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Review Article

Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment

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ABSTRACT

Approximately 15% of patients with coronavirus disease 2019 (COVID-19) experience severe disease, and 5% progress to critical stage that can result in rapid death. No vaccines or antiviral treatments have yet proven effective against COVID-19. Patients with severe COVID-19 experience elevated plasma levels of pro-inflammatory cytokines, which can result in cytokine storm, followed by massive immune cell infiltration into the lungs leading to alveolar damage, decreased lung function, and rapid progression to death. As many of the elevated cytokines signal through Janus kinase (JAK)1/JAK2, inhibition of these pathways with ruxolitinib has the potential to mitigate the COVID-19–associated cytokine storm and reduce mortality. This is supported by preclinical and clinical data from other diseases with hyperinflammatory states, where ruxolitinib has been shown to reduce cytokine levels and improve outcomes. The urgent need for treatments for patients with severe disease support expedited investigation of ruxolitinib for patients with COVID-19.

1. Cytokine storms and the pathogenesis of COVID-19

Coronaviruses are common human and mammalian positive-strand RNA viruses [1]. In December 2019 a new strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the pathogenic cause of coronavirus disease 2019 (COVID-19). As of April 21, 2020, there were 2,397,217 confirmed cases of and 162,956 deaths from COVID-19 worldwide [2].

Although most patients with COVID-19 experience only mild-to-moderate disease, approximately 15% progress to severe pneumonia, and 5% develop acute respiratory distress syndrome (ARDS), septic shock, and/or multiple organ failure, which can rapidly lead to death [3]. No vaccines or specific antiviral treatments have yet proven effective against COVID-19; current clinical management consists of palliative treatments with organ support to moribund patients. Understanding the immunopathologic mechanism and appropriately targeting the key pathways involved has the potential to minimize pulmonary immune injury and mortality.

Following infection, SARS-CoV-2 binds to alveolar epithelial cells and activates innate and adaptive immune responses [1]. $CD4^+$ and $CD8^+$ T cells play an important role in balancing the adaptive immune response against pathogens and the potential development of autoimmunity or excessive inflammation [4]. Activation of cytotoxic $CD8^+$ T cells is vital for clearing virus from infected cells but also induces immune injury in tissues [5]. On the other hand, rapidly activated

Abbreviations: ARDS, acute respiratory distress syndrome; BID, twice daily; CHK2, checkpoint kinase 2; cMET, mesenchymal to epithelial transition; COVID-19, coronavirus disease 2019; EN-RAGE, extracellular newly identified receptor for advanced glycosylation end products–binding protein; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis; IC_{50}, half maximal inhibitory concentration; ICAM-1, intracellular adhesion molecule 1; IFN-γ, interferon gamma; IL, interleukin; IP-10/CXCL10, interferon gamma–induced protein 10; JAK, Janus kinase; MCP-1, monocyte chemotactic protein-1; MF, myelofibrosis; MIP-1α, macrophage inflammatory protein-1α; MMP-2, matrix metalloproteinase 2; PET, post–essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV, post–polycythemia vera myelofibrosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SR-aGVHD, steroid-refractory acute graft-versus-host disease; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; TPO, thrombopoietin; Tyk2, tyrosine kinase 2; VCAM-1, vascular adhesion molecule 1; VEGF, vascular endothelial growth factor.

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$CD4^+$ T cells become pathogenic T helper 1 cells that generate pro-inflammatory cytokines and chemokines [6]. The marked production of cytokines and chemokines leads to recruitment of lymphocytes and leukocytes to the site of infection; however, a massive release of cytokines can occur as part of a positive feedback loop associated with immune response amplification, resulting in cytokine release syndrome, or a "cytokine storm" [1].

Cytokine storm appears to be a common manifestation in severe COVID-19. Compared with healthy controls, patients with COVID-19 experienced elevated plasma levels of interleukin (IL)-1β, IL-1Rα, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-17, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-γ), interferon gamma–induced protein 10 (IP-10/CXCL10), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, platelet-derived growth factor-BB, MIP-1β, basic fibroblast growth factor, tumor necrosis factor alpha (TNF-α), and vascular endothelial growth factor [7]. Furthermore, patients admitted to the intensive care unit had higher plasma levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNF-α compared with patients who did not require critical care. The high levels of pro-inflammatory cytokines lead to massive immune cell infiltration of the lungs in patients with COVID-19, resulting in alveolar damage, decreased lung function, and rapid progression to death [7,8]. Indeed, respiratory failure from ARDS is the leading cause of mortality associated with COVID-19 [9,10].

Among the cytokines implicated in COVID-19–associated cytokine storm, several signal predominantly via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. IL-2, IL-6, IL-7, IL-10, IFN-γ, G-CSF, and GM-CSF are dependent on JAK1, JAK2, or both; furthermore, IP-10, MCP-1, and MIP-1α are IFN-γ dependent [11,12]. TNF-α has been shown to activate JAK/STAT signaling in a TNF receptor 1–dependent manner [13,14]. These data suggest that JAK inhibition could ameliorate the hyperinflammatory state associated with severe COVID-19.

2. Ruxolitinib

Ruxolitinib (INCB018424) is a selective inhibitor of JAK1 and JAK2 that is approved for the treatment of myelofibrosis (MF), polycythemia vera, and steroid-refractory acute graft-versus-host disease (SR-aGVHD) [15]. The in vitro pharmacology of ruxolitinib has been studied using enzymes and cell-based assays. In biochemical assays, ruxolitinib has demonstrated potent inhibition of JAK1 and JAK2, with half maximal inhibitory concentration (IC_{50}) values in the single digit nanomolar range (Table 1) [16]. Ruxolitinib has consistently demonstrated robust inhibition of JAK/STAT signaling in cell-based assays. In whole blood assays for the inhibition of phosphorylated STAT3 following stimulation with IL-6 (a prototype cytokine that signals through JAK1) or TPO (a cytokine that signals exclusively through JAK2), IC_{50} values were approximately 300 nM. Ruxolitinib has demonstrated specificity for JAK1 and JAK2 in biochemical assays compared with a broad panel of non-Janus kinases and other receptors and ion channels. Similarly, following incubation with ruxolitinib, the viability of cells with constitutive JAK/STAT signaling was effectively inhibited, whereas the viability of cells relying on constitutive activation of other tyrosine kinases (eg, BCR-ABL) was not affected, attesting to its on-target cellular activity.

Table 1
In vitro enzymatic and functional potency of ruxolitinib [16].

	IC_{50}, mean ± SD, nM	*N*
Enzyme assays		
JAK1	3.3 ± 1.2	7
JAK2	2.8 ± 1.2	8
JAK3	428 ± 243	5
Tyk2	19 ± 3.2	8
CHK2	>1000[a]	7
cMET	>10 000[a]	1
Whole blood assays		
IL-6 stimulation	282 ± 54	6
TPO stimulation	281 ± 62	4

CHK2, checkpoint kinase 2; cMET, mesenchymal to epithelial transition; IL-6, interleukin-6; JAK, Janus kinase; SD, standard deviation; TPO, thrombopoietin; Tyk2, tyrosine kinase 2.
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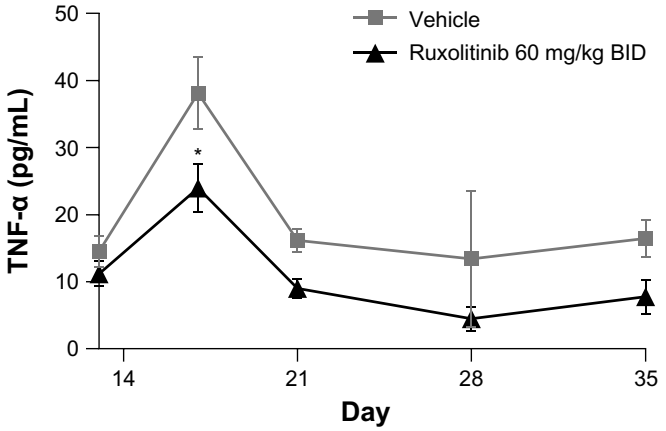
[a] Highest concentration evaluated.

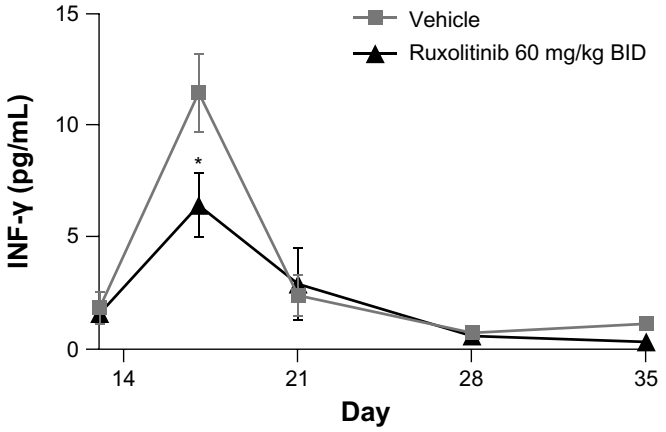
Suppression of cytokine signaling by ruxolitinib has also been observed in in vivo preclinical models. Treatment with ruxolitinib (90 mg/kg twice daily [BID]) resulted in significant suppression of elevated IL-6 levels and normalization of elevated TNF-α levels in mice bearing a *JAK2*^{V617F}-driven malignancy [16]. In a separate report, TNF-α and IL-12 levels were significantly lower on day 4 after allogeneic hematopoietic cell transplant in mice treated with ruxolitinib (30 mg/kg BID dosed on days −1 through 20) compared with those treated with vehicle [17]. On days 8 and 14, TNF-α levels remained significantly lower with ruxolitinib treatment.

The effect of ruxolitinib was also evaluated in a major histocompatibility complex–mismatch mouse model of aGVHD characterized by significant upregulation of inflammatory cytokines (IFN-γ, TNF-α, and IL-6) in peripheral blood (Fig. 1) [18]. Ruxolitinib (60 mg/kg BID) treatment significantly reduced the inflammatory cytokine milieu in circulation. No differences were observed in the proportion of peripheral $CD4^+$ or $CD8^+$ T cells in groups treated with ruxolitinib (Fig. 2), and there were no detrimental effects on donor engraftment. These alloreactive GVHD data are consistent with previous reports suggesting that ruxolitinib has immunomodulatory but not immune-depleting effects [17,19].

Data supporting reduction of the cytokine burden has emerged from multiple clinical studies with ruxolitinib. MF is a type of myeloproliferative neoplasm with progressive cytopenias, bone marrow fibrosis, and splenomegaly, driven by a hyper-inflammatory state [20]. Plasma levels of pro-inflammatory cytokines, including IFN-α, IL-6, IL-8, IL-16, IL-18, as well as C-reactive protein, intracellular adhesion molecule 1, vascular adhesion molecule 1, and matrix metalloproteinase 2, were significantly higher at baseline in patients with MF compared with healthy controls (Fig. 3A). After one cycle of therapy with ruxolitinib (28 days), levels of these pro-inflammatory biomarkers decreased (Fig. 3B). These changes were not related to *JAK2* mutational status or disease subtype, indicating that the effects of ruxolitinib in patients with MF are reflective of a broad anti-inflammatory effect. In addition, constitutive phosphorylation of STAT3 and/or STAT5 was observed at baseline in patients with MF, and a dose- and time-dependent reduction of phosphorylated STAT3 was observed after treatment with ruxolitinib. These observations suggest that the dampening of cytokine levels is related to on-target inhibition of JAK/STAT signaling by ruxolitinib. At starting doses of 15–20 mg BID, ruxolitinib resulted in reduced spleen size, improvement in MF-related symptoms, and improved overall survival in the phase 3 COMFORT-I and COMFORT-II studies of patients with intermediate-2 or high-risk MF [20,21]. Anemia and thrombocytopenia were the most frequent any-grade and grade 3–4 adverse events experienced.

SR-aGVHD is a condition characterized by an allogeneic hyperinflammatory response that can lead to organ damage and death [22]. Ruxolitinib was approved for SR-aGVHD based on the results of the phase 2 REACH1 trial [23]. Ruxolitinib 5 mg BID in combination with corticosteroids resulted in durable responses in this population of patients with poor prognosis. Proteomics analysis revealed robust changes in the expression of inflammatory mediators after treatment with





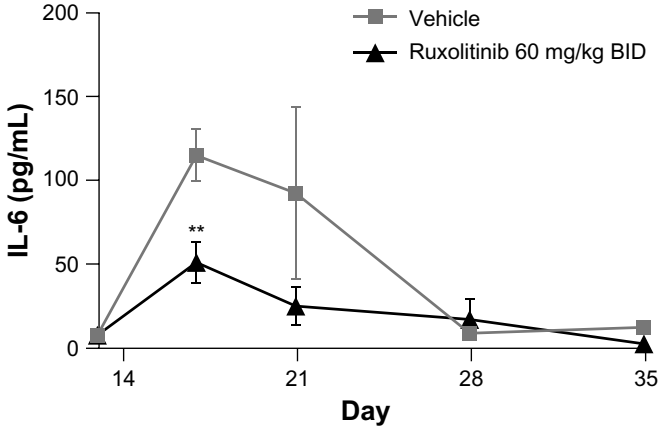
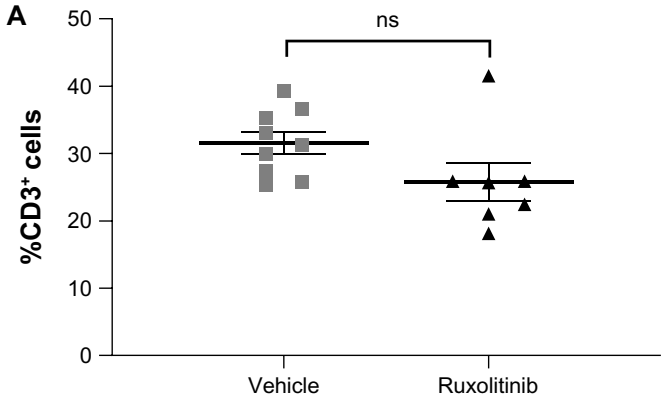
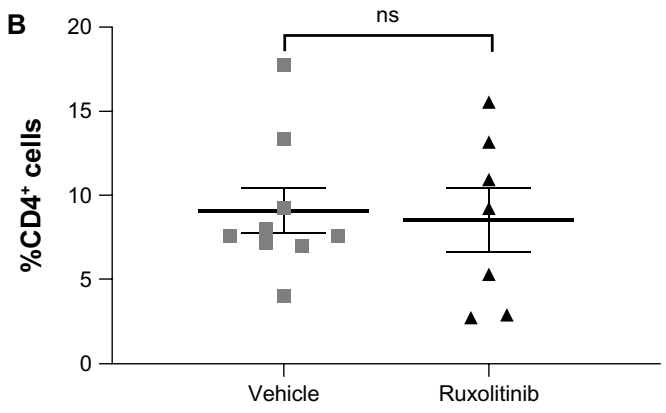


Fig. 1. Ruxolitinib downregulates inflammatory cytokines in blood [18]. The acute MHC mismatch GVHD model was induced via intravenous transfer of donor C57BL/6 mouse splenocytes and CD3-depleted bone marrow into total body irradiated–recipient BALB/c mice. On days 13, 17, 21, 28, and 35 post–donor cell transfer, blood was collected for analysis of inflammatory mediators. Plasma concentrations of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and interleukin-6 (IL-6) were quantified using a multiplex system analyzer (MAGPIX, EMD Millipore, Billerica, MA). *$P < .05$, **$P < .01$, versus the vehicle group, determined by one-way analysis of variance with Holm-Šidák's multiple comparison post-test. Data are presented as mean ± standard error of the mean.
n = 3–4 per group.





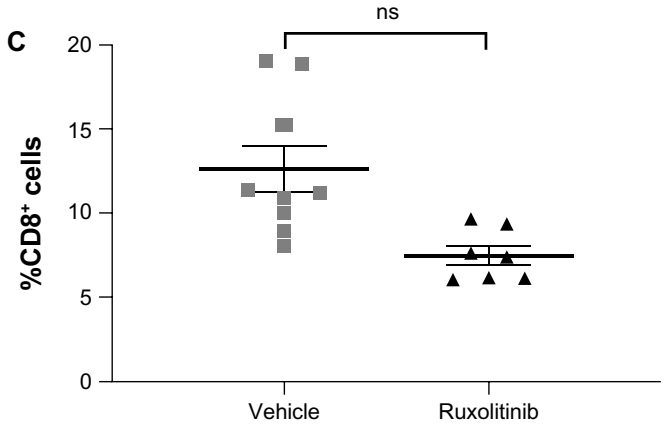


Fig. 2. Ruxolitinib does not reduce the proportion of T cells in peripheral blood in an acute MHC mismatch GVHD model [18]. After treatment with ruxolitinib 60 mg/kg BID starting on day 14 post–donor cell transfer, blood was collected by retro-orbital bleed on day 17 and analyzed by flow cytometry for the presence of (A) $CD3^+$, (B) $CD4^+$, and (C) $CD8^+$ cells. ns, not significant (determined by one-way analysis of variance with Holm-Šidák's multiple comparison post-test). Data are presented as individual values and mean ± standard error of the mean. n = 7–10 per group.

ruxolitinib and corticosteroids, with IL-2–receptor alpha among the most significantly downregulated proteins [24].

Hemophagocytic lymphohistiocytosis (HLH) is another disease with elevation of many pro-inflammatory cytokines (eg, IFN-γ, IL-2, IL-6, IL-10, IL-18, IP-10, MIP-1α, and TNF-α) that frequently results in cytokine storm [25,26]. Ruxolitinib (5–20 mg BID) has demonstrated improvement in symptoms and inflammatory markers in the treatment of patients with HLH [26–28]. In two consecutive patients treated with ruxolitinib, rapid reduction in fever was observed [28]. In a study of 34 patients with HLH, the overall response rate was 73.5% with a complete response rate of 14.7% [26]. In the 25 patients who

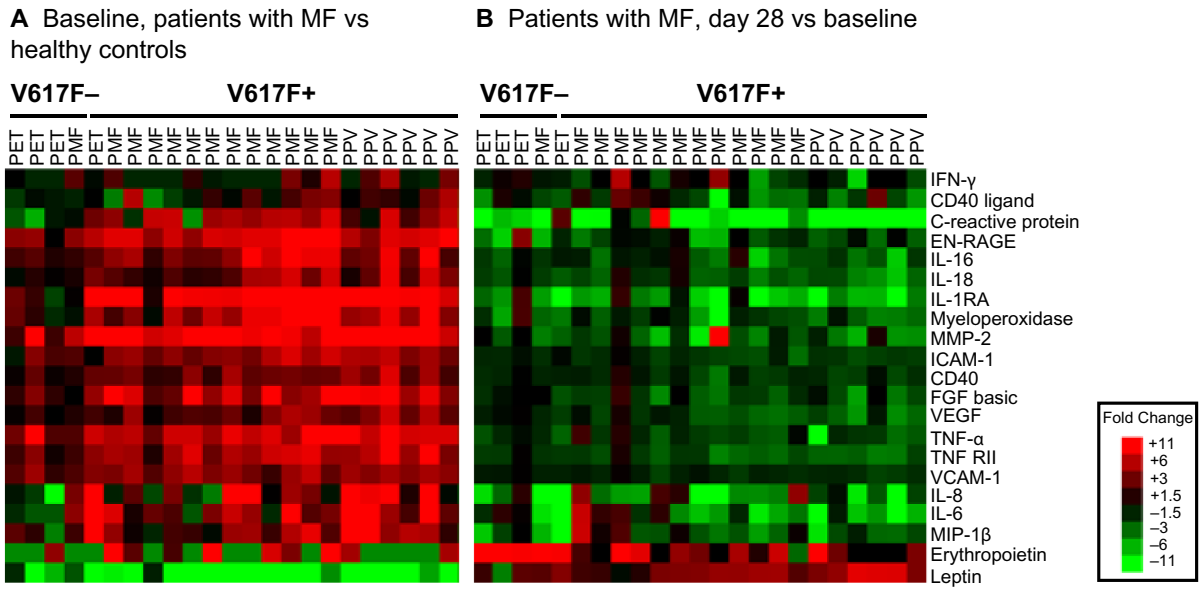


Fig. 3. Effect of ruxolitinib treatment on biomarkers [20]. Plasma levels of various biomarkers were evaluated in samples obtained from healthy controls and patients at baseline and after one cycle of therapy, with the use of the HumanMAP, version 1.6 panel (Rules-Based Medicine, Austin, TX). Plasma levels of selected markers are shown as heat maps (A and B). Each row constitutes one plasma marker, with the data for individual patients organized in columns. Green and red denote markers that are present at lower and higher levels, respectively, in baseline samples from patients relative to control samples. Biomarker data obtained from patients who received ruxolitinib (at a dose of 25 mg BID) after one cycle of treatment were compared with baseline values for the same patients (B). Green denotes markers that decreased with ruxolitinib treatment, and red denotes markers that increased with therapy.
EN-RAGE, extracellular newly identified receptor for advanced glycosylation end products–binding protein; FGF, fibroblast growth factor; ICAM-1, intracellular adhesion molecule 1; MMP-2, matrix metalloproteinase 2; PET, post–essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV, post–polycythemia vera myelofibrosis; VCAM-1, vascular adhesion molecule 1; VEGF, vascular endothelial growth factor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). From The New England Journal of Medicine, Verstovsek S et al, Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis, 363(12); 1117-27, Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

responded, there was a significant reduction in the levels of IFN-γ, IL-18, MIP-1α, and IP-10. In another study of five patients with secondary HLH and two additional patients treated off-protocol, 100% achieved a response at the time of the first assessment (day 14), with three patients achieving a complete response [27]. Furthermore, hematologic parameters including platelet, red blood cell, and neutrophil counts improved within the first week of ruxolitinib treatment. All patients treated on-protocol also experienced substantial improvements in ferritin and soluble IL-2 receptor concentrations. At 15 mg BID, ruxolitinib was generally well tolerated in this population.

3. Ruxolitinib as a treatment for COVID-19–associated cytokine storm

The sudden surge in hospitalization of patients with COVID-19 and the high mortality rate of hospitalized patients has encouraged treating physicians to look to repurpose approved drugs to lessen the burden of disease. Increased understanding of the immunopathology of severe COVID-19 [6–8] has led to the search for drugs that can be effective in controlling the rapid surge in cytokine levels. Cytokine storms can occur in several infectious and non-infectious (sterile) conditions, and the mechanisms of cytokine storm are conserved irrespective of the triggering event. Patients with severe COVID-19 have similar elevated pro-inflammatory cytokines as patients with HLH [25].

Monoclonal antibodies targeting IL-6 are likely to have an impact on the cytokine storm associated with COVID-19 given that IL-6 is among the cytokines reported to be elevated in those patients compared with healthy individuals. At the time of writing, anti–IL-6 antibody products tocilizumab and sarilumab are being evaluated in phase 3 studies [29,30]. However, other cytokines, such as IL-2, IL-7, IL-10, IFN-γ, G-CSF, and GM-CSF, are also elevated and may be equally or more important in the inflammatory response in patients with severe

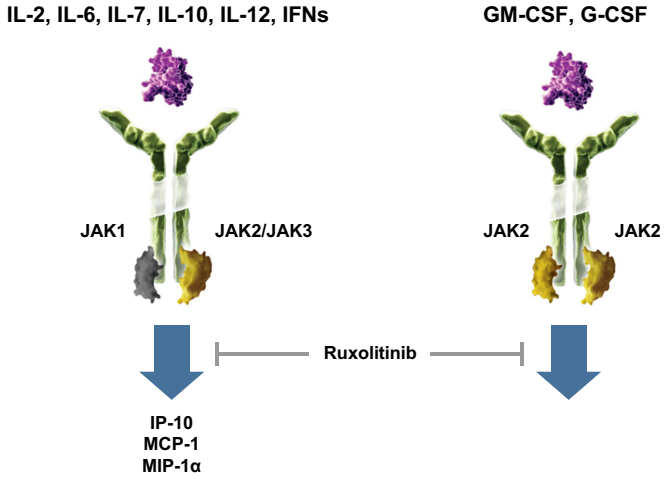


Fig. 4. Summary of COVID-19-associated cytokine signaling through JAK1/JAK2 and potential inhibition with ruxolitinib.

COVID-19. As these cytokines signal through JAK1 and/or JAK2, it is likely that treatment with ruxolitinib will result in broader anti-inflammatory activity than targeting any one of the cytokines alone (Fig. 4).

In addition to MF, SR-aGVHD, and HLH noted above, JAK inhibitors have shown promise in several autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriasis, and ulcerative colitis [31]. Ruxolitinib was the first JAK inhibitor approved in the United States and European Union, indicated first for MF; others have since been approved. There are notable differences in selectivity profiles between approved JAK inhibitors. Ruxolitinib is a balanced JAK1/JAK2

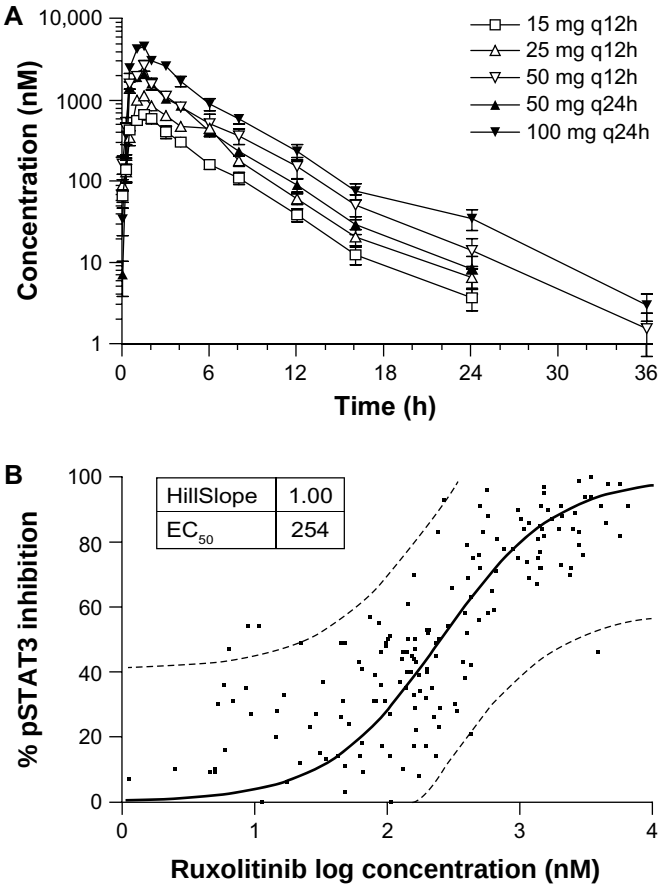


Fig. 5. Ruxolitinib dosing considerations [37]. (A) Ruxolitinib steady-state plasma concentrations (mean ± standard error) in healthy participants observed on day 10 of the multiple-dose study. (B) The pharmacokinetic–pharmacodynamic relationship established from ruxolitinib single-dose study. The solid line and dashed lines are the best-fit curve and 95% predictive interval, respectively. EC_{50}, half maximal effective concentration; q12h, every 12 h; q24h, every 24 h. From Shi JG et al. The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers. J Clin Pharmacol. 51(12);1644-54, Copyright © 2011 American College of Clinical Pharmacology, Published by John Wiley and Sons.

inhibitor with good selectivity over non-Janus kinases, tofacitinib is a pan-JAK inhibitor, upadacitinib is a JAK1 inhibitor, and fedratinib is a JAK2 inhibitor with activity against FLT-kinase and other non-kinase proteins. These differences result in distinct biomarker activity profiles. Singer et al. determined gene signatures of four different JAK inhibitors in a panel of 12 human primary cell systems and concluded that only ruxolitinib has a biomarker profile that is consistent with broad anti-inflammatory activity [32]. These differences in selectivity may in turn be responsible for the differentiated safety profiles. For example, fedratinib shows a high incidence of gastrointestinal intolerance and cases of Wernicke's encephalopathy [33], whereas tofacitinib has been associated with an increased risk for lymphomas as well as cardiovascular events in patients 50 years of age and older with at least one cardiovascular risk factor [34]. Non-melanoma skin cancers and elevated lipid parameters have occurred in patients treated with ruxolitinib [15]. Dose-dependent and reversible cytopenias have been commonly observed with ruxolitinib treatment in patients with MF, PV, and GVHD [15,20,21,35,36]. Use of ruxolitinib has also been associated with viral reactivation, including cytomegalovirus and herpes zoster virus [15,35], suggesting the potential for an increase in infections with ruxolitinib treatment.

The pharmacokinetic profile of ruxolitinib is characterized by rapid oral absorption and a short terminal elimination half-life of approximately 3 h (Fig. 5A) as well as a concentration-dependent and reversible pharmacodynamic effect (Fig. 5B) [37]. This profile is in contrast with that of antibodies such as tocilizumab, which has a half-life of approximately 2 weeks [38], and other JAK inhibitors such as fedratinib, which has a half-life of 62–78 h [39]. Thus, ruxolitinib is more conducive to short-term therapy and withdrawal as needed. Based on the similarity of the reported elevation of cytokine levels in COVID-19 to HLH and MF, dose ranges of 5 to 15 mg BID may result in adequate inhibition of cytokine signaling while minimizing adverse events. Furthermore, it is anticipated that patients would receive ruxolitinib for approximately 14 days, a brief time period that should minimize the risk of long-term infection or other complications, such as severe cytopenias. Although preclinical models and clinical data show a lack of any impact on T-cell function and immune response with ruxolitinib treatment at pharmacologically relevant doses [17,19,40], it would be prudent to both select patients who are likely to develop cytokine storm based on evolving clinical criteria such as H-score, and to identify the best time to initiate treatment based on onset of symptoms and other clinical indicators such as respiratory distress or the need for supplemental oxygen.

Taken together, these data suggest that ruxolitinib at pharmacologically achievable doses may be able to mitigate the hyperinflammatory state observed in patients experiencing COVID-19–associated cytokine storm. Indeed, early clinical evidence supports this premise. A team in Northern Italy has reported on the use of ruxolitinib in four of their hospitalized patients requiring supplemental oxygen, with clinical improvement seen in all four patients [41]. Furthermore, emerging data from ongoing investigator-initiated trials suggest a potential benefit of ruxolitinib with a manageable adverse event profile [42–45]. In a randomized trial of 43 patients in Wuhan, China, patients treated with ruxolitinib had a numerically shorter time to clinical improvement compared with those treated with standard of care (median 12 vs 15 days) and better outcome for survival (0 vs 3 deaths in the control arm) [42]. Importantly, although higher rates of grade 1–2 anemia and thrombocytopenia were observed with ruxolitinib in this study, there was no increase in grade 3–4 cytopenias, and patients receiving ruxolitinib experienced a significantly shorter time to improvement of lymphopenia compared with standard of care (median 5 vs 8 days; hazard ratio, 3.307 [95% CI, 1.097 to 8.409]; $P = .033$). Additionally, no increase in infections was seen with ruxolitinib treatment in these patients.

4. Conclusions

These encouraging early clinical results, combined with a thorough understanding of the evidence supporting the posited mechanism of action of ruxolitinib in COVID-19–associated cytokine storm and the urgent need for treatments in patients with severe disease, support expedited investigation of ruxolitinib for patients with COVID-19 in phase 3 clinical trials.

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Ethical approval

Not required.

Contributors

All authors have made substantial contributions to the analysis and

interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

Data statement

Not applicable; review of existing data.

Declaration of Competing Interest

All authors are employees of and own stock in Incyte Corporation.

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