Baricitinib: From Rheumatoid Arthritis to COVID-19

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Abstract

Baricitinib is a JAK1/2 inhibitor that was first approved for treating moderate to severe rheumatoid arthritis (RA) but that later showed considerable efficacy in the control of exaggerated inflammatory responses that occur in a wide range of diseases. There is a growing body of evidence, obtained from clinical trials and case reports, demonstrating clinical and paraclinical improvement in patients following administration of baricitinib including RA, systemic lupus erythematosus, psoriasis, atopic dermatitis, alopecia areata, interferon-mediated autoinflammatory diseases, graft-versus-host disease, diabetic kidney disease, and, recently, coronavirus disease-19. However, despite overall encouraging results, many adverse effects have been observed in baricitinib-treated patients, ranging from simple infections to increased risk of malignancies, particularly in long-term use. The significant efficacy of baricitinib, versus the probable adverse effects, urge further investigation before establishing it as a part of standard therapeutic protocols. Here, we have provided a review of the studies that have used baricitinib for treating various inflammatory disorders and summarized the advantages and disadvantages of its administration.

Keywords

atopic dermatitis, baricitinib, COVID-19, Janus kinase inhibitors, psoriasis, rheumatoid arthritis

Baricitinib (Olumiant), a small Janus kinase (JAK) inhibitor molecule approved for treating certain autoimmune and inflammatory disorders, has recently been used for managing critically ill coronavirus disease-19 patients. Regarding the remarkable potential of baricitinib in blocking the proinflammatory signaling and its selective effect on immune cells, it could be considered a potential candidate for resolving exaggerated immune responses in a vast number of inflammatory disorders. Rheumatoid arthritis (RA) was the first illness that profited from the anti-inflammatory properties of baricitinib since it was approved for treating moderate to severe forms of RA that were resistant to tumor necrosis factor (TNF) inhibitors. Consequently, severe dermatologic diseases such as alopecia areata and atopic dermatitis (AD), as well as lupus erythematosus and autoinflammatory diseases came into consideration for being controlled with baricitinib. Recently, some clinical trials have been conducted to study the efficacy of this drug in treating severe infectious diseases such as human immunodeficiency virus (HIV) and severe acute respiratory syndrome-corona virus (SARS-CoV) infections. Moreover, there have attempts to apply it for managing posttransplant complications such as graft-versus-host disease. The wide range of diseases in clinical trials for baricitinib therapy and the other inflammatory disorders that could be considered future candidates for treatment with baricitinib made us provide an overview of positive and negative outcomes of administerng baricitinib in the clinic.

Janus Kinases

The Janus kinase (JAK) family consists of 4 members—JAK1, JAK2, JAK3, and TYK3—which principally contribute to cytokine signaling. The JAK molecule structurally comprises 4 domains: N-terminal FERM domain, SH2-like domain, pseudokinase domain (JAK homology 2), and protein tyrosine kinase domain. The SH2-like and FERM domains mediate the interaction of JAKs with the receptor and regulate the kinase activity.[1] Once a cytokine is engaged to its receptor,

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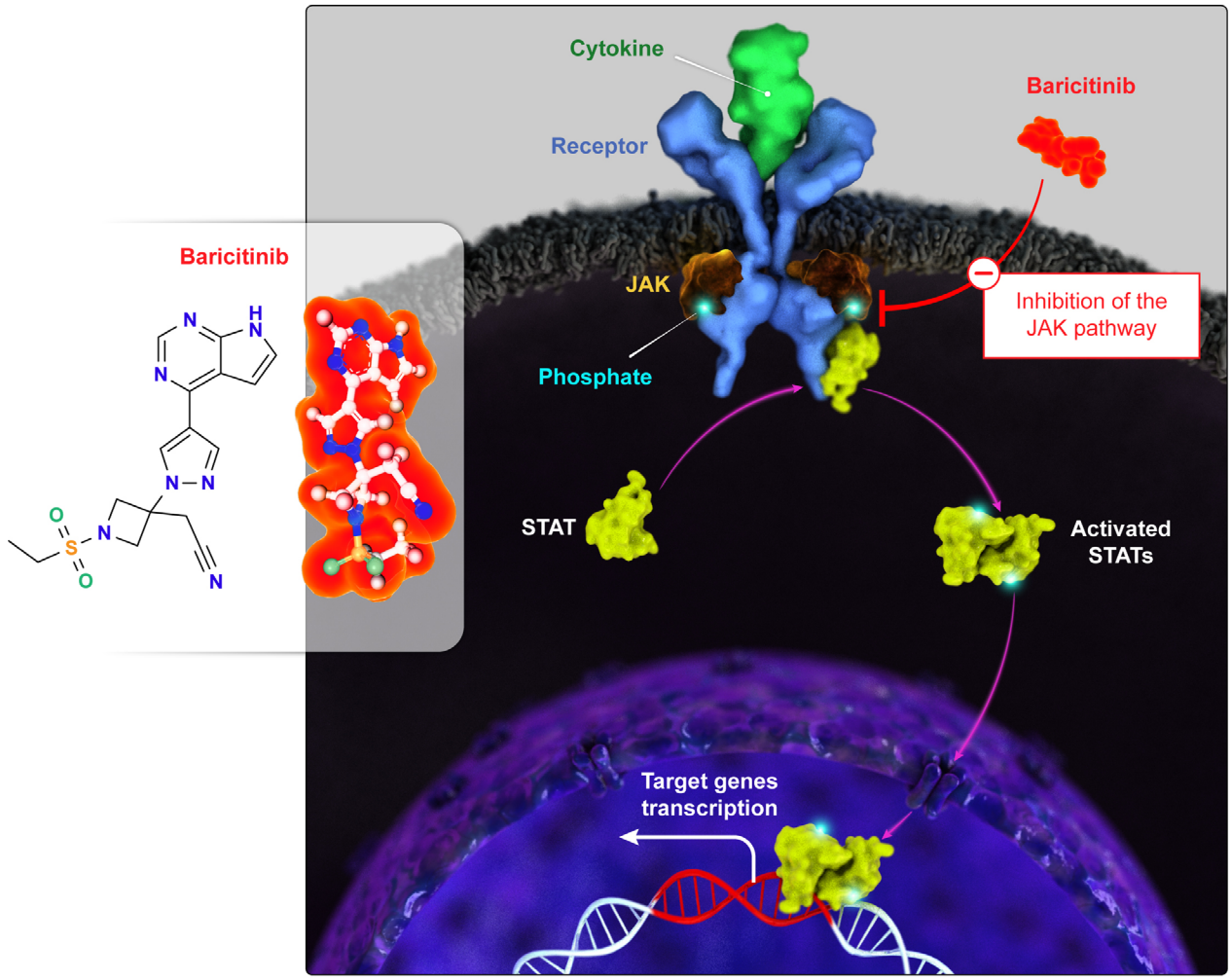

Figure 1. Schematic illustration of JAK/STAT signaling and its inhibition with baricitinib.

JAK enzymes approach the intracytoplasmic domain of the receptor and phosphorylate recruited signal transducers and activators of transcription (STAT) molecules. Seven STAT molecules —STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6—have been recognized as being phosphorylated by JAKs on a single tyrosine or serine residue. The phosphorylated STATs make a dimer form and transfer to the nucleus to trigger gene transcription, generally leading to enhanced immune responses (Figure 1). Therefore, JAK/STAT inhibition could block cytokine signaling and subsequent events such as monocyte activation, antibody secretion, erythropoiesis, and acute phase reactant production. Interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-15, IL-19, IL-21, and IL-23 as well as type I and II interferons (IFNs) are the most affected cytokines by JAK inhibitors.[2]

The approved JAK inhibitors include ruxolitinib (Jakavi) against JAK1/JAK2 used for treating myelofibrosis and polycythemia vera[3]; tofacitinib (Xeljanz/Jakvinus) against JAK3 for psoriasis and RA[4]; oclacitinib (Apoquel) against JAK1 for allergic AD[5]; fedratinib (Inrebic), a JAK2 inhibitor for the treatment of primary and secondary myelofibrosis[6]; baricitinib (Olumiant) against JAK1/JAK2; peficitinib (Smyraf) against JAK3; and upadacitinib (Rinvoq) against JAK1 for treating RA.[7,8] In addition, many others are under investigation such as filgotinib, a new JAK1 inhibitor for treating RA and Crohn's disease.[9]

Pharmacology, Pharmacodynamics, and Pharmacokinetics

Baricitinib ($C_{16}H_{17}N_7O_2S$) is an adenosine triphosphate competitive kinase inhibitor that selectively, strongly, and reversibly inhibits JAK1 and JAK2 enzymes (Figure 1). Half-maximal inhibitory concentrations (IC_{50}) of baricitinib for JAK1 and JAK2 are 5.9 and 5.7 nM, respectively. In high concentrations, it can also inhibit JAK3 ($IC_{50} > 400$ nM) and TYK2 ($IC_{50} = 53$ nM) activity.[10] With a molecular weight of 371.42 Da, baricitinib shows appropriate intracellular

penetration; thus, it has been produced as oral medicine (2-mg tablets) wthat significantly facilitates regular administration. The oral bioavailability of baricitinib is approximately 80%. Peak plasma concentration occurs in about 1 hour. Food is not expected to affect its efficacy, but fatty meals might blunt the absorption process. The volume of distribution is estimated to be 76 L, with 50% plasma protein and 45% serum protein binding.[11]

Baricitinib is a substrate of breast cancer resistance protein (BCRP), organic anion transporter 3 (OAT3), P-glycoprotein, and multidrug and toxin extrusion protein 2-k (MATE2-k) transporters. Its metabolism is mediated by the cytochrome P450 3A4 enzyme. Baricitinib did not inhibit or induce cytochrome P450 enzymes during in vitro studies; however, it inhibited OAT1, OAT2, OAT3, OCT1, OCT2, OATB1B3, BCRP, MATE-1, and MATE2-K transporters without significant clinical impact. Strong OAT3 inhibitors such as probenecid increase the baricitinib area under the curve almost 2-fold; hence, they are not recommended to be used simultaneously.[12]

Body clearance of baricitinib is 8.9 L/h, with a half-life of nearly 12 hours. When eliminated, 69% of the drug is excreted unchanged in urine and 15% via feces. Because it is metabolized and excreted by the kidney and liver, drug concentration might be affected by renal or hepatic disorders, necessitating dose adjustment for certain patients.[13]

Baricitinib and the Immune System

Regarding the considerable number of cytokines and growth factors inhibited by baricitinib, differentiation and function of most immune cells might be affected following its application. Both innate and adaptive immunity have been demonstrated to be suppressed by baricitinib. For instance, in vitro treatment of RA and healthy control neutrophils with baricitinib for 30 minutes prevented apoptosis delay induced by granulocyte-macrophage colony-stimulating factor and IFN-γ in a concentration-dependent manner. In addition, baricitinib diminished the chemotaxis rate toward IL-8 in neutrophils and inhibited the release of reactive oxygen species from primed neutrophils in response to *N*-formylmethionyl-leucyl-phenylalanine.[14] It has also been shown that treating immature human monocyte-derived dendritic cells with JAK inhibitors for 6 hours downregulated CD80/CD86 expression, but not that of human leukocyte antigen (HLA)-DR in a concentration-dependent manner. Moreover, plasmacytoid dendritic cells as the main source of type 1 IFNs produced markedly less cytokine in response to toll-like receptor 9 stimulation in the presence of baricitinib.[15] In addition, the invasion of fibroblast-like synoviocytes into the inflamed joint of RA was inhibited by baricitinib, probably because of an IFN-γ signaling blockade.[16] Baricitinib could also impede human B cell differentiation to plasmablasts and decreased IL-6 production from mature B cells. The proliferation of TCD4+ lymphocytes in response to anti-CD3 and anti-CD28 antibody stimulation was suppressed by baricitinib in a concentration-dependent manner; furthermore, differentiation of T helper (Th) 1 and Th17 cells was inhibited significantly via interfering with the cytokine signaling of IL-12, IL-23, and IL-6 and transforming growth factor beta 1.[15] IL-2 is known as the main cytokine in the development, proliferation, and survival of conventional and regulatory T (Treg) cells that transmits its signaling through the JAK1/JAK3 pathway.[17] Partial inhibition of IL-2 signaling by baricitinib (JAK1) resulted in suppressed T-cell function[18]; nonetheless, the possible disadvantages of suppressing Treg cell function, which expresses the highest amount of IL-2 receptor should be taken into account.

Baricitinib and Inflammatory Diseases

Rheumatoid Arthritis

Baricitinib was approved in 2018 by the US Food and Drug Administration and European Medicines Agency for treating adult patients with moderate to severe rheumatoid arthritis (RA) who have shown an inadequate response to 1 or more TNF-inhibitor therapies.[12] This was subsequent to the conduction of many clinical trials demonstrating the efficacy of baricitinib in alleviating severe RA. One of these clinical trials was RA-BEGIN, which compared 3 therapeutic regimens including baricitinib 4 mg, baricitinib + methotrexate (MTX), and MTX monotherapy in 588 randomized RA patients. This study demonstrated not only the noninferiority but also the significant superiority of baricitinib compared with MTX monotherapy. In week 24, the American College of Rheumatology 20% response (ACR20) obtained from baricitinib-therapy was 77% versus 62% by MTX. Moreover, the proportions of patients in remission measured by the Simplified Disease Activity Index (SDAI), ACR20 and ACR50, were markedly greater in combination therapy than with MTX monotherapy in weeks 24 and 52. According to the radiologic findings, disease progression was slower in both groups receiving baricitinib compared with the MTX monotherapy; nonetheless, the best results were obtained in combination therapy, suggesting beneficial effects of adding baricitinib to the therapeutic plan of RA patients.[19] The recently published extension trial, RA-BEYOND, was a post hoc analysis of patients from the RA-BEGIN study. RA-BEYOND evaluated the long-term efficacy and

safety of baricitinib in 423 patients with active RA who were originally treated with baricitinib monotherapy or switched from MTX or the combination therapy of baricitinib + MTX to baricitinib 4-mg monotherapy. The SDAI, the Clinical Disease Activity Index (CDAI), and the Health Assessment Questionnaire disability index (HAQ-DI) score assessment showed that the patients with lower disease activity at baseline continued to do well with baricitinib monotherapy. Patients receiving MTX had higher disease activity at baseline and showed reduced disease activity after the addition of MTX to baricitinib. The safety evaluation revealed almost similar outcomes in different treatment groups. Therefore, it was concluded that most RA patients profit from continued baricitinib monotherapy or switching from MTX monotherapy to baricitinib monotherapy or baricitinib plus MTX demonstrated by sustained or improved disease control.[20]

One other clinical trial evaluating the efficacy of baricitinib in RA was RA-BEAM, which compared baricitinib, adalimumab, and placebo in 1037 patients with inadequate response to MTX. At the end of week 12, the ACR20 response (70% vs 40%), the proportion of low disease activity, Disease Activity Score-28 for RA with CRP (DAS28-CRP), SDAI, and CDAI were significantly improved in the baricitinib group compared with the placebo. In addition, the rate of progressive radiographic joint damage assessed by modified Total Sharp Score (mTSS) and HAQ-DI was better in week 24. Notably, baricitinib showed superiority to the adalimumab in the first weeks. DAS28-CRP and ACR20 (70% vs 61%) were also improved in the baricitinib group compared with adalimumab in weeks 8 and 12, respectively. In term of adverse effects, treatment-emergent adverse events (TEAEs) through 24 weeks were higher in the baricitinib group (71%) and the adalimumab group (67%) than in the placebo group (60%); the infection rate was 36% and 33% versus 27%, respectively. However, serious adverse event (SAE) rates were similar between baricitinib and placebo groups and lower than adalimumab. Laboratory changes such as increased low-density lipoprotein (LDL) cholesterol and creatinine and decreased neutrophil counts were observed in the baricitinib group.[21]

RA-BUILD was a randomized clinical trial that evaluated the efficacy of baricitinib 2 or 4 mg daily versus placebo in 684 patients with inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and treatment naive to biologics. After week 12 of treatment, ACR20 was 62% for baricitinib 4 mg, 66% for baricitinib 2 mg, and 39% for placebo. Both baricitinib doses resulted in significantly better ACR50, ACR70, DAS28-ESR, SDAI, and CDAI scores as well as greater remission rates in week 24 compared with the placebo. Moreover, baricitinib 4 mg could inhibit the radiographic progression of structural joint damage evaluated in week 48. In week 52, the progression rate of mTSS was 0.7 for placebo, 0.33 for baricitinib 2 mg, and 0.15 for baricitinib 4 mg. TEAE and SAE rates (3%, 5%, and 5% for 2 mg baricitinib, 4 mg baricitinib, and placebo, respectively) showed no significant difference between groups.[22] Likewise, the RA-BEACON study recruiting 527 patients with adequate response to biologics (more than 1 TNF inhibitor for more than 3 months) compared the efficacy of baricitinib 2 or 4 mg with placebo. In week 12, baricitinib 4 and 2 mg showed significant ACR20 achievement. Both doses resulted in improved ACR50 and ACR70 response and reduced disease activity assessed by DAS28-ESR, SDAI, and CDAI compared with the placebo. In addition, the patients receiving baricitinib reported reduced fatigue, pain, and morning joint stiffness and improved physical function more than those on placebo. In week 24, the rates of SAE were 4%, 10%, and 7% in the baricitinib 2 mg, baricitinib 4 mg, and placebo groups, respectively. Serious infection rates were almost similar among groups (approximately 3%). The patients with greater prior biological disease-modifying antirheumatic drugs (bDMARD) use showed more TEAE, especially infections. Similar to the previous studies, baricitinib was associated with increased LDL cholesterol and creatinine.[8,23]

Interferon-Mediated Autoinflammatory Diseases

Interferonopathies are a group of monogenic diseases characterized by dysregulated IFN-mediated immune responses.[24] According to the prominent potential of baricitinib in inhibition of IFNs, its efficacy has been evaluated in 1 clinical trial for treating IFN-mediated autoinflammatory disorders. Ten patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE), 4 patients with stimulator of IFN gene–associated vasculopathy with onset in infancy and 4 patients with other interferonopathies were recruited and treated with baricitinib for a mean duration of 3 years (1.5-4.9 years). By receiving the optimal tolerated doses of baricitinib (initiated by 100 μg daily), the median daily symptom score decreased from 1.3 to 0.25. Daily prednisone doses decreased significantly in all patients, and 5 of 10 patients with CANDLE achieved permanent clinical remission. At baseline, many patients showed cytopenia including anemia, lymphopenia, and thrombocytopenia; nonetheless, the hemoglobin concentration, lymphocyte count, and platelet count increased after treatment with baricitinib. On the other hand, the same indices decreased in patients with normal cell count at baseline. IFN biomarkers reduced and patient quality of life along with height and bone mineral density improved significantly. Three patients showed

no improvement and thus discontinued the treatment; 1 of these patients was excluded from the study because of azotemia and polyomavirus hominis1 (BK) viremia. The upper respiratory infections, gastroenteritis, and BK infection were the most common infectious adverse effects; however, the overall outcome was evaluated as positive.[25]

Diabetic Kidney Disease

It has already been demonstrated that angiotensin II activates intracellular signaling processes that result in JAK/STAT signaling in glomerular mesangial cells. Consequent to JAK/STAT signaling, excessive proliferation and growth of glomerular mesangial cells would occur that contribute to diabetic nephropathy.[26] Kidney biopsy samples of progressive type 2 diabetic nephropathy have shown significant upregulation of JAK1, JAK2, and JAK3 as well as STAT1 and STAT3 mRNA expression that were negatively correlated with glomerular filtration rate (GFR).[27] Moreover, the Affymetrix expression arrays of 44 microdissected human diabetic nephropathy samples exhibited increased expression of JAK1 and JAK2 involved in IFN signaling, platelet-derived growth factor and ephrin receptor signaling, dendritic cell maturation, and monocytes activation.[28] According to these findings, a double-blind dose-ranging study investigated the potential of baricitinib to prevent diabetic kidney disease (DKD). A total of 129 patients with type 2 diabetes and at high risk for progressive DKD were randomized 1:1:1:1:1 to receive placebo or different doses of baricitinib (0.75 mg daily, 0.75 mg twice daily, 1.5 mg daily, or 4 mg daily) for 24 weeks, followed by 4-8 weeks of a washout period. At baseline, the mean GFR, hemoglobin A1c, and first morning urine albumin-creatinine ratio (UACR) were 45.0 ± 12.1, 7.3% ± 1%, and 820 mg/g (407-1632 mg/g), respectively. In week 24, baricitinib 4 mg daily decreased morning UACR by 41% compared with placebo and reduced the inflammatory biomarkers (eg, plasma soluble tumor necrosis factor receptor 1 and 2, intercellular adhesion molecule 1, urine CXCL10 and urine CCL2, and serum amyloid A) significantly. The only considerable adverse effect differing across groups was anemia, observed in 32% of patients on baricitinib 4 mg versus 3.7% in the placebo group.[29]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a wide range of clinical manifestations and an unpredictable relapsing-remitting course. Cytokine dysregulation is a prominent feature of SLE. Moreover, IFN-related genes have been shown to be overexpressed in SLE patients in active phases of disease.[30] Therefore, targeting the JAK/STAT pathway might suppress the exaggerated cytokine responses as demonstrated by in vitro and preclinical studies.[31] One phase 2 multicenter double-blind, randomized, placebo-controlled study recruited 314 SLE patients nonresponsive to the standard treatment and assigned them to receive placebo (n = 105), baricitinib 2 mg (n = 105), or baricitinib 4 mg (n = 104) for 24 weeks. At the end of the study, 67% of patients receiving baricitinib 4 mg and 58% on baricitinib 2 mg showed improved signs and symptoms of the active disease including resolution of the Systemic Lupus Erythematosus Disease Activity Index-2000, SLE arthritis, and rash. Adverse events were observed in 73%, 71%, and 65% of patients in baricitinib 4 mg, baricitinib 2 mg, and placebo groups, respectively. SAEs were seen in 10% of patients receiving baricitinib 4 mg, 10% of those receiving baricitinib 2 mg, and 5% of the placebo group; nonetheless, no deaths occurred. A single episode of deep vein thrombosis occurred in a patient receiving baricitinib 4 mg who was positive for antiphospholipid antibodies. Serious infections were reported in 6 patients on baricitinib 4 mg, 2 patients on baricitinib 2 mg, and 1 receiving placebo.[32] The encouraging results of this study justified further studies including 2 ongoing multicenter phase 3 randomized, placebo-controlled trials (NCT03616912, NCT03616964) that could provide more evidence about the advantages and disadvantages of baricitinib-therapy in SLE patients.[33]

Dermatologic Diseases

Psoriasis

Psoriasis is a chronic inflammatory skin disorder characterized by red, scaly plaques as a result of uncontrolled dermatocyte production. In many occasions, it is accompanied by nondermatologic manifestations such as arthritis. Th1 and Th17 lymphocytes have been shown to be implicated in the pathogenesis of psoriasis; therefore, cytokines like IL-12 and IL-23, which contribute to the differentiation of Th1 and Th17 cells, as well as IFN-γ, IL-17, and IL-22 produced by these cells might be considered therapeutic targets in managing severe cases.[34] Accordingly, the JAK/STAT pathways involved in signal transduction of these cytokines could be inhibited to halt disease progression. One randomized, double-blind, placebo-controlled, dose-ranging phase 2b clinical trial has evaluated the efficacy of baricitinib in 271 patients with moderate to severe psoriasis. The patients were assigned in 5 groups receiving 2-, 4-, 8-, or 10-mg daily oral doses of baricitinib or placebo for 12 weeks. At the end of this time, all patients receiving baricitinib (except 2 mg) showed significant improvement from baseline and had better Psoriasis Area and Severity Index 75% (PASI-75) compared with the placebo group. The number of patients achieving PASI-75 on 8 and

10 mg baricitinib was more than the placebo group, but significant PASI-90 responses were seen only in the 8- and 10-mg groups. Thereafter, an additional 12 weeks of treatment was started according to the obtained PASI score, and almost 80% of patients remained their PASI-75 scores until the end of week 24. The rate of adverse events for the placebo and 2-, 4-, 8-, and 10-mg baricitinib groups were 44%, 50%, 47%, 58%, and 64%, respectively. No opportunistic infection was observed in treatment groups.[35]

Alopecia Areata

Alopecia areata (AA) is an autoimmune disease causing hair loss with no definitive treatment. The role of IFN-γ and JAK/STAT signaling has already been shown in the pathogenesis of AA.[36] Baricitinib appeared to exert beneficial effects on AA as a 17-year-old male patient with chronic AA who had been enrolled in a clinical trial to evaluate the efficacy of this drug in treating his concomitant interferonopathy CANDLE syndrome exhibited considerable improvement in hair regrowth and finally complete resolution of hair loss within 9 months of treatment. He received oral baricitinib 7 mg daily for 6 months, then 7 mg in the morning and 4 mg in the evening with gradual tapering of corticosteroids to 3 mg per day. In addition, in vivo studies using the C3H/HeJ grafted alopecic mice model demonstrated a significant association between the resolution of the IFN signature and disease improvement in baricitinib therapy.[37] In a more recent study, a 60-year-old woman with a history of psoriasis and melanoma and current AA was subjected to baricitinib. She had been resistant to treatment with intralesional triamcinolone, platelet-rich plasma, and tofacitinib 1% solution. Administration of 2 mg daily baricitinib for 4 months showed no significant outcome; thus, the drug dose was increased to 4 mg daily, which resulted in 97% regrowth of scalp hair, eyebrows, and eyelashes within 8 months. The treatment was continued, and after 13 months, no adverse effects were observed.[38]

Allergic Dermatitis

Allergic dermatitis (AD) is the most common chronic inflammatory skin disease of childhood, affecting almost 25% of children and 0.3%-14.3% of the adult population. AD is associated with the over-activation of T lymphocytes, particularly Th2 cells secreting IL-4, IL-5, IL-13, and IL-31 cytokines; hence, cytokine inhibition might restrain disease progression.[39] The efficacy of baricitinib in treating AD has been evaluated in a phase 2 multicenter randomized, double-blind, placebo-controlled clinical trial. The patients ($n = 124$) were assigned to 1 of 3 groups receiving 4 mg baricitinib, 2 mg baricitinib, or placebo daily. One month prior to the study all other medications were discontinued except for topical triamcinolone. At baseline, the median Eczema Area and Severity Index (EASI) score for patients was 21.2. In week 16, the EASI 50 of patients treated with baricitinib 4 mg was significantly better than other patients, whereas their Scoring Atopic Dermatitis scores decreased. Baricitinib 2 mg showed no superiority to the placebo; nonetheless, the patients receiving baricitinib used almost 30% less triamcinolone monthly compared with the placebo group. Moreover, the total Dermatologic Life Quality Index improved in both baricitinib groups compared with placebo. Adverse events including headache, increased creatine phosphokinase (CPK), and nasopharyngitis were seen in 71% of the baricitinib 4-mg group, 46% of the baricitinib 2-mg group, and 49% of the placebo group. One patient in the baricitinib 4-mg group experienced a serious adverse event (benign polyp of the large intestine); no deaths occurred.[40] Subsequently, several phase 3 clinical trials were conducted about the efficacy and safety of baricitinib as a treatment for moderate to severe AD. For instance, BREEZE-AD1 and BREEZE-AD2 recruited more than 1200 adult AD patients with a Investigator's Global Assessment (IGA) score of 3 or 4, EASI $\geq$ 16, body surface area $\geq$ 10%, and inadequate response to more than 1 existing medication. The patients were randomized into 4 groups of placebo and 1, 2, and 4 mg baricitinib daily for 16 weeks. Significant improvement in nighttime awakenings, skin pain, and quality of life was observed as soon as the first week in the patients receiving 4 or 2 mg baricitinib. In week 16, the percentage of patients achieving IGA scale 0 or 1 was significantly greater in groups receiving baricitinib (16.8%, 11.4%, 11.8%, and 4.8% for baricitinib 4, 2, and 1 mg and placebo, respectively, in BREEZE-AD1 and 13.8%, 10.6%, 8.8%, and 4.5% for baricitinib 4, 2, and 1 mg and placebo, respectively, in BREEZE-AD2). Moreover, patient-reported outcome measured by Itch Numerical Rating Scale was 22% in the 4-mg group compared with 12% in the 2-mg and 7% in the placebo groups. Similar to the other studies, the most reported adverse effects were headache, nasopharyngitis, and CPK rise. There were neither thromboembolic events nor considerable hematological changes in baricitinib groups.[41] At the moment, there are other ongoing clinical trials about the efficacy of baricitinib in managing moderate to severe AD of children and adolescents (eg, NCT02576938; NCT03952559; NCT0343508; NCT03334435; NCT03428100), the results of which would provide further evidence for including or excluding baricitinib in the approved medications of AD.[42]

Graft-Versus-Host Disease

Regarding the indispensable role of cytokines in differentiation and stimulation of immune cells, cytokine

inhibition has been suggested to treat severe forms of graft-versus-host disease (GVHD). Proinflammatory cytokines such as IL-1, IL-4, IL-6, and IL-12 as well as increased IFN-γ during GVHD elicit exaggerated immune responses against vulnerable tissues such as liver, intestine, lungs, and skin.[43] JAK inhibitors, in particular, ruxolitinib, have been studied to suppress cytokine signaling in GVHD patients. Of note, there is evidence of preserving the graft-versus-leukemia effect (GVL) while preventing GVHD by JAK inhibitors.[44] Studies have shown that simultaneous blockade of IFN-γ and IL-6 receptors could resolve established GVHD in the animal model of fully major histocompatibility complex (MHC)–mismatched hematopoietic stem cell transplantation. Moreover, signaling inhibition of these 2 cytokines using baricitinib prevented GVHD successfully. Further results of baricitinib therapy included decreased count of Th1 and Th2 cells, reduced expression of MHC and CD80/86 molecules, Treg cell expansion, and enhanced GVL effects.[45] These encouraging preclinical findings wait to be evaluated in human patients by a nonrandomized open-label clinical trial aiming to evaluate JAK1/2 inhibition in chronic GVHD (NCT02759731).[46]

HIV Infection

Despite all advances in treating HIV infection, virus persistence in the host is considered a serious obstacle in treating the disease. highly active antiretroviral therapy appears not to be able to eradicate all viral particles because of virus latency in memory T cells. Because cytokines are deeply implicated in the homeostasis of memory cells, manipulating the JAK/STAT signaling pathway might be a way to control memory T cells' viral reservoir. It has already been shown that JAK/STAT pathway is involved in HIV persistence. Ruxolitinib and tofacitinib were able to decrease the number of TCD4+ cells containing integrated HIV DNA by blocking IL-2, IL-7, and IL-15 cytokine signaling; this could protect the bystander T lymphocytes from infection transmission.[47] Therefore, JAK inhibitors might be suggested to treat HIV+ patients to restrain T-cell activation and further viral expansion. Moreover, in an attempt to reduce central nervous system (CNS) inflammation in HIV, a group administered baricitinib in a murine model of HIV-associated neurocognitive disorders secondary to chronic CNS inflammation. The results indicated that baricitinib could cross the blood-brain barrier and promote HIV-induced cognitive disturbances. This was attributed to the reduced neuroinflammation shown by a diminished number of microglia and astrocytes in brain tissue. In vitro studies also demonstrated the efficacy of baricitinib in reducing the viral reservoir in macrophages.[48] These findings together with the potential safety and tolerability of JAK inhibitors in HIV patients[49] propose them as a probable supplementary medication to control the expansion and alleviate the inflammatory consequences of HIV infection.

Coronavirus Disease-19

In the present pandemic of coronavirus disease-19 (COVID-19), baricitinib has gained considerable interest because of its protective and curative effects on SARS-CoV-2 infection. It has been shown that baricitinib prevents virus endocytosis and reduces viral assembly by inhibiting adaptor-related protein-2 (AP-2)–associated protein kinase 1 and cyclin-G-associated kinase enzymes in alveolar type 2 cells. Because these cells contribute to viral transmission, baricitinib might hinder viral entrance to the underlying tissue.[50] Baricitinib could also exert beneficial effects in treating acute respiratory distress syndrome in COVID-19 patients by alleviating exaggerated inflammatory responses.[51] An in vitro study investigating the effect of baricitinib on cytokine release from whole blood cells of COVID-19 patients in response to SARS-CoV-2 antigens demonstrated decreased spike-specific responses consequent to the reduced expression of IFN-γ, IL-17, IL-1β, IL-6, TNF-α, and other inflammatory cytokines.[52] Although cytokine inhibition is helpful for managing severe cases of COVID-19, the essential role of cytokines, particularly IFNs, in eradicating viral infection should be taken into consideration. Therefore, JAK inhibitors are supposed to be administered preferentially to critical patients for a limited period and regarding their cytokine profiles.[53] Nonetheless, in the rhesus macaque model of SARS-CoV-2 infection, treatment with baricitinib showed encouraging results, as treated animals showed reduced inflammatory damage in lung tissue, decreased NETosis activity, considerable suppression of macrophages, and less neutrophil recruitment compared with the control group, whereas type I IFN antiviral responses and virus-specific T-cell responses were preserved.[54]

During the recent year, there were several clinical trials evaluating the efficacy of baricitinib in managing COVID-19 patients. In 1 of these studies, 20 severe cases received 4 mg baricitinib twice daily for 2 days, followed by 4 mg daily for 1 week. The results showed considerable clinical and paraclinical improvements indicated by elevated oxygen, increased antispike antibodies, reduced TNF-α, IL-6, and IL-1β cytokines, and restored T- and B-cell number in circulation.[55] In another noncontrolled study, 2-4 mg baricitinib and 200-400 mg hydroxychloroquine were administered daily to 15 patients with moderate to severe COVID-19 pneumonia. This combination therapy resulted in the overall recovery of 12 of 15 patients, but 3 patients died. After initiation of baricitinib, reduced CRP,

elevated oxygen saturation, and resolved symptoms were observed.[56] In addition, a pilot study comparing 12 moderate COVID-19 patients under standard treatment (lopinavir/ritonavir and hydroxychloroquine) with 12 patients receiving baricitinib (4 mg/day) plus lopinavir/ritonavir showed significant improvement in clinical and paraclinical indices of the baricitinib group within the first and second weeks of treatment, whereas the control group exhibited no significant improvement compared with baseline.[57] In addition, a double-blind, randomized, placebo-controlled trial compared the efficacy of baricitinib plus remdesivir versus remdesivir plus placebo in hospitalized COVID-19 patients. The patients receiving combination therapy (n = 515) showed a median recovery time 1 day shorter and a 30% greater improvement in clinical status compared with those who were treated with remdesivir alone (n = 518); moreover, the recovery time for the patients receiving oxygen therapy was shorter in the baricitinib group (10 vs 18 days), and the 28-day mortality rate was less than the placebo group (5.1% vs 7.8%). Notably, serious adverse events and new infections were less frequent in the combination group, revealing the superiority of baricitinib plus remdesivir therapy compared with remdesivir plus placebo.[58] Tocilizumab is an anti-IL-6 receptor antibody applied for inhibiting uncontrolled inflammatory responses such as cytokine storm following hematopoietic stem cell transplantation.[59] A retrospective study, treating the COVID-19 patients admitted for interstitial pneumonia with baricitinib and/or tocilizumab (in addition to standard antiviral therapy) demonstrated the lowest death rate in patients receiving baricitinib. Furthermore, no specific severe side effects were found in patients receiving baricitinib or baricitinib plus tocilizumab.[60] One other trial evaluated the efficacy of baricitinib plus corticosteroids in improving the pulmonary function of patients with moderate to severe COVID-19 pneumonia. Two group of patients received lopinavir/ritonavir/hydroxychloroquine plus either high-dose corticosteroids or corticosteroids/baricitinib. At discharge and 1 month later, baricitinib combination therapy resulted in better SpO_2/FiO_2 and improved pulmonary function compared with the corticosteroids alone.[61]

Because immunosenescence has been considered a risk factor in COVID-19 patients researchers have investigated adding baricitinib to the standard treatment of 83 elderly patients (median age, 81 years) with moderate to severe pneumonia. This resulted in a considerably decreased mortality rate and of patients in critical condition, as 16.9% of the baricitinib-treated patients died or progressed to invasive mechanical ventilation compared with 34.9% in the standard-of-care group. Baricitinib was generally well tolerated; however, there were some reports of liver toxicity, infectious diseases, gastrointestinal complication, and cardiovascular side effects, most of which were not definitely attributable to the baricitinib.[62] In addition to the abovementioned studies, at the moment there are at least 10 other ongoing registered clinical trials in different stages including NCT04321993, NCT04345289, and NCT04399798 investigating the efficacy and safety of baricitinib in treating COVID-19 patients.[63]

Safety

Despite all the beneficial effects of baricitinib in controlling various inflammatory conditions, some adverse effects have been observed in patients receiving this drug. Apparently, the most common adverse effect is the occurrence of infectious disease, in particular, upper respiratory tract infections (eg, nasopharyngitis), and reactivation of latent infections such as tuberculosis, hepatitis B, Epstein-Barr virus, varicella zoster, and herpes simplex. Headache is the second most common side effect, followed by LDL and creatinine rise.[64–67] However, the most concerning disadvantage of using baricitinib particularly for a long time is the increased risk of malignancies, particularly lymphoma and nonmelanoma skin cancers.[68,69] These 2 malignancies have occurred in higher rates in patients receiving 4 mg baricitinib for 24 weeks during the RA-BEYOND study, most of them taking additional immunosuppressive drugs.[12] Neutropenia, anemia, and increased alanine aminotransferase have also been attributed to baricitinib administration.[12] Accordingly, baricitinib should not be initiated in patients with an absolute neutrophil count less than 1×109 cells/L, or absolute lymphocyte counts less than 0.5×109 cells/L.[70] This is of particular importance in COVID-19 patients, as severe cases usually have lymphopenia and exhibit exhausted lymphocyte phenotypes.[71] Moreover, liver enzyme dysregulation following baricitinib administration has frequently been observed in patients receiving concomitant hepatotoxic drugs such as MTX or isoniazid. Chronic liver comorbidities and hepatic failure because of SARS-CoV-2 infection could also increase the alanine aminotransferase and aspartate aminotransferase levels, which makes it more confusing to indicate the cause of enzyme rise.[67] Furthermore, there are studies demonstrating the elevated probability of pulmonary embolism, deep vein thrombosis, and retinal artery occlusion in patients receiving baricitinib. This might increase the risk of coagulopathies established as a consequence of severe inflammation in COVID-19 patients.[68,72] Nonetheless, there is no concrete evidence about the additional risk of thrombotic events in COVID-19 patients treated with baricitinib. The other side effect correlated with baricitinib is increased CPK. Considerably, the SARS virus might

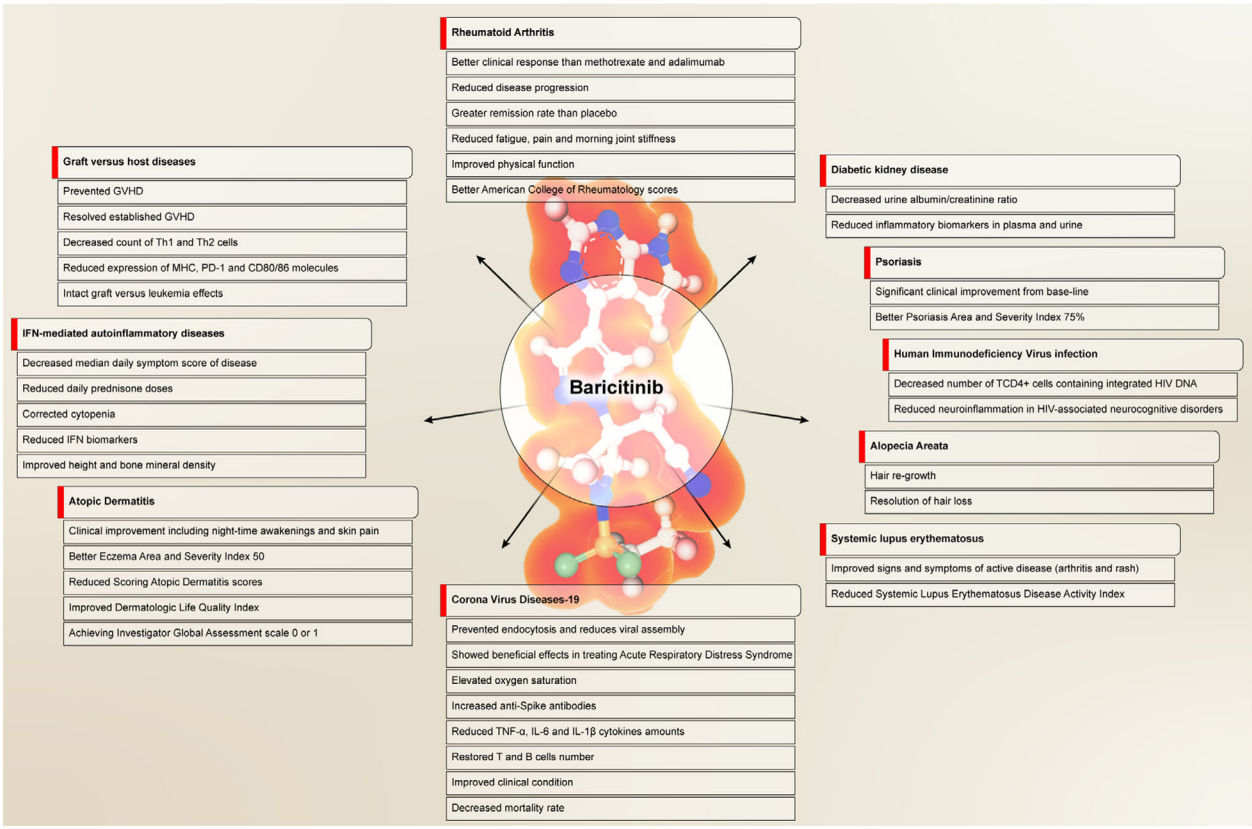

Figure 2. Inflammatory conditions treated with baricitinib.

cause CPK rise, which is usually associated with poor prognosis and later rhabdomyolysis; the aggravating effect of baricitinib in this process should also be taken into account.[73]

Despite the abovementioned adverse effects, it should be noted that the majority of patients receiving baricitinib either were taking other immunosuppressive drugs simultaneously or had been taking them for a long time; in addition, almost all these patients suffered from preliminary disorders that might affect their immune competence, rendering them incapable of appropriate eradication of infectious disease and elimination of tumor cells. These patients may also be more vulnerable to the metabolic dysregulation compared with healthy individuals. Taken together, the reported TEAEs could not be exclusively attributed to the baricitinib-therapy; obviously, further investigations are required to recognize the predisposing factors and describe definite short-term and long-term side effects of this medication.

Future Direction

Because of the considerable (and increasing) number of patients suffering from chronic autoimmune diseases and persistent allergies, as well as transplant recipients, and that all these patients should receive lifelong immunosuppressive drugs, it is necessary not only to exploit the capacity of available immunomodulatory agents but also to introduce novel drugs with more efficacy and fewer side effects to the clinic. JAK inhibitors with substantial efficacy and high selectivity might be considered a plausible option to be integrated in future immunosuppressive regimes; in particular, the critical patients with transplant rejection and those affected by debilitating autoimmune disorders such as multiple sclerosis, ankylosing spondylitis, and systemic sclerosis might profit from the potential of novel JAK inhibitors for controlling dysregulated immune responses.

Discussion and Conclusion

Baricitinib, a JAK1/2 inhibitor, has been successfully used for treating severe inflammatory conditions including resistant RA, SLE, IFN-related autoinflammatory disease, various dermatologic disorders, GVHD, and uncontrolled infections (Figure 2); meanwhile, several adverse effects ranging from simple upper respiratory tract infections to malignant transformations have been observed in patients receiving this drug. Because immunosuppressive agents are generally applied in combination with other anti-inflammatory or

antibiotic drugs, it is essential to study the efficacy and safety of JAK inhibitors in combination with different medications. Accordingly, baricitinib has been evaluated in patients receiving concomitant drugs such as MTX, lopinavir/ritonavir, hydroxychloroquine, corticosteroids, tocilizumab, and remdesivir. Determining the optimal drug combinations could improve the efficacy and diminish undesirable effects of JAK inhibitors; for instance, the adverse effects of tofacitinib have been shown to reduce in transplant recipients receiving rapamycin or belatacept compared with those who were treated with mycophenolate.[74] Moreover, certain adverse effects might be prevented by regular monitoring of patients, especially in terms of infectious diseases and malignancies. There are also laboratory tests to monitor drug potency such as measuring STAT5 phosphorylation, which has been recommended for dose adjustment of tofacitinib, another member of the JAK inhibitor family.[75] The similarity of disease symptoms and drug side effects is the other confusing point in determining the safety of baricitinib. Adverse effects such as liver enzyme dysregulation, thrombosis, lymphopenia, and CPK rise could occur in the natural course of many inflammatory disorders, thus, hardly attributable to baricitinib per se, although this could exacerbate the situation.

In summary, JAK inhibitors, in particular, baricitinib, might be applied to manage various acute and chronic inflammatory conditions efficiently; nonetheless, patients should be monitored cautiously to detect and resolve the probable side effects.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Sharing

Data available on request.

References

1. Zhao L, Ma Y, Seemann J, Huang LJ. A regulating role of the JAK2 FERM domain in hyperactivation of JAK2(V617F). *Biochem J*. 2010;426(1):91-98.
2. Schwartz DM, Bonelli M, Gadina M, O'shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol*. 2016;12(1):25.
3. Vaddi K, Sarlis NJ, Gupta V. Ruxolitinib, an oral JAK1 and JAK2 inhibitor, in myelofibrosis. *Expert Opin Pharmacother*. 2012;13(16):2397-2407.
4. Zerbini CA, Lomonte ABV. Tofacitinib for the treatment of rheumatoid arthritis. *Expert Rev Clin Immunol*. 2012;8(4):319-331.
5. Gonzales A, Bowman J, Fici G, Zhang M, Mann D, Mitton-Fry M. Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. *J Vet Pharmacol Ther*. 2014;37(4):317-324.
6. Blair HA. Fedratinib: first approval. *Drugs*. 2019;79(15):1719-1725.
7. Kivitz A, Gutierrez-Ureña S, Poiley J, et al. Peficitinib, a JAK inhibitor, in the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate. *Arthritis Rheumatol*. 2017;69(4):709-719.
8. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet*. 2019;393(10188):2303-2311.
9. Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10162):2367-2377.
10. Fridman JS, Scherle PA, Collins R, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol*. 2010;184(9):5298-5307.
11. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol*. 2014;54(12):1354-1361.
12. Mogul A, Corsi K, McAuliffe L. Baricitinib: the second FDA-approved JAK inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother*. 2019;53(9):947-953.
13. Markham A. Baricitinib: first global approval. *Drugs*. 2017;77:697-704. https://doi.org/10.1007/s40265-017-0723-3
14. Mitchell TS, Moots RJ, Wright HL. Janus kinase inhibitors prevent migration of rheumatoid arthritis neutrophils towards interleukin-8, but do not inhibit priming of the respiratory burst or reactive oxygen species production. *Clin Exp Immunol*. 2017;189(2):250-258.
15. Kubo S, Nakayamada S, Sakata K, et al. Janus kinase inhibitor baricitinib modulates human innate and adaptive immune system. *Front Immunol*. 2018;9:1510.
16. Karonitsch T, Beckmann D, Dalwigk K, et al. Targeted inhibition of Janus kinases abates interfon gamma-induced invasive behaviour of fibroblast-like synoviocytes. *Rheumatol*. 2018;57(3):572-577.
17. Busse D, de la Rosa M, Hobiger K, et al. Competing feedback loops shape IL-2 signaling between helper and regulatory T lymphocytes in cellular microenvironments. *Proc Natl Acad Sci U S A*. 2010;107(7):3058-3063.
18. McInnes IB, Byers NL, Higgs RE, et al. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther*. 2019;21(1):183.
19. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol*. 2017;69(3):506-517.
20. Fleischmann R, Takeuchi T, Schiff M, et al. Efficacy and safety of long-term baricitinib with and without methotrexate for the treatment of rheumatoid arthritis: experience with baricitinib monotherapy continuation or after switching from methotrexate monotherapy or baricitinib plus methotrexate. *Arthritis Care Res*. 2020;72(8):1112-1121.
21. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376(7):652-662. https://doi.org/10.1056/NEJMoa1608345

22. Dougados M, van der Heijde D, Chen Y-C, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95.
23. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374:1243-1252.
24. Eleftheriou D, Brogan PA. Genetic interferonopathies: an overview. *Best Pract Res Clin Rheumatol*. 2017;31(4):441-459.
25. Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest*. 2018;128(7):3041-3052.
26. Marrero MB, Banes-Berceli AK, Stern DM, Eaton DC. Role of the JAK/STAT signaling pathway in diabetic nephropathy. *Am J Physiology-Ren Physiol*. 2006;290(4):F762-F768.
27. Berthier CC, Zhang H, Schin M, et al. Enhanced expression of Janus kinase-signal transducer and activator of transcription pathway members in human diabetic nephropathy. *Diabetes*. 2009;58(2):469-477.
28. Woroniecka KI, Park ASD, Mohtat D, Thomas DB, Pullman JM, Susztak K. Transcriptome analysis of human diabetic kidney disease. *Diabetes*. 2011;60(9):2354-2369.
29. Tuttle KR, Brosius FC 3rd, Adler SG, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a Phase 2 randomized controlled clinical trial. *Nephrol Dialysis Transplant*. 2018;33(11):1950-1959.
30. Kawasaki M, Fujishiro M, Yamaguchi A, et al. Possible role of the JAK/STAT pathways in the regulation of T cell-interferon related genes in systemic lupus erythematosus. *Lupus*. 2011;20(12):1231-1239.
31. Alunno A, Padjen I, Fanouriakis A, Boumpas DT. Pathogenic and therapeutic relevance of JAK/STAT signaling in systemic lupus erythematosus: integration of distinct inflammatory pathways and the prospect of their inhibition with an oral agent. *Cells*. 2019;8(8):898.
32. Wallace DJ, Furie RA, Tanaka Y, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10143):222-231.
33. Merrill JT, Manzi S, Aranow C, et al. Lupus community panel proposals for optimising clinical trials: 2018. *Lupus Sci Med*. 2018;5(1):e000258.
34. Varma A, Han G. JAK inhibitors for psoriasis and psoriatic arthritis. *Curr Dermatol Rep*. 2020;1-7. https://doi.org/10.1007/s13671-020-00302-5
35. Papp K, Menter M, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *Br J Dermatol*. 2016;174(6):1266-1276.
36. Arca E, Muşabak U, Akar A, Erbil AH, Taştan HB. Interferon-gamma in alopecia areata. *Eur J Dermatol*. 2004;14(1):33-36.
37. Jabbari A, Dai Z, Xing L, et al. Reversal of alopecia areata following treatment with the JAK1/2 inhibitor baricitinib. *EBioMedicine*. 2015;2(4):351-355.
38. Olamiju B, Friedmann A, King B. Treatment of severe alopecia areata with baricitinib. *JAAD Case Rep*. 2019;5(10):892-894.
39. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017;139(4s):S65-S76.
40. Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol*. 2019;80(4):913-921.e9.
41. Simpson EL, Lacour J-P, Spelman L, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Brit J Derm*. 183(2):242-255. https://doi.org/10.1111/bjd.18898
42. Napolitano M, Fabbrocini G, Cinelli E, Stingeni L, Patruno C. Profile of baricitinib and its potential in the treatment of moderate to severe atopic dermatitis: a short review on the emerging clinical evidence. *J Asthma Allergy*. 2020;13 89–94.
43. Henden AS, Hill GR. Cytokines in graft-versus-host disease. *J Immunol*. 2015;194(10):4604-4612.
44. Mannina D, Kröger N. Janus kinase inhibition for graft-versus-host disease: current status and future prospects. *Drugs*. 2019;79(14):1499-1509.
45. Choi J, Cooper ML, Staser K, et al. Baricitinib-induced blockade of interferon gamma receptor and interleukin-6 receptor for the prevention and treatment of graft-versus-host disease. *Leukemia*. 2018;32(11):2483-2494.
46. Saidu NEB, Bonini C, Dickinson A, et al. New approaches for the treatment of chronic graft-versus-host disease: current status and future directions. *Front Immunol*. 2020;11:578314.
47. Gavegnano C, Brehm JH, Dupuy FP, et al. Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors. *PLoS Pathog*. 2017;13(12):e1006740.
48. Gavegnano C, Haile WB, Hurwitz S, et al. Baricitinib reverses HIV-associated neurocognitive disorders in a SCID mouse model and reservoir seeding in vitro. *J Neuroinflammation*. 2019;16(1):1-12.
49. Marconi V, Moser C, Gavegnano C, et al. Randomized trial of ruxolitinib in antiretroviral-treated adults with HIV [published online ahead of print March 6, 2021]. *Clin Infect Dis*. https://doi.org/10.1093/cid/ciab212
50. Praveen D, Puvvada RC, Aanandhi V. Janus kinase inhibitor baricitinib is not an ideal option for management of COVID-19. *Int J Antimicrob Agents*. 2020;55(5):105967.
51. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30.
52. Petrone L, Petruccioli E, Alonzi T, et al. In-vitro evaluation of the immunomodulatory effects of baricitinib: implication for COVID-19 therapy. *J Infect*. 2021;82(4):58-66.
53. Favalli EG, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment?. *Lancet Infect Dis*. 2020;20(9):1012-1013.
54. Hoang TN, Pino M, Boddapati AK, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell*. 2021;184(2):460-475.e21.
55. Bronte V, Ugel S, Tinazzi E, et al. Baricitinib restrains the immune dysregulation in patients with severe COVID-19. *J Clin Invest*. 2020;130(12):6409-6416.
56. Titanji BK, Farley MM, Mehta A, et al. Use of baricitinib in patients with moderate to severe coronavirus disease 2019. *Clin Infect Dis*. 2020;72(7):1247-1250.
57. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. *J Infect*. 2020;81(2):318-356.
58. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. 2020;384(9):795-807.
59. Mosharmovahed B, Fatahi Y, Mohebbi B, Ghorbanian SA, Assadiasl S. Tocilizumab in transplantation. *Eur J Clin Pharmacol*. 2020;76(6):765-773.
60. Rosas J, Liaño FP, Cantó ML, et al. Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to coronavirus COVID19: a real-world study. *Reumatol Clin*. 2020; https://doi.org/10.1016/j.reuma.2020.10.00

61. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuete JM, Martinez-Alfaro E. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. *Rheumatology (Oxford)*. 2021;60(1):399-407.
62. Stebbing J, Sánchez Nievas G, Falcone M, et al. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. *Sci Adv*. 2021;7(1):eabe4724.
63. Luo W, Li Y-X, Jiang L-J, Chen Q, Wang T, Ye D-W. Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19. *Trends Pharmacol Sci*. 2020;41(8):531-543.
64. Mehta S, Crusian B, Pierson D, Sams C, Stowe R. Monitoring immune system function and reactivation of latent viruses in the Artificial Gravity Pilot Study. *J Gravit Physiol*. 2007;14(1):P21-P25.
65. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
66. Xu J, Yang X, Yang L, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. *Crit Care*. 2020;24(1):1-11.
67. Jorgensen SC, Tse CL, Burry L, Dresser LD. Baricitinib: a review of pharmacology, safety, and emerging clinical experience in covid-19. *Pharmacotherapy*. 2020;40(8):843-856.
68. Peng L, Xiao K, Ottaviani S, Stebbing J, Wang Y-J. A real-world disproportionality analysis of FDA Adverse Event Reporting System (FAERS) events for baricitinib. *Expert Opin Drug Saf*. 2020;1-7.
69. Harigai M, Winthrop K, Takeuchi T, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open*. 2020;6(1):e001095.
70. Chaplin S. Janus kinase inhibitors for autoimmune disorders. *Prescriber*. 2017;28(12):33-37.
71. Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol*. 2020;17(5):533-535.
72. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18(7):1738-1742.
73. Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19. *Emerg Infect Dis*. 2020;26(7):1618-1620.
74. Baan CC, Kannegieter NM, Felipe CR, Silva HT Jr. Targeting JAK/STAT signaling to prevent rejection after kidney transplantation: a reappraisal. *Transplantation*. 2016;100(9):1833-1839.
75. Quaedackers ME, Mol W, Korevaar SS, et al. Monitoring of the immunomodulatory effect of CP-690,550 by analysis of the JAK/STAT pathway in kidney transplant patients. *Transplantation*. 2009;88(8):1002-1009.