of receptors that are stimulated.

Tofacitinib and baricitinib are the only two JAK inhibitors currently approved for rheumatoid arthritis.

The safety profile for JAK inhibitors includes the possibility of developing opportunistic vi-

ral infections, including the reactivation of the varicella zoster virus leading to herpes zoster.

The authors of this review, which was led by Katie Bechman of the Centre for Rheumatic Disease at King's College London, sought to determine the extent of serious infectious complications with particular focus on serious infections and herpes zoster infections in rheumatoid arthritis patients. The review included 21 phase two and three randomized controlled trials of tofacitinib (5 mg), baricitinib (4 mg) and upadacitinib (15 mg).

The primary outcome was defined as the presence of a serious infection leading to death, requiring hospitalization or intravenous antibiotics. The secondary outcome was defined as the frequency of opportunistic infections.

Serious infections were identified in 40 patients who received 5 mg of tofacitinib with 2,032 patient exposure years; in 26 patients who received 4 mg baricitinib with 822 patient exposure years and, in five patients who received 15 mg or near equivalent of upadacitinib with 166 patient exposure years.

“The absolute serious infection rates were low. However, across JAK inhibitors, the incidence of herpes zoster was higher than expected for the population (3.23 per 100 patient years). While the risk was numerically greatest with baricitinib, indirect comparisons between the drugs did not demonstrate any significant difference in risk,” the authors wrote.

### TAKE-HOME POINTS FOR CLINICIANS

Two main points can be garnered from these data:

1. The absolute rates of serious infections in rheumatoid arthritis patients on JAK inhibitors are low. This speaks to the safety of these medications.
2. Herpes zoster is more common in rheumatoid arthritis patients on JAK inhibitors.

The likely mechanism for increased risk of

herpes zoster risk in rheumatoid arthritis patients on JAK inhibitors is likely complicated and rooted in disrupting immune surveillance and cell-mediated immunity leading to varicella reactivation. However, clinicians should keep in mind that there is an increasing incidence in herpes zoster with age in the general population, which may mute these findings.

Both a limitation of the study and a positive outcome was that indicator opportunistic infections were too rare to provide meaningful incidence rates. This fact should reassure clinicians who prescribe JAK inhibitors for rheumatoid arthritis as well as patients with regards to safety.

While relief is paramount on the minds of patients and, in turn, clinicians, we must examine risk lest we throw the baby out with the bath water. Often pain and low quality of life make patients desperate for treatment. Safety is the first priority as prevention of harm precedes treatment.

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#### THE REVIEW INCLUDED 21 STUDIES

- 11 on tofacitinib with 5,888 patients
- 6 on baricitinib with 3,520 patients
- 4 on upadacitinib with 1,736 patients

#### INFECTION RATE FOR EACH OF THREE STUDY GROUPS

- Serious infections: 1.97, 3.16 and 3.02, respectively
- Herpes zoster infections: 2.51, 3.16 and 2.41, respectively