

Interleukins and Janus Kinases: Emerging Therapeutic Targets in Rheumatoid Arthritis

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Advances in the understanding of the pathogenesis of autoimmune diseases, such as rheumatoid arthritis (RA), have led to new treatments that improve quality of life.¹ The use of empiric treatments, such as methotrexate (MTX), has given way to newer biologic therapies that target specific molecules and cellular structures known to be involved in the chronic inflammatory process. For some individuals, these disease-modifying biologic agents can slow or even reverse the deleterious physical effects associated with RA, making remission possible. Nevertheless, despite the availability of various biologic agents for the treatment of RA, some patients do not achieve the desired response, do not maintain treatment responses over time, or experience intolerable adverse effects (AEs) that lead to treatment discontinuation. In addition, these treatments can be expensive and require subcutaneous (SC) or intravenous (IV) administration. This unmet need has prompted investigation into alternative drivers of RA pathogenesis that may serve as therapeutic targets.¹

Ongoing research is focusing on molecules that are involved in intracellular signaling following ligand binding to receptors on inflammatory cells.¹ Through inhibition of 1 or more of the kinases involved in signal transduction, it may be possible to interrupt intracellular signaling, modulate the function of cellular structures, and subdue the inflammatory process.

Currently, investigators are exploring 2 promising targets in RA: interleukins (ILs) and intracellular Janus kinases (JAKs). Small molecular agents targeting IL-17, such as secukinumab and ixekizumab, are already being used clinically for patients with psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.^{2,3} Tofacitinib, an oral JAK inhibitor, is approved for RA unresponsive or intolerant to MTX.⁴

The Interleukin-Cytokine Family

Intracellular signaling pathways transmit information regulating cellular responses and gene transcription to the cellular cytoplasm and nucleus.⁵ Cytokines carry out many crucial biological processes like cell growth, proliferation, differentiation, inflam-

ABSTRACT

Treatment of rheumatoid arthritis (RA) has evolved from the use of conventional treatments, such as methotrexate, to disease-modifying biologic agents that can slow the disease process and make remission possible for some patients. Although these targeted therapies have improved the clinical management of patients with active RA, no current approach meets the goals of therapy for RA: slowing disease progression while improving the patient's well-being and, ideally, creating complete clinical remission that is verifiable by radiography and patient report. Consequently, investigators continue to look for additional drivers of RA and for interventions that will target specific pathways with few adverse effects.

Aberrant helper T (Th)-cell activation has been implicated as a mechanism leading to several autoimmune diseases that seem to have common roots (RA, psoriatic arthritis, and Crohn's disease). Research into the pathophysiology of RA is focusing on Th cells, as well as molecules involved in intracellular signaling. Through kinase inhibition, it may be possible to interrupt signal transduction and potentially reduce proinflammatory cytokine production. Two promising targets are interleukins and Janus kinases. Oral inhibitors of interleukins or Janus kinases may enable more patients to achieve disease remission.

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For author information and disclosures, see end of text.

mation, tissue repair, and regulation of the immune response. IL-1, IL-6, and IL-17 use a variety of signaling cascades that are being investigated as therapeutic targets. These cytokines are substantially involved in the pathogenesis of RA and are responsible for the associated inflammation and joint destruction.⁵ Inflammation is caused by the predominance of proinflammatory cytokines over anti-inflammatory cytokines. Patients with RA exhibit an imbalance between IL-1 receptor antagonist (IL-1Ra) and IL-1 levels. High concentrations of IL-1b in plasma and synovial fluid are associated with increases in RA disease markers, as well as morning stiffness. IL-1 increases the release of synovial fibroblast cytokine, prostaglandins, and matrix metalloproteinases. Osteoclast activation and expression of endothelial cell adhesion molecules have also been observed.⁵

Involvement in Autoimmunity and Chronic Inflammation

Regulatory T cells (Tregs) are a specialized group of CD4+ T cells that are considered to be involved in autoimmunity and chronic inflammation.^{6,7} To achieve effective immunologic homeostasis, there must be a steady balance between Th-cell activation and Treg suppression.⁶ When an imbalance occurs, homeostasis is disrupted. Consequently, the immune system becomes activated, leaving the host susceptible to autoimmunity. Experts have proposed that an imbalance between Th17 and Treg cells, as well as elevated levels of IL-17, may contribute to the development and progression of RA.^{6,7}

Compared with healthy individuals, patients with RA, including those with treatment-naïve early-stage disease, have increased numbers of Th17 cells and elevated expression of IL-17 in peripheral circulation, as well as in the synovium and synovial fluid.^{7,8} Tregs also accumulate in the joints of patients with RA.⁸ The inflammatory cytokine environment in a rheumatoid joint may contribute to an imbalance between Th17 and Treg cells in some way. IL-17-producing Th17 cells mediate 3 phases of RA: inflammation, cartilage destruction, and bone erosion.⁶

Effects on Inflammation

IL-1 and IL-6 are key mediators of cell migration and inflammation in RA.⁹ IL-6 acts directly on neutrophils via IL-6R, which promotes inflammation by secreting proteolytic enzymes and reactive oxygen intermediates.⁹ IL-17 plays a central role in inducing and promoting the chronic inflammatory disease response through the induction of proinflammatory cytokines from various cell types, such as synovial fibroblasts, monocytes, macrophages, chondrocytes, and osteoblasts.¹⁰ Not only do these proinflammatory cytokines contribute to RA flares, but they also create chronic inflammation.¹¹ The effects of chronic inflammation can lead to cartilage damage and bone erosion.

IL-1 Family

The IL-1 gene family consists of IL-1a, IL-1b, and IL-1Ra.¹² RA disease activity and progression of joint destruction correlate with the plasma and synovial fluid levels of IL-1. IL-1 is produced in response to inflammatory stimuli and mediates various physiologic responses, including inflammatory and immunological responses. IL-1a and IL-1b are proinflammatory agonist molecules. IL-1a is primarily bound to the membrane, whereas IL-1b is predominantly extracellular. Two specific immunoglobulin-like membrane-bound IL-1 receptors (IL-1Rs), types I and II, are found in humans. IL-1R type I (IL-1RI) is expressed by T cells, endothelial cells, and fibroblasts; IL-1R type II (IL-1RII) is expressed primarily on B cells, monocytes, and neutrophils (and is not functionally active). Both receptors bind IL-1b with similar affinities. IL-1RII has a substantially lower binding affinity for IL-1a than does IL-1RI. A complete biological response requires about 2% occupancy of IL-1RI receptors on a target cell. Both types of receptors are produced naturally and compete for circulating IL-1a and IL-1b. IL-1Ra is the third member of the IL-1 family.¹²

IL-6 Family

IL-6 has pro- and anti-inflammatory properties.⁵ It is produced by B cells, T cells, fibroblasts, endothelial cells, monocytes, macrophages, keratinocytes, chondrocytes, and some tumor cells. Evidence suggests that, depending on the signaling (classic), IL-6 trans-signaling is a major factor in RA pathogenesis.⁹ A high level of IL-6 has been found in the blood and cerebrospinal fluid of many patients with RA.⁵

IL-17 Family

The IL-17 family of cytokines plays a key regulatory role in host defense and inflammatory diseases. Currently, 6 IL-17 family ligands have been identified (Table¹³). The biologic function and regulation of IL-17A and IL-17F are the best understood. The IL-17 cytokine family mediates its biologic functions via cell surface receptors. Five IL-17 receptors have been identified: IL-17RA, IL-17RB/IL-25R, IL-17RC, IL-17RD/SEF, and IL-17RE.¹³

Both IL-17 and IL-17F defend the host against certain pathogens.¹¹ Their function is most apparent at epithelial and mucosal barriers, such as the lung, gut, and oral cavity. Mucosal surfaces, in particular, are rich with cells that produce IL-17. Moreover, Th17 cells express a receptor that enables them to target mucosal surfaces.¹¹

With regard to defensive immunity, IL-17 induces and regulates the production of proinflammatory cytokines that mediate a variety of defensive responses.¹¹ Some of these IL-17-induced cytokines demonstrate antimicrobial activity and are able to directly kill invading microorganisms, whereas others act to further amplify Th17 cell differentiation.¹¹

In particular, IL-17 and IL-17F are vital for the clearance of extracellular bacteria, such as *Staphylococcus aureus*, *Citrobacter*

TABLE. IL-17 Family Ligands and Their Functions¹³

Ligands	Function
IL-17A (commonly referred to as IL-17)	Mediates proinflammatory responses
IL-17B	Induces production of proinflammatory cytokines, but biological function is largely unknown
IL-17C	Induces production of proinflammatory cytokines, but biological function is largely unknown; may be involved in mucosal immunity and autoimmune responses
IL-17D	Induces production of proinflammatory cytokines, but biological function is largely unknown
IL-17E (also referred to as IL-25)	Regulates Th2 cell response against helminthic parasites and allergic inflammation
IL-17F	Mediates proinflammatory responses

IL indicates interleukin; Th2, T helper 2.

rodentium, and *Klebsiella pneumoniae*, and the control of fungal infections, such as *Pneumocystis carinii* and *Candida albicans*.¹³ The protective activity of IL-17 is not limited to extracellular pathogens. IL-17 also defends against intracellular bacteria; however, the exact mechanisms by which it does so are not completely clear.¹¹

Janus Kinases

Protein kinases are enzymes involved in intracellular signaling. They are capable of changing the function of proteins via phosphorylation.¹⁴ Numerous fundamental processes, such as cell growth and differentiation, are regulated by phosphorylation. Furthermore, several key immune receptors, including those that drive inflammation, exert their effects through protein kinases.¹⁴

From over 500 protein kinases that are currently known, 90 are protein tyrosine kinases, which are classified into 2 groups: receptor tyrosine kinases and nonreceptor tyrosine kinases.^{1,15} JAKs belong to the nonreceptor protein tyrosine kinase group and have been identified as potential inhibitory targets in RA. JAKs engage with many different cytokines, growth factors, and hormones, and mediate tyrosine phosphorylation of their associated receptors and recruited signaling proteins. JAKs exert their effect primarily through activation of specific signaling proteins known as signal transducers and activators of transcription (STATs).^{1,15} STATs can then modulate intracellular activity, including the expression of target genes. This leads to expression of proinflammatory cytokines, which activate other immune cells. There are 7 different STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, which pair up with 1 of 4 members of the JAK family of protein kinases. The 4 that have been identified are JAK1,

JAK2, JAK3, and tyrosine kinase 2 (Tyk2). The cytokines known as interferon alpha, beta, and gamma, signal through the JAK-STAT pathway. This immune response can also stimulate tumor necrosis factor (TNF), IL-1, and IL-17.¹⁶

JAKs are critical components of many cytokine receptor systems regulating growth, survival, differentiation, and pathogen resistance.¹⁵ Functional JAK signaling is necessary for innate and adaptive immune responses that protect the organism from infections and immunodeficiencies. Conversely, activating mutations or loss-of-function mutations in JAK genes, which impair JAK signaling, leads to inflammatory disease, erythrocytosis, gigantism, and malignant transformation of lymphocytes or myeloid cells.^{15,17}

Type I and II cytokine receptors are important to regulate immune-mediated diseases. Cytokines that bind to types I and II initiate the JAK-STAT pathway to block immune-mediated diseases.¹⁶ Numerous receptors use JAK1, JAK2, JAK3, and Tyk2 for intracellular signal transduction.^{14,18} JAK1 is involved in the signal transduction of many type I and type II cytokine receptors.¹⁹ Although some JAKs, such as JAK1, associate with multiple cytokine receptor subunits, JAK3 is unique in that it associates with only 1 receptor subunit: the common gamma chain.^{14,18} Several proinflammatory cytokines signal through the common gamma chain, including interferon gamma, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, and IL-15, all of which are associated with synovial inflammation.²⁰ Thus, inhibiting the signaling of these cytokines may be a reasonable therapeutic target in RA. The synovial tissue of patients with RA expresses JAK3 and STAT.²¹ Successful disease-modifying antirheumatic drug (DMARD) treatment was found to reduce synovial expression of both JAK3 and STAT.

IL and JAK Inhibitors in Development for RA Treatment

Several agents directed toward IL-17 are being investigated in RA, including brodalumab, ixekizumab, secukinumab, ABT-122, and CNTO-6785. Multiple drugs targeting JAK are also in development. Tofacitinib, a JAK inhibitor that has immediate-release and extended-release (XR) formulations, is already approved for use in RA.⁴ Other JAK inhibitors under investigation include baricitinib, decernotinib, filgotinib, peficitinib, ABT-494, and INCB039110.

IL-1 Inhibitors

Anakinra

Anakinra is a recombinant, nonglycosylated form of the human IL-1 α that is FDA-approved for the treatment of RA.²² It inhibits the biologic activity of IL-1 α and IL-1 β by competitively inhibiting IL-1 binding to IL-1RI. Anakinra 100 mg SC daily reduces the signs and symptoms, and slows the progression, of structural damage in moderately to severely active RA in patients 18 years or older who have failed 1 or more DMARDs.²²

Three randomized, double-blind, placebo-controlled trials of 1790 patients with active RA assessed the efficacy and safety of anakinra.²² Patients treated with anakinra were more likely to achieve an American College of Rheumatology 20% (ACR20) response (22% vs 38%; $P < .001$ at 6 months) or higher magnitude of response (ACR50 and ACR70) than patients treated with placebo. Most clinical responses were noted within 3 months of enrollment.²²

IL-6 Inhibitors

Tocilizumab

Tocilizumab is a humanized anti-IL-6R monoclonal antibody that is approved for patients with RA who have failed to improve with at least 1 anti-TNF therapy. Tocilizumab blocks IL-6's proinflammatory effects.²³ Seven phase III tocilizumab clinical trials evaluated the efficacy, safety, and radiographic progression of RA. Tocilizumab 8 mg/kg IV monotherapy had higher rates of ACR20 ($P \leq .001$), ACR50 ($P < .002$), and ACR70 ($P \leq .001$) scores at 6 months than did MTX. Tocilizumab 8 mg/kg IV plus MTX 10 to 25 mg by mouth weekly had a higher ACR20 response rate than did oral MTX plus placebo in patients with RA who failed to respond to MTX or anti-TNF therapy ($P \leq .001$). Patients receiving tocilizumab 8 mg/kg had less radiographic progression than the control group (85% vs 67% with no progression; $P \leq .001$). Neutropenia, thrombocytopenia, hyperlipidemia, and transaminitis were observed more often with tocilizumab therapy than with placebo.²³

Sarilumab/REGN88

Sarilumab is an anti-IL-6 antibody in development for the treatment of RA and noninfectious uveitis.^{24,25} In a phase 3 monotherapy study (SARIL-RA-MONARCH), sarilumab was superior to adalimumab in improving signs, symptoms, and physical function, at 6 months in 369 patients with active RA who were inadequate responders to, intolerant of, or inappropriate candidates for MTX. Patients were randomly assigned to receive either sarilumab 200 mg SC every other week or adalimumab 40 mg SC every other week. Patients who did not respond adequately to adalimumab could receive weekly dosing. The 28-Joint Disease Activity Score (DAS28) with erythrocyte sedimentation rate at 24 weeks was statistically better in patients receiving sarilumab compared with adalimumab (-3.25 vs -2.22 ; $P < .0001$). ACR20 scores were 72% for sarilumab versus 58% for adalimumab ($P < .01$); ACR50 and ACR70 scores were also significantly better with sarilumab ($P < .01$). The incidence of serious AEs was 5% for sarilumab versus 7% for adalimumab. Infections (29% vs 28%, respectively) and serious infections (1% for both groups) were generally similar between groups. Neutropenia was more common with sarilumab than with adalimumab (14% vs 1%, respectively) and was not associated with infections. Injection-site erythema was more common with sarilumab (8% vs 3%).^{24,25}

Sarilumab has 6 ongoing clinical studies, projected to enroll 2800 patients with RA. The FDA recently accepted the biologics license application for sarilumab for review, with a target action date of October 30, 2016.²⁴

Sirukumab

Sirukumab is a human anti-IL-6 monoclonal antibody being studied in adults with moderately to severely active RA.²⁶ The SIRROUND-D study was conducted in patients with RA who had an inadequate response to treatment with DMARDs.²⁶ Patients received sirukumab 50 mg SC every 4 weeks ($N = 557$) and sirukumab 100 mg SC every 2 weeks; both groups were compared with a placebo group ($N = 556$). Results showed that inhibition of joint destruction (as shown by radiographic progression assessment) was significantly higher among sirukumab-treated patients. ACR20 at 4 months was observed in 54.8% and 53.5% of patients receiving sirukumab 50 mg and sirukumab 100 mg, respectively, compared with 26.4% of the placebo group (both $P < .001$).²⁶ Four additional phase 3 sirukumab studies, with a projected total of 3000 patients, are planned to assess patients with an inadequate response to anti-TNF agents and other biologic agents, as well as MTX.²⁶

Olokizumab

Olokizumab is a humanized anti-IL-6 monoclonal antibody being investigated for the treatment of patients with moderate to severe RA who had previously failed TNF inhibitor therapy.²⁷ A phase 2b trial compared placebo to olokizumab (60, 120, or 240 mg) SC every 2 weeks or every 4 weeks and to tocilizumab 8 mg/kg every 4 weeks. Results for the 221 patients with RA showed that olokizumab produced significantly greater reductions in the DAS28 with C-reactive protein from baseline levels compared with placebo ($P < .001$), and at all olokizumab doses tested. ACR20 and ACR50 responses were higher for olokizumab than placebo. At several doses, olokizumab demonstrated similar efficacy to tocilizumab across multiple end points. Most AEs were mild or moderate and similar among treatment groups. No new safety signals were identified.²⁷ Olokizumab is also being studied in patients with Crohn's disease.²⁸ Additional phase 2 studies have been completed. It is unclear if additional studies are planned.

IL-17 Inhibitors

Brodalumab

Brodalumab is a human monoclonal antibody that binds to the IL-17 receptor and inhibits inflammatory signaling by blocking the binding of several types of IL-17 to the receptor. By preventing IL-17 from activating its receptor, brodalumab prevents the body from receiving signals that may lead to inflammation.²⁹ In a phase 2 trial, brodalumab SC was investigated in 252 patients with RA

who had inadequate responses to treatment with MTX.³⁰ Patients were randomly assigned to receive placebo or brodalumab 70, 140, or 210 mg. The study failed to meet its primary end point, which was ACR50 at week 12. Seven participants reported serious AEs during the study (5 in the brodalumab groups and 2 in the placebo group). None of the AEs were treatment-related. One patient died from cardiopulmonary failure approximately 1 week after the last dose in the 140-mg group. The investigators concluded that the results did not support further evaluation in RA.³⁰ Suicidal ideation and depression have also been reported.

Ixekizumab

Ixekizumab (LY2439821) has been evaluated in patients with RA in a phase 2 clinical trial.³¹ Investigators enrolled 201 biologically-naïve and 99 TNF inhibitor-resistant patients.³² Treatment-emergent AEs occurred in 72% of biologically-naïve patients and in 73% of TNF inhibitor-resistant patients. Most AEs were mild to moderate in severity. Seventeen (7%) biologically-naïve patients experienced serious AEs, including 5 (2%) serious infections and 2 (1%) deaths. In TNF inhibitor-resistant patients, 18 serious AEs occurred; these included 4 (3%) serious infections and 1 (1%) death. No mycobacterial or invasive fungal infections were reported. All outcome measures (ACR20, ACR50, ACR70, and DAS28 with C-reactive protein) at week 16 were maintained or improved through week 64. The most common treatment-emergent AEs included upper respiratory tract and urinary tract infections, systemic allergic or hypersensitivity reactions, injection-site pain, and headache. Each AE occurred in fewer than 10% of patients.³² No additional clinical trials of ixekizumab in patients with RA were identified.³¹ In March 2016, ixekizumab, a monoclonal antibody, was approved by the FDA to treat adults with moderate to severe plaque psoriasis.³

Secukinumab

Secukinumab is another agent directed toward IL-17 that has been investigated in patients with RA. In 1 trial, investigators randomly assigned 237 patients with inadequate response to MTX to receive monthly SC injections of placebo or secukinumab 25, 75, 150, or 300 mg.³³ The primary end point, which was the ACR20 response at week 16, was not achieved. During 20 weeks of treatment, there were no unexpected safety signals and no specific organ-related toxicities. Most AEs were mild to moderate in severity. Infections developed more frequently in patients treated with secukinumab than with placebo. Six serious AEs were reported: 1 with secukinumab 75 mg, 4 with secukinumab 300 mg, and 1 with placebo. On the basis of these results, investigators concluded that further trials with secukinumab in RA were warranted.³³

The long-term safety and efficacy of secukinumab were assessed in 174 of the 237 patients who participated in the previ-

ous study.³⁴ Patients who had demonstrated responses at week 16 sustained those responses through week 52. The rate of AEs from weeks 20 to 60 was 64.8%, and the overall rate of infections was 31.9%. Serious AEs were reported in 21 patients (8.9%). There were 3 reports of malignancies (ovarian, lung, and basal cell) and no deaths between weeks 20 and 60.³⁴

At the present time, secukinumab is FDA-approved to treat adults with moderate to severe plaque psoriasis, ankylosing spondylitis, and psoriatic arthritis.² No phase 3 clinical trials in RA were identified.³⁵

ABT-122

ABT-122 is a novel immunoglobulin that specifically targets both TNF-alpha and IL-17.³⁶ Such dual neutralization aims to achieve greater clinical response in immune-mediated inflammatory diseases than blocking either cytokine alone. ABT-122 is in early-stage development and has been investigated in phase 1 and phase 2 clinical trials.³⁷ Preliminary results support further investigation of ABT-122 in RA.³⁶

CNTO-6785

Injectable CNTO-6785 is another IL-17 modulator currently in phase 2 clinical development for patients with active RA despite treatment with MTX.³⁸ No study results have yet been reported.

JAK Inhibitors

Tofacitinib and Tofacitinib XR

Tofacitinib is an oral JAK inhibitor⁴ that preferentially inhibits phosphorylation of JAK1 and JAK3 and subsequently inhibits STAT-1 and expression of STAT-1-inducible genes.³⁹ It is the first in a class of JAK inhibitors.

Tofacitinib is available as immediate-release and XR formulations.⁴ Both formulations are indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. Tofacitinib and tofacitinib XR may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. The recommended dose of tofacitinib is 5 mg by mouth twice daily. The recommended dose of tofacitinib XR is 11 mg by mouth once daily.⁴

The tofacitinib clinical development program comprised 2 dose-ranging studies and 5 confirmatory trials ranging from 6 months to 2 years.⁴ In these trials, tofacitinib was evaluated as monotherapy or in combination with MTX or other nonbiologic DMARDs. In addition, 2 ongoing, long-term, extension studies that enrolled patients from prior qualifying index phase 2 or 3 studies were part of the clinical development program.⁴⁰

In clinical trials, patients treated with tofacitinib 5 or 10 mg by mouth twice daily had higher ACR20, ACR50, and ACR70 response rates at months 3 and 6 compared with placebo, with or without background DMARD treatment.⁴ Higher ACR20 response

rates were observed within 2 weeks compared with placebo. In 12-month trials, ACR response rates in patients treated with tofacitinib were consistent at 6 and 12 months.⁴

In a pooled analysis of infections and all-cause mortality across phase 2, phase 3, and long-term extension studies, 4789 patients received tofacitinib for the equivalent of 8460 patient-years of exposure.³⁹ The all-cause mortality rate among patients receiving tofacitinib, including deaths occurring within 30 days of the last dose, was 0.30 events per 100 patient-years (95% CI, 0.20-0.44). The mortality rate, including deaths occurring at any time after the last dose, was 0.53 events per 100 patient-years (95% CI, 0.40-0.71). The overall rate of serious infection was 3.09 events per 100 patient-years (95% CI, 2.73-3.49). Several factors were independently linked to the risk of serious infection, including age, corticosteroid dose, diabetes, and tofacitinib dose. Lymphocyte counts of less than $0.5 \times 10^3/\text{mm}^3$ were rare, but were associated with an increased risk of treated and/or serious infection. Infection-associated AEs were the most frequent cause of treatment discontinuation.³⁹

Baricitinib

Another agent that met primary clinical end points in phase 3 clinical trials in RA is baricitinib (LY3009104), an oral selective and reversible inhibitor of JAK1 and JAK2.^{41,42} It also may inhibit cytokines implicated in RA, such as granulocyte-macrophage colony-stimulating factor, IL-6, IL-12, IL-23, and interferon gamma.⁴¹ In January 2016, the clinical trial sponsor submitted a new drug application to the FDA for the approval of oral once-daily baricitinib for the treatment of moderately to severely active RA.⁴²

The baricitinib regulatory submission is supported by 4 completed pivotal phase 3 trials in patients with moderately to severely active RA.⁴² An additional phase 3 study has been initiated to support clinical development in China. The clinical trial program enrolled a wide range of patients, including those who were DMARD-naïve, inadequate responders to MTX, inadequate responders to conventional DMARDs, or inadequate responders to biologic DMARDs. Patients completing any of the phase 3 studies are eligible to enroll in a long-term extension study.⁴²

In 1 randomized, placebo-controlled, 24-week trial of 684 patients with active RA, the ACR20 response at week 12 was 62% for baricitinib 4 mg once daily compared with 40% for placebo ($P \leq .001$).⁴¹ Once-daily oral baricitinib also inhibited radiographic joint damage. Rates of serious AEs were 3% for baricitinib 2 mg, 5% for baricitinib 4 mg, and 5% for placebo.

Similar results were seen in another randomized, placebo-controlled trial that evaluated 2-, 4-, and 8-mg doses of baricitinib.⁴¹ Significantly more patients who received baricitinib 4 and 8 mg achieved an ACR20 response at week 12 compared with placebo (76% vs 41%; $P < .001$). The proportions of patients experienc-

ing at least 1 AE were similar in the placebo and baricitinib groups. Serious infections developed in 3 patients receiving baricitinib.⁴¹

Decernotinib

Oral decernotinib (VX-509) is a selective inhibitor of JAK3 that is currently in phase 2 clinical trials for RA. Decernotinib shows approximately 25- to 120-fold selectivity for JAK3 compared with similar cell-based assays that use JAK1, JAK2, or Tyk2.¹⁸ In clinical trials, patients with MTX-resistant RA displayed responses as early as 1 week and achieved ACR20 responses of 50% to 70% in 12 to 24 weeks.^{18,43}

A key question being scrutinized is whether decernotinib's greater specificity for JAK3 confers an improved safety profile.⁴⁴ In a phase 2b trial, AEs occurred in 42.3% of patients in the placebo group, as well as in 59.9% of patients treated with decernotinib up to week 24.⁴³ Among decernotinib-treated patients, the most common AEs were headache (8.7%), hypercholesterolemia (5.2%), diarrhea (4.5%), bronchitis (4.2%), cough (4.2%), nasopharyngitis (3.8%), upper respiratory tract infection (3.5%), nausea (3.5%), and increased hepatic enzyme levels (3.1%). Six patients receiving decernotinib developed herpes zoster infection. AEs leading to permanent treatment discontinuation occurred in 26 patients (9.1%) who received decernotinib and in 6 patients (8.5%) who received placebo.⁴³

Filgotinib

Oral filgotinib (GLPG0634) is a highly selective inhibitor of JAK1 that has advanced to phase 3 clinical trials in patients with moderate to severe RA who showed an inadequate response to MTX.⁴⁵ In phase 2 clinical trials in 877 patients, filgotinib demonstrated 3-fold more selectivity for JAK1 than did ABT-494 (another JAK1 inhibitor currently under investigation, discussed below) and met the primary end point of significant improvement in ACR20 response rate. In the DARWIN 1 study at 24 weeks, an ACR20 response was seen in 61%, 74%, and 78% of patients receiving once-daily filgotinib 50, 100, and 200 mg, respectively, compared with 45% of those receiving placebo. Filgotinib showed a clear dose-dependent increase in hemoglobin concentration without any impact on natural killer cells and lymphocyte counts. It is also under investigation in Crohn's disease.⁴⁵

Peficitinib

Peficitinib (ASP015K) is in phase 3 clinical development for RA.⁴⁶ Peficitinib inhibits all members of the JAK family—JAK1, JAK2, JAK3, and Tyk2—and is moderately selective for JAK3. In a 12-week, randomized, placebo-controlled, phase 2b study of 281 patients with RA with active disease not on concomitant DMARD therapy, an ACR20 response was seen in 23.6%, 31.6%, 54.5%, and 65.5% of patients receiving 25, 50, 100, or 150 mg of once-daily

peficitinib, respectively, compared with 10.7% of patients receiving placebo.⁴⁷ Treatment-emergent AEs were reported in 64.3% of patients receiving placebo and 64% of patients receiving any dose strength of peficitinib. There were no serious infections or malignancies; however, herpes zoster infection developed in 2 patients in the 25-mg group and 2 patients in the 100-mg group. These findings led the investigators to conclude that further study of peficitinib in patients with RA is warranted.⁴⁷

ABT-494

After positive results in phase 2 trials, ABT-494, a selective inhibitor of JAK1, has progressed to phase 3 clinical trials in patients with RA who demonstrate inadequate responses to conventional or biologic DMARDs, as well as MTX-naïve patients with RA.⁴⁸ Five phase 3 trials will evaluate more than 4000 patients; the first 2 trials are currently underway. One trial will assess ABT-494 in combination with MTX in patients who had inadequate treatment response to prior MTX treatment; adalimumab will be the active comparator. The second trial will enroll patients with inadequate treatment response to, or intolerance of, conventional synthetic DMARDs. Both trials will examine efficacy, safety, and tolerability.⁴⁸

INCBO39110

INCBO39110 is a selective JAK1 inhibitor that demonstrates greater than 20-fold and greater than 200-fold JAK1 selectivity over JAK2 and JAK3, respectively.⁴⁹ It is currently being studied in RA, psoriasis, and myelofibrosis to define its efficacy and safety profile. In a 12-week, randomized, placebo-controlled, phase 2 study of patients with active RA, an ACR20 response was seen in 50%, 44%, 50%, and 100% of patients receiving 100 mg twice daily, 300 mg once daily, 200 mg twice daily, or 600 mg once daily of INCBO39110, respectively, compared with 38% of patients receiving placebo. Responses were seen as early as 2 weeks. No patients experienced grade 3 or grade 4 AEs; 1 patient experienced a grade 2 alanine transaminase elevation. There were no serious or opportunistic infections.⁴⁹

Adverse Effects of JAK Inhibitors

A frequent important AE of JAK inhibitors is infection, including not only upper respiratory infections, but also opportunistic infections, such as herpes zoster.¹⁴ Patients receiving JAK inhibitors also can develop anemia, leukopenia, and thrombocytopenia, likely as a result of interference of molecules that depend on JAK2 for their signaling, such as erythropoietin and other colony-stimulating factors. Another AE, hyperlipidemia, may be a consequence of direct effects on cholesterol metabolism.¹⁴ Lymphoma and other malignancies also have been observed in patients treated with a JAK inhibitor. Consequently, tofacitinib comes with a black-box warning about the serious risk of infection and malignancy.⁴

Conclusion

Agents directed toward ILs and JAKs have the potential to improve outcomes in patients with autoimmune and inflammatory diseases, but not all agents under investigation have demonstrated sufficient efficacy to warrant further clinical development in RA. Targeting ILs has been found to be effective for the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis, and monoclonal antibodies directed toward ILs have been approved for these conditions. To date, however, none of these agents has been approved for RA.

Targeting JAKs, which are involved in signal transduction for several proinflammatory cytokines, has been found in randomized clinical trials to be an efficacious approach to the treatment of RA. Tofacitinib has been approved for patients with moderate to severe RA who have had an inadequate response or intolerance to MTX.⁴ Baricitinib currently is undergoing FDA review, and other JAK inhibitors are in phase 2 and 3 clinical development.

More data are needed to clearly delineate the safety profile of JAK inhibitors. In addition, the increased rates of opportunistic infections, such as herpes zoster, will need to be monitored. Nevertheless, these novel approaches that use small molecules to disrupt signal transduction of inflammatory mediators have shown efficacy and great promise in the treatment of patients with RA.

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