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A Decade of Jakinibs: what have we learned and what may be the future

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Abstract

The discovery of cytokines and their role in immune and inflammatory disease led to the development a plethora of targeted biologic therapies. Later, efforts to understand mechanisms of cytokine signal transduction led to the discovery of Janus kinases (JAKs), which themselves were quickly identified as therapeutic targets. It has been a decade since the first JAK inhibitors (jakinibs) were approved and now there are nine jakinibs approved for treatment of rheumatologic, dermatologic, hematologic, and gastrointestinal indications along with emergency authorization for Covid-19. In this review, we will summarize relevant discoveries that led to first generation jakinibs and review their efficacy and safety demonstrated in pivotal clinical studies. We will discuss the next generation of more selective jakinibs, along with agents that target kinase families beyond JAKs. Finally, we will reflect on both the opportunities and challenges ahead as we enter the second decade of the clinical use of jakinibs.

Keywords

Cytokines; JAK; Autoimmunity; Inflammation; Kinase Inhibitors; COVID-19

Introduction

Cytokines serve as critical means of intercellular communication among immune and other cells, controlling many aspects of normal immune responses. However, their aberrant production, results in the loss of immune homeostasis and exaggerated immune responses that underlie pathologies from autoimmunity to “cytokine storm.”

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The introduction of targeted anti-cytokine biologic (protein) therapies at the end of the 20th century led to dramatic improvements in our ability to treat many diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis (PsO), atopic dermatitis (AD), and inflammatory bowel disease (IBD). Their clinical success was largely driven by our understanding of the cells and molecules that drive these pathologies to produce effective, generally safe, molecules that inhibit relevant inflammatory pathways. The development of biologic disease-modifying anti-rheumatic drugs (bMARDs) — namely, engineered proteins, capable of selectively binding cytokines or their cognate receptors that include Tumor Necrosis Factor (TNF), Interleukin (IL)-1, IL-4/IL-13, IL-6, IL-17, and IL-12/23 — was the capstone of years of research.

Many, but not all, of the cytokines that drive immunopathology act via type I or type II cytokine receptors. Cytokine binding to these receptors activates phosphotransferases (kinases) associated with the intracellular portion of these receptors. These kinases belong to a small family termed Janus kinase (JAKs), comprising four members: JAK1, JAK2, JAK3 and TYK2. Different receptors are coupled with different JAKs working in pairs, either in a heterodimeric or homodimeric complex. Following receptor engagement, the JAKs phosphorylate themselves and tyrosine residues on the receptor chains that recruit the Signal Transducers and Activator of Transcription (STAT) family of DNA binding proteins. These factors are phosphorylated by the JAKs resulting in their dimerization, translocation to the nucleus, and subsequent regulation of gene expression.

A series of mutant cell lines revealed the essential functions of JAKs in cytokine signaling,¹ but identification of *JAK3* mutations in patients with severe combined immunodeficiency (SCID) revealed *in vivo* criticality,² as did various knockout mice. These insights led to the proposition that JAK inhibitors could represent a new class of immunomodulatory drugs.³ Recognition of *JAK2* gain-of-function mutations in myeloproliferative neoplasms⁴ provided further evidence of JAK inhibition as an attractive therapeutic option. *TYK2* mutations in humans result in primary immunodeficiency⁵ and *TYK2* variants are linked to a wide range of autoimmune diseases. Specifically, *TYK2* protein-coding variants (e.g. rs34536443, P1104A) provide protection against multiple sclerosis, RA, PsO, and systemic lupus erythematosus (SLE).^{5, 6}

The development of jakinibs has accelerated over the past decade with the subsequent approval of multiple agents and more candidates under investigation in various diseases. In this review, we will briefly discuss the efficacy of the approved jakinibs and their adverse events (AEs). Though these jakinibs are relatively specific for JAK family kinases, several inhibit multiple members of the family; other jakinibs demonstrate improved *in vitro* selectivity, which is influenced by a number of factors that will be discussed. We will also discuss the role of this class of drugs in the management of Coronavirus disease 2019 (Covid-19) patients.

Efficacy of approved jakinibs

The group of inhibitory molecules initially developed exert their effect by blocking the ATP binding pocket of the JAK catalytic domain. Although these compounds are relatively

selective with limited off-target effects compared to other kinases, these jakinibs block the activity of multiple JAKs both *in vitro* and *in vivo*. Nonetheless, the promising results of these jakinibs in a wide-range of preclinical disease models quickly led to investigation in multiple clinical settings and for diverse pathologies; regulatory agencies have now approved nine jakinibs (Table 1).

The first jakinib to enter clinical trials was tofacitinib, which inhibits JAK1/JAK2/JAK3, initially for renal transplantation; however, ruxolitinib, a JAK1/JAK2 inhibitor, was the first agent to receive approval for myeloproliferative neoplasms (MPN) that often exhibit gain-of-function (GOF) *JAK2* mutations. Ruxolitinib is also approved for steroid refractory acute graft-versus-host disease (GvHD).

Tofacitinib was the first jakinib to be approved for a rheumatologic disease, specifically for patients with RA with an incomplete response to a conventional synthetic DMARD (csDMARD) either as monotherapy or in combination with a csDMARD.^{7, 8, 9, 10, 11} Subsequently, tofacitinib has been approved for PsA^{12, 13} and ulcerative colitis (UC).¹⁴ Tofacitinib has been approved for the treatment of polyarticular course juvenile idiopathic arthritis (JIA) in the US.

Baricitinib, a JAK1/JAK2 inhibitor, is approved for patients with RA in the United States limited to 2 mg QD in combination with a csDMARD or as monotherapy in patients with RA refractory to a bDMARD based on phase 3 trial results. In many other countries, both 2 and 4 mg are approved in csDMARD incomplete responders.^{15, 16, 17, 18} Baricitinib is also approved for treatment of AD in Europe.

Peficitinib, a pan JAK inhibitor, is approved in Japan, S. Korea, and Taiwan for the treatment of RA in csDMARD incomplete responders.^{19, 20} Tofacitinib, baricitinib, and peficitinib have shown clinical, functional, and radiographic efficacy after failure of a csDMARD, prior to a bDMARD, or after a bDMARD. Broadly speaking, with the exception of peficitinib, jakinibs have been documented to be more effective than MTX.^{7, 18}

Selective targeting of JAK1 should block the broadest cytokine profile compared to other JAKs while avoiding negative impact on hematopoiesis by sparing erythropoietin (EPO), thrombopoietin (TPO), and granulocyte colony stimulating factor (G-CSF) signaling. Two jakinibs with relative JAK1 selectivity have been approved in RA: upadacitinib in many countries including the United States, the European Union (EU), Canada, and Japan, and filgotinib in the EU and Japan. Phase 3 trials demonstrated clinical, functional, and radiographic efficacy both in combination with a csDMARD or as monotherapy in patients with incomplete response to a csDMARD or a bDMARD.^{21, 22, 23, 24, 25, 26, 27} Upadacitinib monotherapy has also been shown to be more effective than MTX in MTX naïve patients with RA.²⁴ Both have been referred to as “second generation jakinibs” as they both preferentially inhibit JAK1 *in vitro* but their clinical efficacy and safety, to a large extent, is similar to pan jakinibs in RA, although anemia and herpes zoster is seen less with filgotinib.

The clinical responses of jakinibs are more rapid than bDMARDs, with an earlier clinical effect shown as early as the first week of therapy as well as more rapid and deeper pain alleviation. Of clinical interest, tofacitinib, baricitinib, upadacitinib and filgotinib were all

at least as effective as a bDMARD in MTX incomplete responders, which suggests that after an incomplete response to a csDMARD, one can utilize a jakinib prior to a bDMARD. Additionally, if a patient does not respond adequately to a jakinib (upadacitinib), they may respond to a TNF inhibitor (adalimumab).^{17, 25, 26, 28, 29}

Whether more selectivity of JAK inhibition will lead to different outcomes remains unclear and there is currently a lack of well-designed clinical studies evaluating the efficacy or safety of one jakinib compared to another. Determination of selectivity is not simple and is dependent upon the nature of the assay, whether the assay is done in whole blood and exactly what is being measured. Evaluation of the *in vitro* cellular selectivity of baricitinib, tofacitinib, upadacitinib and filgotinib have shown that: all four agents inhibit IL-6 and IFN α signaling; upadacitinib and tofacitinib were more potent inhibitors of JAK1/3-dependent cytokines (IL-2, IL-4, IL-15, and IL-21) than baricitinib and filgotinib; baricitinib, tofacitinib, and upadacitinib but not filgotinib inhibited JAK2/2 and JAK2/TYK2 cytokines IL-3, GM-CSF, and G-CSF but to varying degrees.^{30, 31} Upadacitinib was the most potent inhibitor of JAK2/2-dependent cytokines IL-3 and GM-CSF, followed by baricitinib and tofacitinib; filgotinib was the least potent JAK2 inhibitor. Tofacitinib was the most potent inhibitor of JAK2/TYK2-dependent cytokine G-CSF, followed by upadacitinib and baricitinib.³¹ A common measure of JAK inhibition is the assessment of cytokine-induced STAT phosphorylation and a nuanced aspect of the assay is exactly what STAT is being measured; measurement of different STATs can give different answers. Thus, interpretation of selectivity appears to also be influenced by the cytokine and STAT being assessed. Most receptors use JAKs in pairs, but the importance of one JAK versus the other in signaling is still not fully understood and will require more basic research and likely more specific agents. Perhaps most important in terms of safety and efficacy is that no jakinib mediates sustained reduction in cell signaling throughout the dosing interval – a high degree of JAK inhibition is very transient. This is likely to be relevant for side effects.

Nonetheless, while the clinical relevance of these differences is unclear, jakinibs all appear to have similar efficacy and safety with the exception of fewer cases of anemia and herpes zoster with filgotinib.

Ongoing trials are investigating the efficacy of jakinibs in a wide range of additional indications. Phase 3 studies involving patients with active ankylosing spondylitis (AS) demonstrated promising efficacy and improvement with tofacitinib³² and upadacitinib.³³ Efficacy of upadacitinib in PsA has also recently been reported with the 30 mg upadacitinib group was superior to adalimumab.^{34, 35} Upadacitinib has been evaluated in dose ranging trials assessing efficacy in Crohn's disease (CD) and UC and has shown efficacy in both.^{36, 37} Upadacitinib was found to be more effective than placebo in AD³⁸ and phase 3 trials are ongoing.

Although there were positive results with filgotinib in phase 2 studies of PsA, AS, CD, and UC, these clinical development programs have been halted subsequent to the complete response letter from the FDA for filgotinib denying approval at present.^{39, 40, 41}

An open label trial of subjects with refractory dermatomyositis receiving tofacitinib and a trial of tofacitinib in combination with glucocorticoids in subjects with amyopathic dermatomyositis-associated interstitial lung disease both suggested efficacy and reasonable safety profiles.^{42, 43} In a compassionate use program for refractory juvenile dermatomyositis patients, preliminary data indicated clinically significant improvements with baricitinib treatment.⁴⁴

Other indications being investigated include alopecia areata (AA), SLE, interferonopathies including Down syndrome, relapsing giant cell arteritis, GvHD, myasthenia gravis, and vitiligo (Table 2).

Delgocitinib (JTE-052) is a topical jakinib approved in Japan for AD and oclacitinib, a JAK1/JAK2/JAK3 inhibitor, is approved for canine allergic dermatitis.

Safety of approved jakinibs

Jakinibs have been confirmed to be reasonably safe with an AE profile that is similar to bDMARDs, although the specific AEs are somewhat different (Table 3). Many of the AEs seen with jakinibs could have been predicted based on their mechanism of action (MOA) while others were not. Common side effects are infection, including serious and opportunistic infections and herpes zoster (HZ).^{45, 46, 47} Vaccination with recombinant adjuvanted HZ subunit is generally safe in patients with autoimmune disease, although flares are not uncommon.^{48, 49} Investigation of the serological response to the recombinant vaccine, in RA patients treated with jakinibs suggests satisfactory antibody responses and acceptable tolerability.⁵⁰ By contrast to HZ, the rate of influenza AEs in a RA clinical program were comparable in the tofacitinib, adalimumab, MTX, and placebo treated groups.⁵¹

Cytopenias such as neutropenia and anemia are also common AEs, likely due to JAK2 inhibition. Upadacitinib, a relatively JAK1-selective molecule, has similar effects as pan-jakinibs on anemia, whereas filgotinib appears to produce less anemia. Jakinibs can also result in lymphopenia, in particular reduction in NK cells, related to JAK3 inhibition. Jakinib administration has been associated with elevated serum lipids due to reduced cholesterol ester catabolism, increasing cholesterol levels toward those in healthy volunteers and improvement in markers of antiatherogenic HDL function.⁵² The FDA requested a long-term safety study post approval of tofacitinib in 2012, evaluating the safety of tofacitinib at 5 mg and 10 mg twice daily versus a TNF inhibitor (TNFi), all on MTX in subjects with rheumatoid arthritis (RA) 50 years of age or older and who had at least one additional cardiovascular (CV) risk factor (ORAL-Surveillance). The co-primary endpoints were non-inferiority of the combined tofacitinib doses (5 and 10 mg BID) compared to the TNFi (etanercept or adalimumab) regarding (1) major adverse cardiovascular events (MACE) and (2) malignancies. Non-inferiority was defined by the upper bound of the confidence interval not being greater than 1.8 (lower bound not calculated). The top-line results have been reported. Although the incidence rates for both endpoints for both mechanisms were lower than 1.2 per 100/pt-yrs with differences between tofacitinib and TNFi being 0.25-.35, the prespecified non-inferiority

criteria were not met for the primary comparison of the combined tofacitinib doses to TNFi. As seen in the general RA population, for tofacitinib, the most frequently reported MACE was myocardial infarction, and the most frequently reported malignancy was lung cancer. Of note, most of the events with both mechanisms occurred in subjects with a higher prevalence of known risk factors for MACE and malignancy (e.g., older age, smoking) and one can only conclude that there is probably a slight advantage of TNFi over tofacitinib for these events but cannot conclude that tofacitinib increases these events. (https://www.fda.gov/drugs/drug-safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart-related-problems-and-cancer-arthritis?utm_medium=email&utm_source=govdelivery accessed on 2-24-2020).⁵³

Concern of increased incidence of pulmonary embolism and venous and arterial thrombosis (VTE) was originally raised with baricitinib. During the placebo-controlled portion of the phase 3 studies, there was an imbalance in the development of VTEs, occurring only in the 4 mg group and not in the 2 mg or placebo group. However, in a report of over eight years of follow-up, the incidence rate of VTE was comparable between 2 and 4 mg and similar to what has been observed in RA patients treated with other MOAs.⁴⁶ No disparity was seen in the clinical trials of tofacitinib³⁴ and upadacitinib⁵⁴. Other reports have shown there is no evidence of short-term risk of MACE or VTEs in RA patients initiating jakinibs.⁵⁵ However, the situation has been confused because of the results of ORAL-Surveillance. Prior to completion of the study, data was released suggesting that, while there was not a statistically significant risk of the development of VTE between the tofacitinib 5 mg BID and TNF inhibitors for VTE and pulmonary embolism, there was one for tofacitinib 10 mg BID and a numerical difference favoring TNF inhibitors for 5 mg BID. For that reason, the EMA placed severe restrictions on the use of tofacitinib while the FDA strengthened its guidance. In a systemic review and meta-analysis of nine RCTs, risk of thromboembolism was increased in patients treated with jakinibs compared to placebo; baricitinib was the only jakinib that showed statistically significant increased thrombosis risk when compared to ruxolitinib, tofacitinib, and upadacitinib.⁵⁶ To complicate matters further, there has been no clear mechanism that explains an increased risk of VTE with jakinibs, and thus, this is an area that requires further exploration.

Regarding the risk of developing malignancies in RA, patients treated with jakinibs revealed higher rates of malignancy in the treated groups versus controls in a meta-analysis of 36 trials, but these rates did not reach statistical significance.⁵⁷

A long-term safety study of tofacitinib integrating data from phase 1, 2, 3b/4, and long-term extension studies in adult patients with RA (N = 7061) found AEs were stable over time and that incident rates were consistent with previous reports. No new safety risks were observed over the span of 9.5 years of cumulative tofacitinib exposure, and rates of safety events were comparable to bDMARDs and other jakinibs.⁵⁸

Filgotinib, but not other jakinibs, produced defects in spermatogenesis in rodent models which prompted conduction of a safety study in male patients investigating whether the 200 mg dose will have similar effects in humans. The top-line results were reported: 8.3% patients on placebo and 6.7% patients on filgotinib had a 50% or

more decline in sperm concentration at week 13. The study is ongoing and results as to whether the decrease will persist or affect more patients on filgotinib over time is still pending. Assessed April 23, 2021 <https://www.globenewswire.com/news-release/2021/03/04/2186756/0/en/GALAPAGOS-REPORTS-PRIMARY-ENDPOINT-FOR-THE-ONGOING-FILGOTINIB-MANTA-AND-MANTA-RAY-SAFETY-STUDIES.html>

In summary, multiple trials support the conclusion that in RA, jakinibs are at least equivalent or superior to TNF inhibitors when used with csDMARD in inducing a rapid response, observing a reduction in pain in as early as one week. Jakinibs have safety profiles generally comparable to biologics with the exceptions of increased HZ and the hematologic effects but perhaps with a slightly higher risk of MACE and malignancy in older patients with a history of smoking.

Next generation jakinibs

The success of jakinibs has motivated the development of yet more jakinibs (Table 4). CTP-543, a deuterium-modified form of ruxolitinib, has received breakthrough and fast track designation by the FDA and is currently being assessed in phase 2 and 3 studies of AA. Deuterated compounds have the potential advantage of improved pharmacokinetics with lower rates of metabolism, hence a longer half-life.

Another JAK1-selective jakinib, abrocitinib, has been evaluated in phase 3 trials in AD and plaque psoriasis,^{59, 60} showing efficacy in both diseases. AEs included Herpes simplex and HZ infection, appendicitis, pancreatitis, and IBD. No cases of VTEs, malignancies, MACE, or deaths were observed. Decreased platelets were noted with no decrease in hemoglobin. The JAK1-selective inhibitor, itacitinib, is currently being assessed in multiple clinical trials for oncologic indications as well as for chronic and acute GvHD, including GvHD prophylaxis. ARQ-252 is a selective topical JAK1 inhibitor, and a phase 1/2b trial for adults with chronic hand eczema is underway.

Inhibition of TYK2 would be expected to impact type I and type III IFNs, IL-10 family cytokines, IL-12, and IL-23, but not other cytokines. The success of monoclonal antibodies targeting IL-12 and IL-23 with acceptable AEs along with *TYK2* coding variants being associated with reduced incidence of autoimmunity^{61, 62} support the potential efficacy of TYK2 inhibition. Deucravacitinib (BMS-986165) has shown efficacy in psoriasis trial⁶³ and significantly greater American College of Rheumatology (ACR)20 responses in PsA compared to placebo. No anemia, cytopenias, serious infections, HZ, opportunistic infections, or thrombotic events were observed.⁶⁴ Trials are ongoing in SLE, including lupus nephritis, CD and UC. Unlike other jakinibs, deucravacitinib binds to the kinase-like domain.⁶⁵ Since the kinase-like domain is a relatively unique feature of JAKs, in principle, this strategy could provide increased kinome selectivity.

PF-06826647 is a TYK2-selective jakinib⁶⁶ currently in trials for psoriasis, UC, and hidradenitis suppurativa; brepocitinib is a TYK2/JAK1 inhibitor that was assessed in a phase 2 trial of psoriasis where clinical responses were seen with all doses.⁶⁷ Ongoing

investigations with brepocitinib with either oral administration or topical application include trials in AD, SLE, CD, UC, AA, hidradenitis suppurativa, and vitiligo.

Though the goal of JAK1- and TYK2-selective inhibitor use is to minimize JAK2 signaling interference and subsequent cytopenias, specifically targeting JAK2 can offer a treatment advantage for myeloproliferative neoplasms and potentially other hematological malignancies. Fedratinib is a selective JAK2 inhibitor approved for primary and secondary myelofibrosis. An important AE observed with fedratinib is Wernicke's encephalopathy in patients taking the highest daily dosage (500 mg).⁶⁸ Fedratinib exerts off-target inhibitory activity against bromodomain-containing protein 4 (BRD4) and is effective regardless of JAK2 mutational status. Phase 3 trials are ongoing to assess fedratinib's effects on long-term safety, efficacy, and overall survival.⁶⁹

Gandotinib is a JAK2-selective inhibitor that has potential increased potency for the *JAK2*^{V617F} mutant kinase and has shown efficacy in MPN.⁷⁰, although there are currently no ongoing clinical investigations of gandotinib.

JAK3's action is seemingly most restricted within the JAK family because of its exclusive association with the common γ -chain (γ c), a shared subunit used by IL-2, IL-4, IL-7, IL-19, IL-15 and IL-21. Mutations of either the γ c (encoded by *IL2RG*) or *JAK3* lead to complete absence of signaling of these cytokines and the consequent development of severe combined immunodeficiency disease (SCID) characterized by depletion of T, B, and natural killer (NK) cells but with no other defects. Thus, JAK3 has been identified as a potential target to treat various inflammatory and autoimmune diseases.

Developed to target the kinase domain of JAK3, decernotinib (VX-509) showed selective *in vitro* inhibition of JAK3 over the other JAKs and efficacy in RA.^{71, 72} However, a CYP3A4-mediated drug-drug interaction was also described, potentially limiting decernotinib's use; development of this molecule has currently been halted.⁷³

Beyond just JAKs

Despite the effort to search for drugs with greater specificity, there may be advantages in efficacy in targeting JAKs along with kinases involved in other signaling pathways (Table 4).

Ritlecitinib is an irreversible covalent inhibitor that binds to a distinct cysteine residue in the JAK3 catalytic domain, which other JAK family members lack. However, TEC family kinases possess this cysteine residue in their kinase catalytic domains. TEC family kinases consists of five members: Bruton's tyrosine kinase (BTK), bone marrow tyrosine kinase on chromosome X (BMX), interleukin 2-inducible T cell kinase (ITK), resting lymphocyte kinase (RLK), and tec protein tyrosine kinase (Tec). These kinases are important mediators of signaling for T cell antigen receptors, B cell antigen receptors (BCR), and chemokine receptors. Thus, ritlecitinib targets more than just type I/II cytokine receptor signaling. Ritlecitinib was found to be superior to placebo in a phase 2 study in RA patients with inadequate response to MTX.⁷⁴ AEs included lymphopenia and infection such as herpes simplex. Ritlecitinib is currently in phase 2 trials for CD, UC, AA, and vitiligo.

The spleen tyrosine kinase (SYK) is highly expressed in hematopoietic cells and plays important and varied roles in immune cell signaling from BCR and FcR to lectins and integrins. Thus, simultaneous targeting of SYK along with JAKs could have utility in the treatment of immune and inflammatory disease. Gusacitinib (ASN002) is an oral JAK/SYK inhibitor that showed clinical efficacy in a phase 2 trial in AD associated with decreased expression of inflammatory biomarkers.⁷⁵ Another JAK/SYK inhibitor, cerdulatinib (PRT062070), has been tested in several trials for leukemia and lymphoma, and a topical formulation is being tested in phase 2 trials in patients with vitiligo.

Momelotinib is a JAK1/JAK2 inhibitor as well as an activin receptor-like kinase (ACVR1) inhibitor. Because ACVR1 is a receptor for bone morphogenic proteins, momelotinib is undergoing testing in myelofibrosis.⁷⁶ Pacritinib is a JAK2 and interleukin-1 receptor-associated kinase 1 (IRAK1) inhibitor also being evaluated in myelofibrosis. Blocking IL-1 and toll receptor signaling might offer some interesting opportunities for autoimmune disease treatment.

Jakinibs in Covid-19

The emergence of a pandemic due to novel coronavirus SARS-CoV-2 with its associated severe systemic immune hyperactivation has motivated the search for novel therapeutics to treat Covid-19 cytokine release syndrome, also termed cytokine storm. The extreme elevated levels of multiple cytokines are associated with pulmonary and endothelial disease, myocardial damage, and mortality. Consequently, the search for effective drugs to manage Covid-19 has focused on modulation of cytokines. While treatment of Covid-19 with dexamethasone has shown efficacy in the RECOVERY trial, use of biologics has not consistently demonstrated efficacy.

Many of the cytokines elevated in Covid-19 including IL-2, IL-6, IL-12, IFN- γ , and GM-CSF signal via JAKs. For this reason, jakinibs were considered potential therapeutic candidates. However, an obvious argument against the use of jakinibs is the risk of increased infection. While jakinibs generally have a reasonable degree of kinome selectivity, baricitinib additionally inhibits the numb-associated kinase (NAK) family, AAK1 and cyclin G-associated kinase (GAK)^{77, 78} involved in viral entry of SARS-CoV-2. Several small trials have shown efficacy of ruxolitinib in the context of severe SARS-CoV-2.^{79, 80}

Baricitinib has shown utility in small trials in Covid-19.^{81, 82} However, Adaptive Covid-19 Treatment Trial (ACTT)-2⁸³ is a double-blind, randomized, placebo-controlled trial testing remdesivir plus 4 mg daily baricitinib or remdesivir plus placebo. This study enrolled 1033 hospitalized adults with Covid-19 in 67 sites in 8 countries, assessing the outcomes of time to recovery and clinical status at day 15. The results showed that baricitinib and remdesivir were safe and superior to remdesivir alone for patients with Covid-19 pneumonia. The observed benefit of combination treatment was most evident in patients receiving supplemental oxygen, high-flow oxygen, or noninvasive ventilation. Overall, patients receiving baricitinib had a median time to recovery of 7 days compared to 8 days for control patients, whereas the time to recovery for patients receiving oxygen or noninvasive ventilation was 10 days for baricitinib plus remdesivir versus 18 days for remdesivir and

placebo. The benefit of the combination treatment was less evident in patients not requiring oxygen or in patients requiring mechanical oxygenation or extracorporeal membrane oxygenation. Importantly and perhaps surprisingly, serious AEs, including infection, were less frequent in the combination group than in the control group.

ACTT-4, the fourth adaptive Covid-19 treatment trial, randomized patients to either remdesivir, intravenous dexamethasone, and placebo tablets or remdesivir, baricitinib tablets, and an IV placebo. The goal was to assess which combination was more effective at preventing adults hospitalized with COVID-19 on supplemental oxygen from progressing to requiring mechanical ventilation or death. Upon review of the current data, the data safety monitoring board determined that it is unlikely that the study will show a significant difference between these two arms even if the trial continued to full enrollment of 1,500 participants. As a result, enrollment in the trial was closed after slightly more than 1,000 participants. Thus, at present, the two strategies appear to be equivalent (<https://www.nih.gov/news-events/news-releases/nih-closes-enrollment-trial-comparing-covid-19-treatment-regimens>).

An important outstanding question is the relevance of baricitinib's potential anti-viral activity via inhibition of the JAK family. The COV-BARRIER trial examined addition of baricitinib versus placebo to standard of care. The results have been announced but not yet been published. The primary endpoints were progression to non-invasive or invasive mechanical ventilation or death, which was not statistically significant in the baricitinib group; although, reduction in mortality was seen without additional adverse events (<https://investor.lilly.com/news-releases/news-release-details/lilly-and-incyte-announce-results-phase-3-cov-barrier-study>).

Many other trials with a variety of jakinibs are underway and will hopefully assess the utility of baricitinib versus other jakinibs. Beyond Covid-19, the data beg the question as to whether jakinibs have broad use in sepsis and acute respiratory distress syndrome (ARDS).

Conclusions and challenges ahead

The year 2011 witnessed the approval of the first jakinib, ruxolitinib. Since this time, it has been remarkable to see the rapid development of multiple jakinibs and their approval for use of a broad range of indications, crossing multiple clinical specialties. We now know that jakinibs are generally as safe and effective as biologics, albeit with some differences in safety, and exert their effect more rapidly. Not surprisingly, they are being tested in a plethora of disorders from genetic interferonopathies to Covid-19. Despite the impressive advances, many questions remain.

In RA, should jakinibs be used prior to MTX, assuming equal patient access and affordability? Tofacitinib, baricitinib and upadacitinib have been shown to be more efficacious than MTX, but there are some differences in safety and tolerability - some of which favor MTX while others favor jakinibs. Should jakinibs be employed prior to bDMARDs considering that each jakinib has been shown to be at least as effective as bDMARDs and have the advantage of oral administration with rapid benefit? It has been

shown with each of the jakinibs in RA that they are more effective in combination with a csDMARD although monotherapy is effective in many patients. If a jakinib is added to a csDMARD and the patient achieves sustained control of their disease, should the jakinib or csDMARD be tapered or discontinued first? Many patients are initially treated with glucocorticoids (GC) as “bridge therapy,” but in many, the “bridge” lasts for a prolonged time. Can jakinibs decrease the total exposure to GC and thus prevent their significant toxicity? Importantly, what is the real risk of VTE, MACE and malignancy with use of a jakinib versus another MOA? As discussed above, issues surrounding specificity are not straightforward; do different *in vitro* specificities, measured by various assays, correlate with differences in efficacy and safety amongst the jakinibs? We still don't know but well-designed head-to-head trials will need to be performed to answer all these questions. Many of the same questions lack answers in PsA and AS, such as initial versus later use, monotherapy versus combination therapy, and treatment with a second jakinib after failure of the first. The GC question is not as relevant; however, we do not know the efficacy of jakinibs compared to non-TNF bDMARDs, such as the inhibitors of IL-17 or IL-23.

The use of jakinibs in combination with other inhibitors, whether intracellular or bDMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is currently not recommended. However, it is conceivable that there are combinations which are more efficacious and/or safer; obviously, this too will need to be assessed in the setting of a rigorous randomized control trials – again, not a trivial undertaking. Mechanistic studies have been performed that elucidate relevant aspects jakinib action in terms of efficacy;^{84–87} however, more work is required to understand how transient blockade of signaling by jakinibs versus sustained blockade of cytokines by biologics impacts relevant cell populations and immunopathogenesis.

In disorders such as lupus nephritis or vasculitis, aggressive approaches are warranted. Use of jakinibs have the potential for reducing toxicities of other agents, but as was clear in transplant trials, they also have the potential for over-immunosuppression.⁸⁸ We now know that jakinibs have utility in Covid-19 cytokine storm; remarkably, these agents are safe in patients with severe, life-threatening infectious disease. However, it is by no means clear that we have identified the right dose and the right combination of agents. Also remarkable is that a parenteral jakinib has yet to be generated. An advantage of this class of drugs is their rapid onset of action and short half-life, but it is not clear that in severely ill patients that the current doses and formulations are optimal to interdict inflammatory responses quickly and effectively.

The utility of jakinibs in Covid-19 cytokine storm suggests that these agents may be useful in additional clinical scenarios. Cytokine storm associated with chimeric antigen receptor (CAR) T cell therapies is one possible setting. A concern of course would be that first generation jakinibs might be toxic for the engineered T cells; however, this is a setting in which a selective JAK2 inhibitor might be advantageous. Similarly, in autoimmune disease associated with checkpoint blockade inhibitors, jakinibs might also have utility in dampening immune responses.⁸⁹ On one hand, jakinibs are being studied as therapy for a number of cancers – many of which are driven by a cytokine/STAT signature.⁹⁰ On the other hand, jakinibs have the capacity to block IFNs and limit the ability of immune cells

to kill cancer cells. However, there is an additional wrinkle here – by attenuating the action of IFNs, jakinibs have the capacity to reverse T cell exhaustion and promote elimination of tumors.⁹¹

These musings are certainly not an exhaustive list of challenges and opportunities in the jakinib arena. We present a few ideas of issues that will need to be addressed by thoughtful clinical studies, the need for which will likely increase as generic forms of jakinibs become available and jakinibs are more accessible to more patients. Considering a decade in, especially for those of us in the specialty, the advances in the jakinib field have been astonishing; however, we hope we have made the case that, in many respects, we are still at the beginning of what needs to be understood.

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Abbreviations

JAK	janus kinase
Jakinib	JAK inhibitor
STAT	signal transducers and activator of transcription
IFN	interferon
GOF	gain of function
RA	rheumatoid arthritis
PsO	psoriasis
PsA	psoriatic arthritis
AS	ankylosing spondylitis
IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn’s disease
JIA	juvenile idiopathic arthritis
TNF	tumor necrosis factor
SLE	systemic lupus erythematosus
MPN	myeloproliferative neoplasms

GvHD	graft-versus-host disease
AD	atopic dermatitis
AA	alopecia areata
AE	adverse events
MTX	methotrexate
EPO	erythropoietin
TPO	thrombopoietin
G-CSF	granulocyte colony stimulating factor
MOA	mechanism of action
HZ	herpes zoster
MACE	major adverse cardiovascular events
BRD4	bromodomain-containing protein 4
SYK	spleen tyrosine kinase
BTk	Bruton's tyrosine kinase
TEC	tec protein tyrosine kinase
BMX	bone marrow tyrosine kinase on chromosome X
ITK	interleukin 2-inducible T cell kinase
BCR	B cell antigen receptors
CC	case control study
RCT	randomized control trial
ICU	intensive care unit
NOS	nitric oxide synthase
ARDS	acute respiratory distress syndrome
SARS-CoV2	Severe Acute Respiratory Syndrome Corona Virus 2
Covid-19	Coronavirus Disease 2019
NAK	numb-associated kinases
AAK1	AP2-associated protein kinase 1
GAK	cyclin G-associated kinase
GC	glucocorticoids

CAR chimeric antigen receptor

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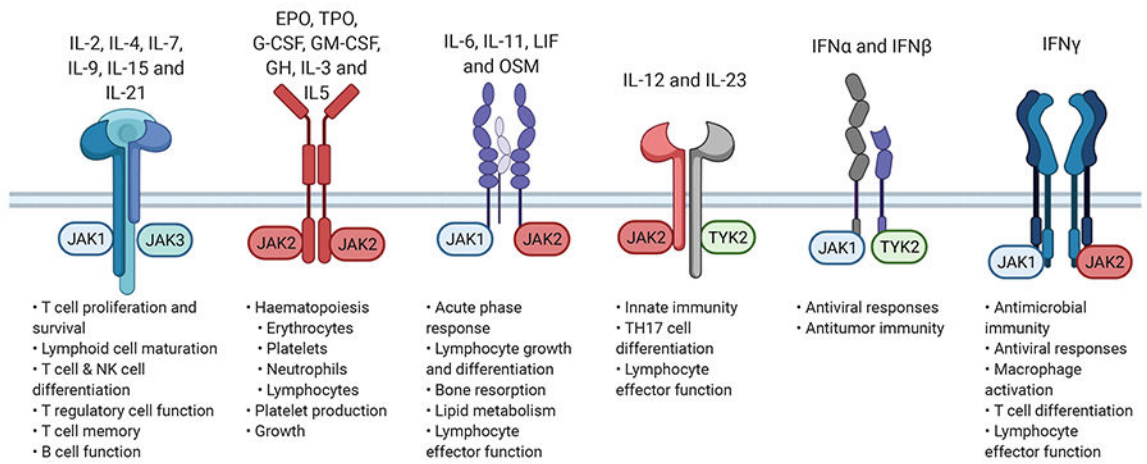
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Pan-jakinibs						
Tofacitinib	Delgocitinib	×	×	×	×	×
Oclacitinib	Gusacitinib					
Peficitinib						
JAK1/JAK2-selective						
Baricitinib	Cerdulatinib	×	×	×	×	×
Ruxolitinib	Momelotinib					
CTP-543						
JAK1-selective						
Filgotinib	Itactinib	×		×	×	×
Upadacitinib	ARQ-252					
Abrocitinib						
JAK2-selective						
Gandotinib			×	×	×	×
Fedratinib						
Pacritinib						
JAK1/TYK2-selective						
Breprocitinib		×		×	×	×
JAK3-selective						
Ritlecitinib		×				
TYK2-selective						
BMS-986165				×	×	

Figure 1:

Type I and type II cytokine receptors associate with different members of the Janus kinase family (JAK1, JAK2, JAK3, and TYK2) in order to transduce intracellular signals. Selective blockade of specific JAK molecules should inhibit specific biologic actions while allowing other JAK-dependent cytokines to signal normally. For example, by selectively inhibiting JAK1, the adverse events related to JAK2 inhibition such as anemia and neutropenia should be avoided. JAK3 mediated signaling, which is associated exclusively with the common γ -chain receptor, should also be unaffected, sparing T, B, and NK (natural killer) cell function. JAK, Janus kinase; TYK, tyrosine kinase; IL, interleukin; EPO, erythropoietin; TPO, thrombopoietin; granulocyte colony-stimulating factor (G-CSF); GM-CSF, granulocyte-macrophage colony-stimulating factor; GH, growth hormone; OSM, oncostatin M; IFN, interferon. Created with [BioRender.com](https://www.biorender.com)

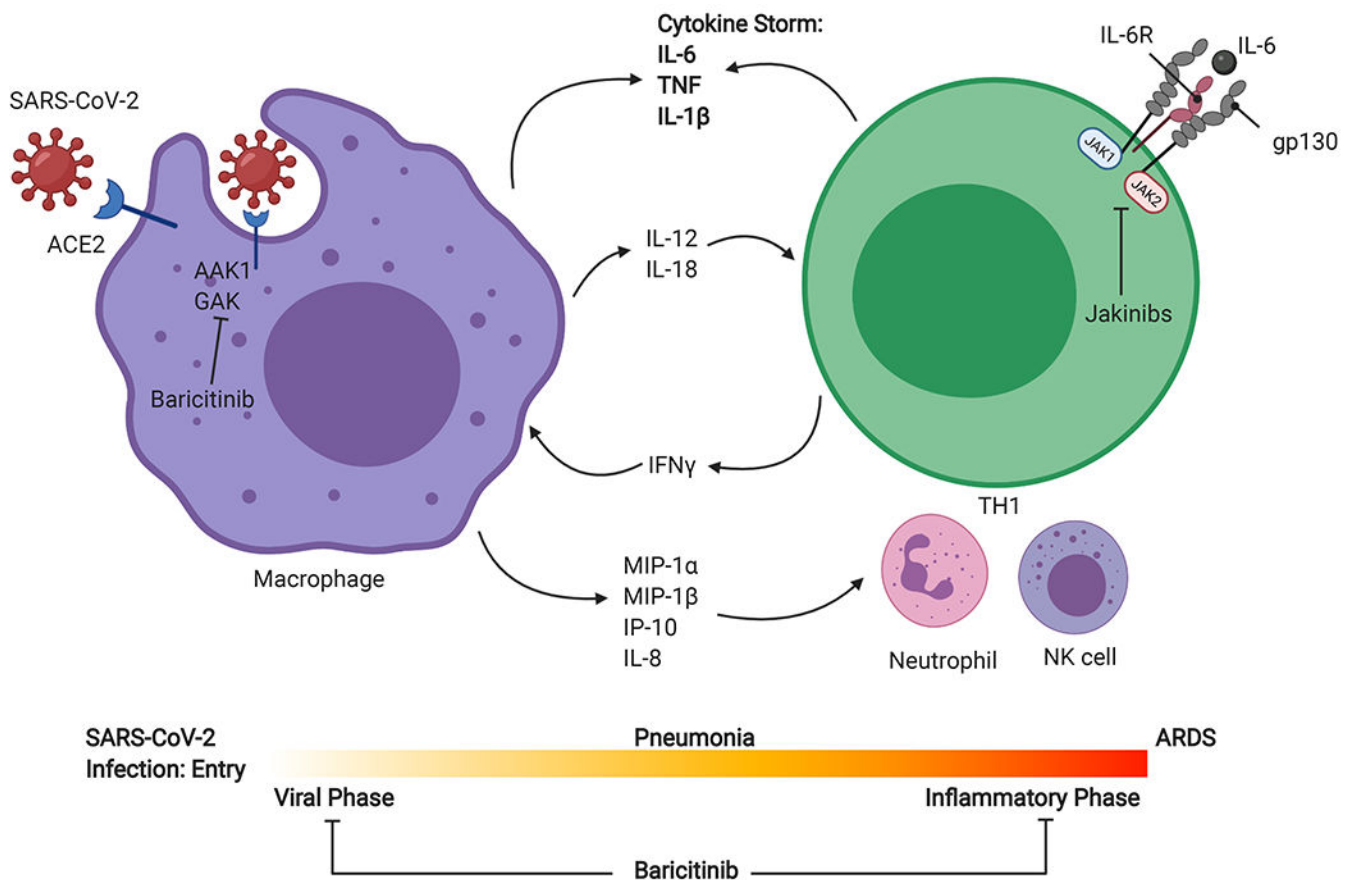


Figure 2:

SARS-CoV-2 entry is mediated by ACE2 (Angiotensin converting enzyme 2), a receptor widely expressed in the lungs, heart, vasculature, kidneys, and gastrointestinal tract. Primary site of infection is alveolar epithelial cells in the lungs, and rapid replication of virus can lead to a hyperimmune response. Macrophage activation and chemokine release for neutrophil, TH1, and NK cell recruitment can lead to a massive cytokine release responsible for the clinical evolution to acute respiratory distress syndrome (ARDS). Jakinibs such as baricitinib can potentially block viral entry by inhibiting numb-associated kinase family (NAK) proteins AAK1 and cyclin G-associated kinase (GAK). During the inflammatory phase, many of the cytokines elevated in Covid-19 (IL-6, IL-12, and IFN γ) signal via JAKs, and therefore, jakinibs are being considered as potential therapeutics in severe SARS-CoV-2. JAK, Janus kinase; TYK, tyrosine kinase; IL, interleukin; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor; IP, interferon γ -induced protein. Created with [BioRender.com](https://www.biorender.com)

Table 1:

Approved Jakinibs and their current indications

Drug	Target	Indication
Tofacitinib	JAK1/JAK2/JAK3	RA, PsA, UC, polyarticular course JIA
Baricitinib	JAK1/JAK2	RA, Covid-19 (EUA)
Upadacitinib	JAK1	RA
Filgotinib	JAK1	RA (approved in EU, Japan)
Peficitinib	Multiple JAKs	RA (approved in Japan, Korea)
Ruxolitinib	JAK1/JAK2	MPN, acute GvHD
Fedratinib	JAK2/FLT3/RET/BRD4	MPN
Delgocitinib (Topical)	Multiple JAKs	AD (approved in Japan)
Oclacitinib	Multiple JAKs	AD (dogs)

RA, rheumatoid arthritis; PsA, psoriatic arthritis; UC, ulcerative colitis; JIA, juvenile idiopathic arthritis; MPN, myeloproliferative neoplasms; GvHD, graft-versus-host disease; AD, atopic dermatitis

Table 2:

Selected ongoing clinical trials of first generation Jakinibs

Agent	Specificity	Disease
Tofacitinib	JAK1/JAK2/JAK3	Down's Syndrome: NCT04246372 Covid-19: NCT04332042, NCT04415151, NCT04390061, NCT04469114 Inflammatory Eye Disease (Uveitis & Scleritis): NCT03580343 Sjogren's Syndrome: NCT04496960 SLE: NCT03288324
Ruxolitinib *	JAK1/JAK2	Covid-19: NCT04348071, NCT04477993, NCT04414098, NCT04359290, NCT04377620, NCT04348695, NCT04374149, NCT04424056, NCT04338958, NCT04403243, NCT04334044 Vitiligo: NCT04530344, NCT04057573, NCT04052425, NCT03099304 Thrombocytopenia and Polycythemia Vera: NCT04644211, NCT04116502, NCT02962388, NCT03669965, NCT02577926, NCT03952039, NCT04455841 Hypereosinophilic Syndrome or Primary Eosinophilic Disorders: NCT03801434, NCT00044304 AD: NCT03745638 Hidradenitis Suppurativa: NCT04414514
Baricitinib	JAK1/JAK2	Covid-19: NCT04340232, NCT04320277, NCT04399798, NCT04421027, NCT04393051, NCT04373044, NCT04640168, NCT04321993 AA: NCT03570749, NCT03889259 JIA: NCT03773965, NCT04088396, NCT03773978 SLE: NCT03843125, NCT03616964, NCT03616912 AD: NCT03559270, NCT03952559, NCT03435081, NCT03334435, NCT03428100 GvHD: NCT02759731 Giant Cell Arteritis: NCT03026504 Uveitis: NCT04088409 Aicardi Goutieres Syndrome: NCT03921554 Idiopathic Inflammatory Myopathies: NCT04208464 PMR: NCT04027101
Fedratinib	JAK2/FLT3/RET/BRD4	Myelofibrosis/Polycythemia Vera: NCT03755518, NCT03952039, NCT04282187, NCT04446650, NCT04629508, NCT04562870, NCT04370301
Delgocitinib	JAK1/JAK2/JAK3/TYK2	AD: NCT03826901, NCT03725722 Chronic Hand Eczema: NCT03683719
CTP-543	JAK1/JAK2	AA: NCT03898479, NCT04518995

* Trials for cancer and/or malignancies have been excluded

AA, alopecia areata; AD, atopic dermatitis; GvHD, graft-versus-host disease; JIA, juvenile idiopathic arthritis; MPN, myeloproliferative neoplasms; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UC, ulcerative colitis

Table 3:

Major side effects of jakinibs

Infection
Serious and opportunistic infections
Herpes Zoster
Hematologic
Anemia
Leukopenia
Thrombocytopenia
Venous Thrombosis?
Hyperlipidemia

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Table 4:

Ongoing clinical trials of selective jakinibs

Agent	Specificity	Disease
Upadacitinib	JAK1	AD: NCT03569293, NCT03738397, NCT03568318, NCT03661138, NCT04195698, NCT03607422, NCT04666675 Hiradenitis Suppurativa: NCT04430855 Spondyloarthritis: NCT04169373 PsA: NCT03104374, NCT03104400 AS: NCT03178487 SLE: NCT03978520, NCT04451772 UC: NCT03653026, NCT03006068, NCT02819635, CD: NCT03345836, NCT03345823, NCT02782663, NCT02365649 Takayasu Arteritis: NCT04161898 Giant Cell Arteritis: NCT03725202
Filgotinib	JAK1	RA: NCT02065700, NCT03025308 PsA: NCT03320876, NCT04115839, NCT04115748 CD: NCT02914600, NCT02914561, NCT03077412 AS: NCT04483700, NCT04483687 UC: NCT02914535 IBD: NCT03201445 Noninfectious Uveitis: NCT03207815
Abrocitinib	JAK1	AD: NCT04345367, NCT03422822, NCT03915496
Itacitinib	JAK1	Acute GvHD: NCT03846479 Chronic GvHD: NCT04200365, NCT03584516, NCT04446182 Prophylaxis for GvHD and Immune Effector Cell Therapy (Prevention of Cytokine Release Syndrome): NCT04071366, NCT04339101 Asthma: NCT04129931 MPN/Myelofibrosis: NCT04640025, NCT03144687, NCT01633372, NCT04629508 Non-Small Cell Lung Cancer: NCT03425006, NCT02917993
ARQ-252	JAK1	Hand Eczema: NCT04378569
BMS-986165	TYK2	SLE: NCT03252587, NCT03920267 Lupus Nephritis: NCT03943147 CD: NCT03599622 UC: NCT03934216, NCT04613518 PsA: NCT03881059 Plaque Psoriasis: NCT03624127, NCT03611751, NCT04167462 Psoriasis: NCT04036435, NCT03924427
Brepocitinib (PF-06700841)	TYK2/ JAK1	Psoriasis: NCT03850483 Acne Inversa: NCT04092452 Hidradenitis suppurativa: NCT04092452 NSV: NCT03715829 PsA: NCT03963401 SLE: NCT03845517 CD: NCT03395184 UC: NCT02958865
Ritlecitinib	JAK3/Tec kinases	RA: NCT02969044 CD: NCT03395184 UC: NCT02958865 NSV: NCT03715829 AA: NCT03732807, NCT04006457, NCT04517864
Cerdulatinib *	JAK1/JAK2/Syk	Vitiligo: NCT04103060
Momelotinib	JAK1/JAK2/ACVR1	MPN: NCT04173494
Pacritinib *	JAK2/IRAK1	GvHD: NCT02891603

Agent	Specificity	Disease
		MPN: NCT03645824, NCT03165734 Covid-19: NCT04404361
Gusacitinib* (ASN002)	JAK1/JAK2/JAK3/ TYK2/Syk	Chronic Hand Dermatitis: NCT03728504 AD: NCT03531957

* Trials for cancer and/or malignancies have been excluded

AA, alopecia areata; AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's Disease; GvHD, graft-versus-host disease; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; MPN, myeloproliferative neoplasms; NSV, non-segmental vitiligo; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UC, ulcerative colitis

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