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Opinion

Targeting JAK-STAT Signaling to Control Cytokine Release Syndrome in COVID-19

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Recent advances in the pathophysiologic understanding of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has indicated that patients with severe coronavirus disease 2019 (COVID-19) might experience cytokine release syndrome (CRS), characterized by increased interleukin (IL)-6, IL-2, IL-7, IL-10, etc. Therefore, the treatment of cytokine storm has been proposed as a critical part of rescuing severe COVID-19. Several of the cytokines involved in COVID-19 employ a distinct intracellular signaling pathway mediated by Janus kinases (JAKs). JAK inhibition, therefore, presents an attractive therapeutic strategy for CRS, which is a common cause of adverse clinical outcomes in COVID-19. Below, we review the possibilities and challenges of targeting the pathway in COVID-19.

COVID-19 and Cytokine Release Storm

In December 2019, cases with a new type of viral pneumonia with unknown etiology occurred in Wuhan, China. A novel coronavirus SARS-CoV-2 was found to be a causal agent and the disease was named COVID-19 [1]. With the number of confirmed cases and deaths rapidly expanding, the COVID-19 pandemic is currently the focus of global attention.

Accumulating evidence indicate that patients with severe COVID-19 infection may present with CRS [2] where, similar to the pathogenesis of severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), higher plasma levels of cytokines, including IL-2, IL-6, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon- γ (IFN γ), macrophage inflammatory protein 1 α (MIP1A), and tumor necrosis factor- α (TNF- α) were found in patients with severe COVID-19 [3,4]. Extensive changes in these cytokines are related to the severity and prognosis of the disease [5]. Moreover, pathological findings from a patient who died of severe SARS-CoV-2 infection revealed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, indicating acute respiratory distress syndrome (ARDS) [6]. These findings suggested that CRS was involved in the progression of COVID-19.

COVID-19 induces a cytokine storm resembling the secondary hemophagocytic lymphohistiocytosis (sHLH), which had previously been reported in patients with SARS [7]. sHLH is a potentially life-threatening complication of the hyperinflammatory syndrome, commonly triggered by severe viral infections [8] and characterized by CRS, cytopenias, and multiorgan dysfunction [9]. Apart from the elevated serum cytokines, aberrantly activated macrophages are also a hallmark of sHLH and implicated as the source of the observed increased ferritin. Therefore, sHLH is also known as macrophage activation syndrome (MAS) [10].

Zhou *et al.* retrospectively found that serum ferritin was also elevated in COVID-19 fatalities [11]. Giamarellos-Bourboulis *et al.* investigated the immune responses in COVID-19 patients with

Highlights

Recent advances in the pathophysiologic understanding of COVID-19 infection have suggested a critical role of cytokine release syndrome (CRS) in severe COVID-19 patients.

Several inflammatory cytokines that are involved in CRS and correlate with adverse clinical outcomes in COVID-19 employ a distinct intracellular signaling pathway mediated by Janus kinases (JAKs).

JAK-STAT signaling may be an excellent therapeutic target for the development of much needed therapies for COVID-19.

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severe respiratory failure (SRF) and suggested that compared with typical bacterial community-acquired pneumonia and sepsis, severe COVID-19 patients are admitted in a relatively good clinical state but suffer from sudden deterioration of the clinical condition 7–8 days after the first symptoms. The immune classification revealed that all patients with COVID-19-related SRF have either immune dysregulation or MAS, both of which have overproduction of proinflammatory cytokines [12]. They further revealed that increased absolute lymphocyte blood count was observed in the six patients treated with the anti-IL-6R antibody, tocilizumab, which could partially rescue the immune dysregulation state driven by SARS-CoV-2 [12]. These findings lead one to opine that patients with COVID-19 who present with CRS- and sHLH-like serum cytokine elevations may benefit from treatments that target IL-6/IL-6R signaling and other cytokine signaling.

JAK-STAT Signaling Pathway in CRS

Cytokine and chemokine responses have been considered as a critical part of immunity and immunopathology during pathogenic human coronavirus infections [13]. Despite no direct evidence indicating the involvement of proinflammatory cytokines and chemokines in the pathology of COVID-19, the increased concentrations of the serum cytokines and chemokines were correlated with the disease severity and adverse clinical outcome [3]. An elevated serum level of proinflammatory cytokines was reported in severe COVID-19 patients, including IL-2, IL-4, IL-6, IL-7, IL-10, TNF- α , and IFN γ [3,11,14]. Among these, several cytokines employ one distinct intracellular signaling pathway mediated by Janus kinases (JAKs) (Box 1) [15]. For example, IL-6, which has been proven to act as a pivotal part in the CRS, activates the Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathway to confer various biological functions, including immune regulation, lymphocyte growth and differentiation, oxidative stress, and so on (Figure 1, Key Figure) [16,17]. Elevated serum IL-6 has been commonly reported in patients with severe COVID-19 and correlated significantly with nonsurvivors [11,18]. Consequently, researchers have started clinical trials evaluating the therapeutic efficacy of IL-6 antagonists in patients with COVID-19 [19]. These findings further support the rationale of repurposing licensed JAK inhibitors to improve the currently available clinical management strategies for COVID-19 and address the global urgency of mitigating the disease.

Potential of JAK Inhibitors in COVID-19

Multiple small-molecule JAK inhibitors are in use for the treatment of many inflammation-driven pathologies such as inflammatory bowel disease, rheumatoid arthritis (RA), and psoriasis [20]. There are several JAK inhibitors currently approved by the US FDA and European Medicine Association. These include ruxolitinib [21], baricitinib [22], tofacitinib [23], fedratinib [24], oclacitinib [25], and upadacitinib [26], with more candidate JAK inhibitors in clinical trials (Figure 1) [27–29]. Ruxolitinib, an oral JAK1/2 inhibitor, was the first approved JAK inhibitor for neoplastic diseases [30]. Preliminary studies have also supported the therapeutic implications of ruxolitinib in the context of sHLH and other cytokine-driven inflammatory syndromes [31]. Given a cytokine profile resembling sHLH, severe COVID-19 cases with immune dysregulation may benefit from ruxolitinib. Cao *et al.* recently reported the efficacy of ruxolitinib in patients with severe COVID-19, where patients receiving ruxolitinib plus standard-of-care (SoC) had a faster clinical improvement and a favorable safety compared with the control group [32]. Indeed, there are several clinical trials currently underway evaluating ruxolitinib in patients with severe COVID-19 (Table 1).

Studies have shown that SARS-CoV-2 shares the same cell entry receptor, angiotensin converting enzyme II (ACE2), as SARS-CoV and it binds to the ACE2 receptors to infect host cells mainly through endocytic pathways (Figure 2) [33]. By using artificial intelligence-derived

Box 1. The JAK-STAT Pathway

The Janus kinases (JAKs) are a family of receptor-associated tyrosine kinases. This small family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), which can transmit extracellular signals from many proinflammatory cytokines to activate signal transducers and activators of transcription (STATs) [40]. The canonical JAK-STAT pathway is initiated upon high-affinity interaction between extracellular signaling cytokines and their cognate receptors (Figure 1). This interaction leads to the apposition of receptor-associated JAKs and STAT phosphorylation. The phosphorylated STATs form dimers, are translocated into the nucleus and bind to DNA, and then transmit extracellular cytokine signals into a transcriptional response (Figure 1) [15]. The JAK-STAT signal pathway is also regulated by different mechanisms of negative regulators, such as the suppressors of cytokine signaling (SOCS) proteins, which act as a classical negative feedback circuit that could inactivate the JAKs and block the access of the STATs to receptor binding sites (Figure 1) [74].

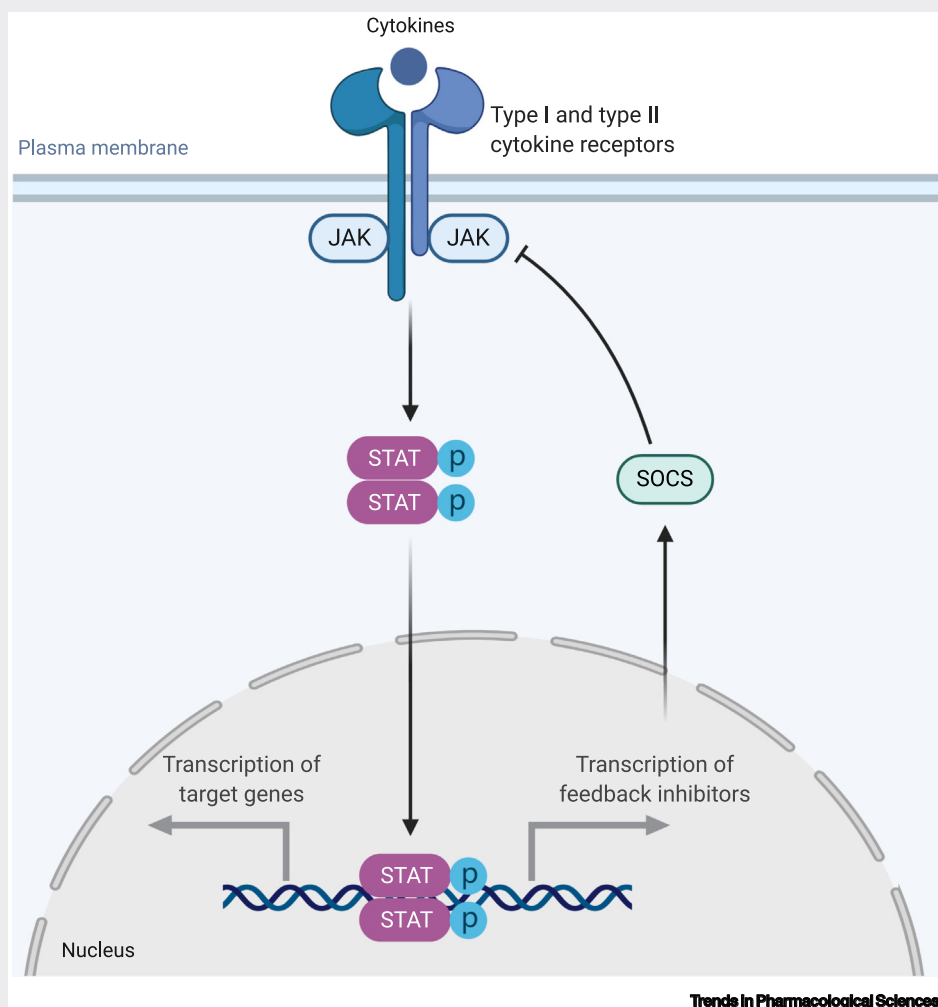
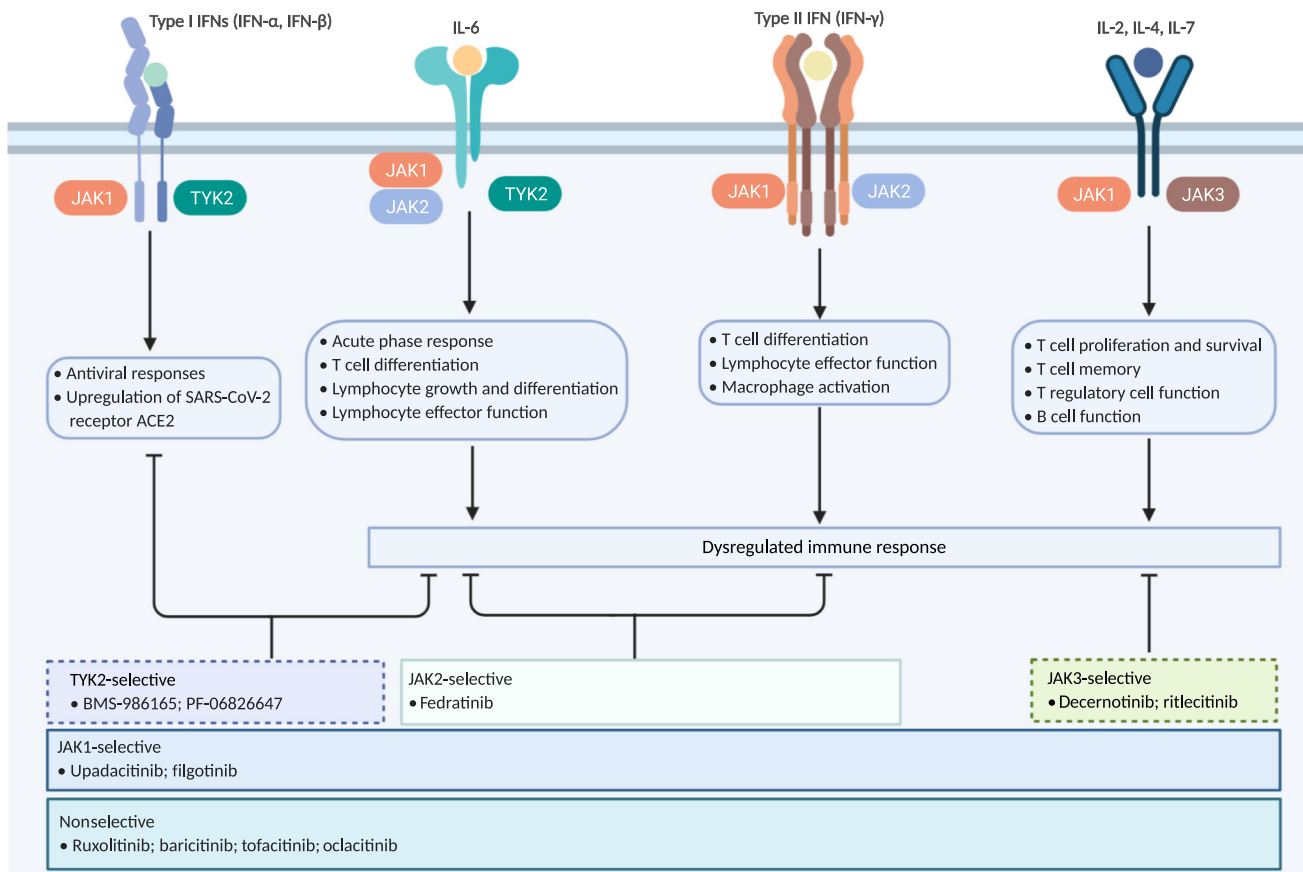


Figure 1. Schematic Showing the JAK-STAT Signaling Pathway. Abbreviations: JAK, Janus kinase; SOCS, suppressors of cytokine signaling; STAT, signal transducers and activators of transcription.

knowledge graph, Richardson *et al.* initially reported that baricitinib (JAK1/2 inhibitor) may affect the cellular viral entry of SARS-CoV-2 because of potential inhibitory effects on the known regulators of endocytosis, such as AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK) [34]. Moreover, the therapeutic dose of baricitinib at either 2 or 4 mg once daily is sufficient to effectively inhibit AAK1 and GAK [34]. Stebbing *et al.* later confirmed the anticytokine and antiviral activity of baricitinib *in vitro* experiments and reported that treatment with baricitinib

Key Figure

Schematic Showing JAK-Dependent Cytokines That Are Involved in the Development of COVID-19 and the JAK-Associated Receptors Each Interacts With



Trends in Pharmacological Sciences

Figure 1. The types of cellular responses elicited by these interactions are shown. The FDA-approved (unbroken boxes) and candidate JAK inhibitors in clinical trials (in broken boxes), along with their selectivity, are also shown. Abbreviations: ACE2, angiotensin converting enzyme II; IFN, interferon; IL, interleukin; JAK, Janus kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TYK2, tyrosine kinase 2.

improved the clinical condition in four patients with COVID-19 [35]. As baricitinib has minimal interaction with CYP enzymes (involved in drug metabolism in the body) and low plasma protein binding, it may be a good candidate for combination therapy with other promising treatments, such as remdesivir (an antiviral in clinical trials for COVID-19) [36].

Indeed, Spinelli *et al.* recently highlighted the potential role of baricitinib in the management of COVID-19 patients [37]. Results from a pilot study by Cantini *et al.* evaluated the safety and efficacy of baricitinib therapy in 12 patients with moderate COVID-19. Greater clinical improvements were observed in patients receiving baricitinib with no observed infections and hematologic adverse effects till 2 weeks post-treatment [38], leading clinicians to believe that short-term use of baricitinib (1–2 weeks) is less likely to promote significant infection but may be able to reduce viral replication and the aberrant host inflammatory response on therapeutic dosing. These

Table 1. Ongoing Trials with JAK Inhibitors for COVID-19 (as of 11 June 2020)^a

Name	Mode of action	Patient category	Use	Primary endpoint	Estimated enrollment	Clinical trial identifier
Ruxolitinib	JAK1 and JAK 2 inhibitor	COVID-19-associated ARDS	Compassionate use: ruxolitinib	To evaluate the 28-day mortality rate of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC compared with placebo + SoC therapy, in participants with COVID-19-associated ARDS who require mechanical ventilation	500	NCT04377620 ^b
		Patients with COVID-19-associated CRS	Phase III: ruxolitinib	The proportion of patients who die, develop respiratory failure (require mechanical ventilation), or require ICU care	402	NCT04362137
		COVID-19	Phase II: ruxolitinib	Patients achieving 25% reduction in hyperinflammation score compared with baseline at day 7	200	NCT04338958
		ARDS due to COVID-19	Phase II: ruxolitinib	Evaluate the efficacy of ruxolitinib in the treatment of COVID-19 ARDS	100	NCT04414098
		COVID-19	Phase II: ruxolitinib plus simvastatin	Percentage of patients who develop severe respiratory failure	94	NCT04348695
		COVID-19	Phase II/III: ruxolitinib	Safety (Phase II) and efficacy (Phase II and III) of ruxolitinib	80	NCT04348071
		COVID-19	Phase II: colchicine, ruxolitinib, secukinumab, and standard care	Change from baseline in clinical assessment score	70	NCT04403243
		COVID-19 pneumonia	Compassionate use: ruxolitinib	Proportion of patients with COVID-19 pneumonia who become critically ill; all-cause mortality rate; average duration of hospital stay; number of occurrences of secondary infections	64	NCT04331665
		COVID-19	Phase II: intravenous anakinra and ruxolitinib	IL-1 and IFN γ inhibition during COVID-19 inflammation	50	NCT04366232
		COVID-19	Phase I/II: ruxolitinib	Recovery from pneumonia characterized by ceasing of respiratory symptoms	20	NCT04334044
		COVID-19 positive patients with PENN grade 2, 3, 4 CRS	Pilot study: therapeutic plasma exchange alone or in combination with ruxolitinib	Greater than or equal to 33% decrease in cytokine load in one-third or more participants	20	NCT04374149
		Severe COVID-19	Phase II: ruxolitinib	Overall survival through 28 days after registration into trial	15	NCT04359290
		ARDS with COVID-19 infection	Compassionate use: ruxolitinib	Number of patients who avoid mechanically assisted ventilation in ARDS in patients with SARS-CoV-2	13	NCT04361903
		CRS due to COVID-19	Compassionate use: ruxolitinib	To provide ruxolitinib through an expanded access program for the treatment of cytokine storm due to COVID-19 in the United States to patients who are eligible but not able to be hospitalized or who are hospitalized with a clinical diagnosis and/or positive test for SARS-CoV-2 infection		NCT04355793

(continued on next page)

Table 1. (continued)

Name	Mode of action	Patient category	Use	Primary endpoint	Estimated enrollment	Clinical trial identifier
		Severe/very severe COVID-19 illness	Compassionate use: ruxolitinib	To allow access to ruxolitinib for eligible patients diagnosed with severe/very severe COVID-19 illness		NCT04337359
		Severe COVID-19	Compassionate use: ruxolitinib in combination with MSCs	Safety and efficacy of ruxolitinib; improvement rates at 7 days and 1 month, the cure rates at 2 months		ChiCTR2000029580 ^{iv}
Baricitinib	JAK1 and JAK2 inhibitor	COVID-19	Phase III: convalescent plasma, sarilumab, hydroxychloroquine, baricitinib, intravenous and subcutaneous placebo, or oral placebo	All-cause mortality or need of invasive mechanical ventilation	1500	NCT04345289
		COVID-19	Phase IV: baricitinib and ravulizumab	Time to incidence of the composite endpoint of: death, mechanical ventilation, ECMO, cardiovascular organ support, or renal failure	1167	NCT04390464
		COVID-19	Phase III: combination of baricitinib and remdesivir compared with remdesivir alone	Time to recovery	1032	NCT04401579
		COVID-19	Phase II: the study includes four arms: (i) lopinavir/ritonavir; (ii) hydroxychloroquine sulfate; (iii) baricitinib; and (iv) sarilumab.	Clinical status of subject at day 15	1000	NCT04321993
		COVID-19	Observational: baricitinib or anakinra	Mortality for all causes	576	NCT04362943
		COVID-19	Observational: specific treatments, including but not limited to baricitinib	Composite of death and mechanical ventilation	400	NCT04365764
		COVID-19	Phase III: baricitinib	Percentage of patients requiring transfer to ICU; percentage of patients requiring transfer to ICU	200	NCT04320277
		COVID-19 pneumonia	Phase II: hydroxychloroquine together with baricitinib, imatinib, or early lopinavir/ritonavir	Time to clinical improvement	165	NCT04346147
		COVID-19	Observational: specific treatments, including but not limited to baricitinib	Composite of death and mechanical ventilation	143	NCT04366206
		COVID-19	Phase II: baricitinib	Need of invasive mechanical ventilation	126	NCT04393051
		COVID-19	Phase II/III: baricitinib	Safety (Phase II) and efficacy (Phase II and III) of baricitinib	80	NCT04340232
		COVID-19	Phase II: baricitinib	Proportion of patients requiring invasive mechanical ventilation or dying	59	NCT04373044
		COVID-19 pneumonia	Phase II: baricitinib	Response to treatment: absence of moderate to severe oxygenation impairment	13	NCT04399798
		COVID-19 pneumonia	Phase II/III: baricitinib + lopinavir/ritonavir	To assess the safety of baricitinib combined with antiviral (lopinavir-ritonavir) in terms of incidence rate of serious or nonserious adverse events	12	NCT04358614

Table 1. (continued)

Name	Mode of action	Patient category	Use	Primary endpoint	Estimated enrollment	Clinical trial identifier
Tofacitinib	JAK1, JAK 2, JAK3, and TYK2 inhibitor	COVID-19	Phase II: tofacitinib	Clinical status using ordinal scale	256	NCT04412252
		COVID-19	Phase II: tofacitinib plus hydroxychloroquine versus hydroxychloroquine	Prevention of severe respiratory failure requiring mechanical ventilation	116	NCT04390061
		COVID-19	Phase II: tofacitinib	Disease severity	60	NCT04415151
		SARS-CoV-2-related interstitial pneumonia	Phase II: tofacitinib	Rate of patients needing mechanical ventilation, admission to the ICU, death, and adverse events	50	NCT04332042

^aAbbreviations: ARDS, acute respiratory distress syndrome; BID, twice a day; CRS, cytokine release storm; ECMO, extracorporeal membrane oxygenation; MSCs, mesenchymal stem cells; SoC, standard of care.

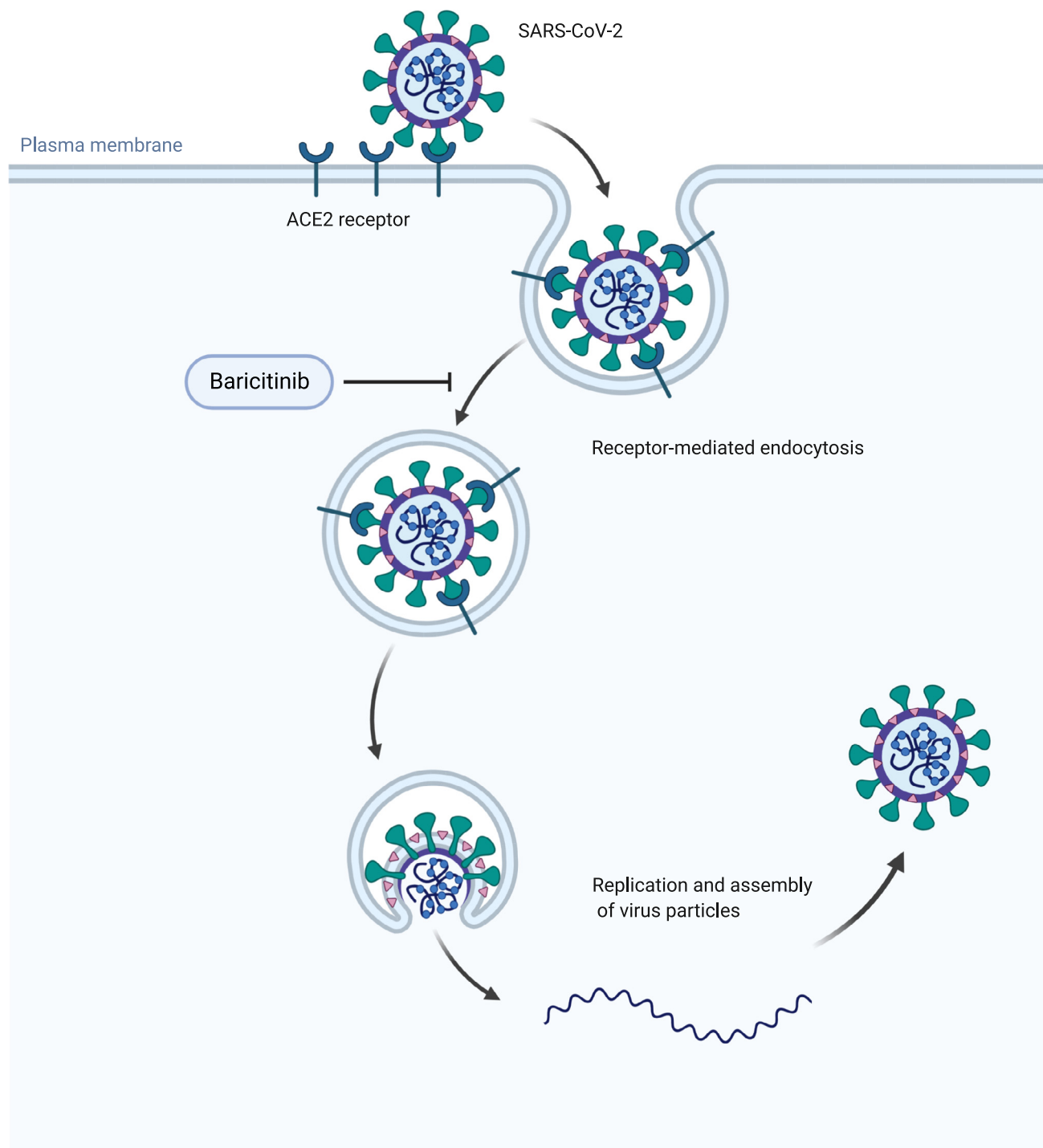
data encourage the further evaluation of baricitinib in larger, randomized trials. As of June 11 2020, several clinical trials are evaluating the potential role of baricitinib in the treatment of COVID-19 (Table 1); although it should be noted that the effect against viral endocytosis at tolerated doses only applies to baricitinib. Whether other JAK inhibitors share the same effect remain to be discovered.

Tofacitinib is an effective oral pan-JAK inhibitor that is approved for use in RA, an autoimmune and inflammatory disease where cytokines play an important role in the disease pathogenesis [39]. It is a specifically potent JAK3 and TYK2 inhibitor (EC50 less than 5 nM) [40] and thus can effectively block IL-2, IL-4, IL-6, and IL-7 (Figure 1). Jacobs *et al.* recently reported a case of SARS-CoV-2 infection in a woman with a 13-year history of ulcerative colitis, on tofacitinib. Despite testing positive for SARS-CoV-2, the patient remained on the treatment of tofacitinib because of improved clinical symptoms without holding therapy. Two weeks later, all symptoms have been resolved without the necessity of hospitalization [41]. Although this does not prove that tofacitinib contributed to the recovery from COVID-19 in this case, it shows that the treatment of tofacitinib can potentially be continued in patients infected with SARS-CoV-2. While studies that directly show benefits of use of tofacitinib in COVID-19 are not yet available, several clinical trials have been launched to investigate its potential benefits against the disease (Table 1).

Results of studies in clinical studies have demonstrated an important role of T helper 17 (Th17) cells and IL-17 in the pathogenesis of inflammation and autoimmunity [42]. Moreover, immature T helper (Th0) cells can differentiate into Th17 mainly in the presence of IL-6, a cytokine involved in CRS in COVID-19 that also employs JAK2 to activate downstream signal (Figure 1) [43]. Xu *et al.* investigated the pathological characteristics of a patient that succumbed to severe COVID-19 and found a remarkably high number of Th17 cells [6], indicating a Th17 type CRS involved in the severe immune injury progression in COVID-19. Wu *et al.* initially reported that fedratinib, a highly selective JAK2 inhibitor that has been approved for myelofibrosis [44], could inhibit the expression of IL-17 in murine Th17 cells [45]. These findings suggest a possible role for JAK2 inhibition and a potential use of JAK2 selective inhibitors, such as fedratinib, in blocking Th17-associated cytokine activation in COVID-19 management.

Implications on Antibacterial and Antiviral Immunity

More than half of COVID-19 patients are currently treated with antibiotics [46]. In a retrospective cohort study of inpatients with COVID-19 in Wuhan, Zhou *et al.* found that 15% of patients with



Trends in Pharmacological Sciences

Figure 2. Proposed Mechanism of Action of Baricitinib in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)-Infected Cells. SARS-CoV-2 enters cells through receptor-mediated endocytosis via interactions with receptors that include angiotensin converting enzyme II (ACE2), a cell surface protein on cells in the kidney, intestine, blood vessels, heart, and, importantly, alveolar epithelial type II cell. Baricitinib, a JAK inhibitor, can inhibit the process of receptor-mediated endocytosis and thus can be a viable therapeutic agent against COVID-19.

COVID-19 experienced secondary infection but the proportion among eventual nonsurvivors increased to 50% [11], highlighting that patients with COVID-19 may be susceptible to bacterial infection. Concerns regarding JAK inhibitors in treating COVID-19 have centered on the increased risk of infection. The JAK-STAT signaling pathway is considered to be crucial in the signal transduction of Type I IFNs (Figure 1), which are produced in response to bacterial infections [47] and are also major players in preventing viral replication at the early stage of infection [48,49]. The activation of Type II IFN (IFN γ) signaling, mediated by JAK1–JAK2 complexes, is known to enhance antibacterial immunity [47] and upregulate the expression of several IFN-stimulated genes that are major contributors to virus clearance [50]. These beneficial antibacterial and antiviral processes mediated by Type I IFN and IFN γ may be affected by JAK inhibition.

Indeed, previous studies have reported increased incidence of infections in patients receiving JAK inhibitors [51,52]. Bacterial infections, particularly urinary tract infections, were the most common adverse effects reported in patients treated with ruxolitinib [53]. Data from the European Medicines Agency suggested that upper respiratory tract infections were the most significant side-effect (14.7%) in patients treated with baricitinib. While the risk of infections associated with JAK inhibition appears to be similar to that associated with biologic disease-modifying anti-rheumatic drugs [51,54], patients treated with JAK inhibitors also have a different risk of viral infections. The most commonly reported complication was infections from herpes virus reactivation (e.g., herpes zoster, herpes simplex) [55]. Gaspari *et al.* reported two cases of COVID-19 who developed hematologic toxicity during the ruxolitinib treatment. One patient had a soft-tissue infection and the other developed herpes labialis. Ruxolitinib treatment was suspended in both patients because of the severe drug reactions [56].

However, although the IFN response is imperative for antibacterial and antiviral immunity, its role in human coronavirus infections has not been fully understood. Previous results in animal models of MERS-CoV infection have shown that Type I IFN administration was beneficial during early but not late stages of infection. Instead, administration of exogenous Type I IFNs in later stages increased the risk of lethality [57]. In line with these observations, Cameron *et al.* reported that IFN α as well as Type II IFN (IFN γ) signaling was prominent in patients with SARS who developed hypoxemia and died and low in the majority of SARS patients who recovered after a relatively moderate illness [58].

Blanco-Melo *et al.* recently reported that SARS-CoV-2 induces a limited IFN-I and -III response but a strong chemotactic and inflammatory response, marked by a significantly increased level of IL-6, IL-1 β , IL1RA, CCL2, and CCL8. They indicated that the low IFN expression in COVID-19 patients may be an antagonistic mechanism of SARS-CoV-2, which eludes the Type I IFN response to avoid immune cell activation and induction of IFN-stimulated genes (ISG) [59]. Further, it is worth noting that ACE2, the putative receptor of SARS-CoV-2, is an ISG expressed predominantly in human airway epithelial cells [60]. Whether the IFN-I treatment would lead to the upregulation of ACE2 and potentially enhance infection in putative target cells for SARS-CoV-2, or the use of JAK inhibitors targeting IFN signal transduction to reduce the risk of SARS-CoV-2 infection, requires further investigation. While further work is necessary to characterize the IFN responses in SARS-CoV-2 infection, these observations lead us to opine that the strategy of JAK inhibition can still be used in the management of COVID-19, especially in the stage of exuberant inflammatory cytokine production where patients failed to initiate a robust IFN response to SARS-CoV-2.

The point of concern can also be at least partially abrogated by use of selective JAK inhibitors. As an example, fedratinib, a JAK2 specific inhibitor with little inhibitory effects on JAK1, JAK3,

and TYK2 (Figure 1), would be beneficial over other pan-JAK inhibitors as fedratinib would not compromise Type I IFN (IFN α and IFN β)-mediated antiviral and antibacterial immunity. Likewise, tofacitinib, the pan-JAK inhibitor that is a specifically potent JAK3 and TYK2 inhibitor [40], could be more beneficial as it would not interact with the activation of Type II IFN (IFN γ)-mediated antibacterial immunity.

The Need to Identify Patient Cohorts Who Might Benefit from JAK Inhibitors

There is a significant need to identify patients who stand to benefit most from treatments with JAK inhibitors, as some groups of patients might benefit more than others. For example, previous studies have suggested that patients with an absolute neutrophil count less than 1×10^9 cells/l or an absolute lymphocyte count less than 0.5×10^9 cells/l should not be treated with baricitinib, or should temporarily interrupt baricitinib treatment [61]. Epidemiological studies for COVID-19 has revealed a subgroup of patients with severe symptoms, who have lower absolute lymphocyte count closer to the threshold levels [3,11,62]. These patients should not be treated with baricitinib.

Another example displaying the need to identify the best patients to treat with JAK inhibitors arises from the possible concern of thromboembolic risk associated with the use of JAK inhibitors. Increasing numbers of studies suggest that COVID-19 patients, especially those who are severely and critically ill, can develop coagulation abnormalities. Patients at high risk of venous thromboembolism also had an increased risk of bleeding and were associated with a worse prognosis [63]. The direct attack of SARS-CoV-2 on endothelial cells and the presence of the overwhelming CRS and antiphospholipid antibodies may potentially contribute to the coagulopathy in COVID-19 [64,65]. Cases of venous thromboembolism have been reported in patients treated with JAK inhibitors [66]. Therefore, JAK inhibitors should be administered with caution in COVID-19 patients with factors for thrombotic risk, such as old age, immobilization, mechanical ventilation, and central venous catheter use. Also, proper evaluation of the risk of venous thromboembolism risk before the use of JAK inhibitors has great importance in patients with COVID-19. Ultimately, these scenarios highlight that stratification of patients would be required to understand which cohort of patients might benefit from JAK inhibitors.

Concluding Remarks and Future Perspectives

The occurrence of CRS in COVID-19, which involves cytokines mediated by the JAK-STAT pathway, suggests that inhibition of the pathway can be a therapeutic strategy for the management of COVID-19. The potential role of JAK inhibitors in treating patients with COVID-19-associated CRS is an area of active investigation with multiple ongoing clinical trials (Table 1). This strategy can be more beneficial than inhibition of IL-6 only, a cytokine whose elevated levels have been commonly reported in patients with severe COVID-19 [18]. Recent studies have shown that the IL-6-JAK-STAT3 axis is closely involved in the development of severe COVID-19 [12,67]. As mentioned earlier, tocilizumab has been proposed as an effective drug in severe and critical COVID-19 patients and results from clinical trials of tocilizumab have been encouraging in improving the respiratory and laboratory parameters of patients with severe COVID-19 [19,68,69]. JAK inhibitors are also known to block the activity of IL-6 [15]. However, while IL-6 antagonists target one cytokine, IL-6, JAK inhibitors can simultaneously target actions of multiple cytokines inside the cells, including IL-2, IL-4, and IFN γ (Figure 1). Moreover, the theoretical benefit of JAK inhibition in the management of COVID-19-associated CRS would be applicable to currently available FDA-approved JAK inhibitors and also extend to candidate JAK inhibitors currently in clinical trials for other disease indications, that, while not yet approved by FDA, can in future be repurposed for COVID-19.

Outstanding Questions

What is the precise role of JAK-STAT in the dysregulated immune response in severe COVID-19?

Can we target JAKs and the molecular pathways they mediate in complex immune dysregulation, including COVID-19?

How can the efficacy and safety of currently available JAK inhibition therapies be improved?

Some of these candidate JAK inhibitors also have potential in addressing the concern underlying the use of JAK inhibitors on host antiviral and antibacterial immunity responses. For example, BMS-986165 and PF-06826647, TYK2 selective inhibitors currently in Phase II clinical trials for psoriasis [70] (Clinical Trial Numbersⁱ: NCT03881059 and NCT03895372) (Figure 1), can be tested in COVID-19. These inhibitors would potentially not interact with the Type II IFN response (IFN γ) necessary in antibacterial immunity but still inhibit other cytokines in COVID-19. Similarly, potential JAK3-specific inhibitors, such as decernotinib (VX-509), currently in a Phase II clinical trial for RA [71] (Clinical Trial Number: NCT01590459) and ritlecitinib (PF-06651600ⁱⁱⁱ) (Figure 1), currently in a Phase III clinical trial for alopecia areata (Clinical Trial Number: NCT04006457) can also be tested against COVID-19 either as monotherapy or in combination with IL-6/IL-6R antagonists. These JAK inhibitors can be expected to not interact with both Type I and Type II IFN-mediated antibacterial and antiviral responses, a concern when using pan-JAK inhibitors currently in clinical trials for COVID-19.

Such immunosuppressive therapies may be limited by the side effects and contraindication to some of these regimes, which emphasizes the need to identify the patients who stand to benefit most from such treatments, as discussed earlier. Additionally, results from ongoing clinical trials (Table 1) would also be needed to confirm the optimum time and dosing regimens to administer JAK inhibitors in COVID-19. Finally, the identification of alternative targeted therapeutics with greater isoform selectivity, while minimizing adverse reactions, is the need of the hour. In this regard, the negative feedback loop that regulates JAK-STAT signaling via suppressor of cytokine signaling (SOCS) (Box 1) may also provide novel mechanisms of action to generate new therapeutics, such as SOCS mimetics or stabilizers for management of COVID-19 (see Outstanding Questions) [72,73]. In summary, JAK inhibition appears to be an attractive therapeutic option for the development of much needed therapies in view of the global urgency of ameliorating the COVID-19 pandemic. The full exploitation of these opportunities requires a better understanding of the mechanisms involved in the disease.

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Disclaimer Statement

Dr Jianfeng Zhou is the PI who designed a prospective, multicenter, single-blind, randomized controlled Phase II trial involving patients with severe COVID-19 to evaluate the efficacy and safety of ruxolitinib. This trial is registered at www.chictr.org.cn as ChiCTR-OPN-2000029580.

Resources

ⁱwww.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf

ⁱⁱ<https://clinicaltrials.gov/>

ⁱⁱⁱwww.pfizer.com/science/drug-product-pipeline

^{iv}www.chictr.org.cn/

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