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Design of Clinical Trials Evaluating Ruxolitinib, a JAK1/JAK2 Inhibitor, for Treatment of COVID-19–Associated Cytokine Storm

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Abstract

Recent insight into the pathophysiology of severe coronavirus disease 2019 (COVID-19) has implicated hyperactivation of the immune response, resulting in a "cytokine storm," which can lead to excessive immune-cell infiltration of the lungs, alveolar damage, decreased lung function, and death. Several cytokines implicated in the COVID-19–associated cytokine storm predominantly signal through the Janus kinase (JAK)/signal transducer and activator of transcription pathway. Ruxolitinib is a selective inhibitor of JAK1 and JAK2 that has been explored in small studies of patients with COVID-19–associated cytokine storm. Early clinical data from these trials, combined with a body of preclinical and clinical evidence in other inflammatory conditions, support exploration of the efficacy and safety of ruxolitinib in these patients in larger, well-controlled trials. Here we describe the designs of three such ongoing clinical trials. RUXCOVID is a phase 3 randomized, double-blind, multicenter study of ruxolitinib 5 mg twice daily (BID) vs placebo (both plus standard of care) in patients with COVID-19–associated cytokine storm. 369-DEVENT is a phase 3, randomized, double-blind, placebo-controlled, multicenter study of ruxolitinib 5 or 15 mg BID vs placebo (all plus standard of care) in patients with COVID-19–associated acute respiratory distress syndrome who require mechanical ventilation. Patients with severe COVID-19–associated cytokine storm who are ineligible for these trials can receive ruxolitinib through an Expanded Access Program (EAP) in the United States and similar programs outside of the United States. RUXCOVID and 369-DEVENT will provide insight into the efficacy and safety of ruxolitinib in hospitalized patients prior to or during ventilator use. If these trials are successful, ruxolitinib could improve outcomes for patients with COVID-19 as well as lessen the overall burden on the health care system.

Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global health crisis. Approximately 15% of patients with COVID-19 will progress to severe pneumonia, and 5% will develop acute respiratory distress syndrome (ARDS), septic shock, and/or multiple organ failure, resulting in rapid progression to death.[1] Recent insight into the pathophysiology of severe infection has implicated hyperactivation of the immune response, resulting in a "cytokine storm."[2] The overproduction of pro-inflammatory cytokines leads to excessive infiltration of the lungs by immune cells, resulting in alveolar damage, decreased lung function, and, ultimately, death (Figure 1A).[2,3]

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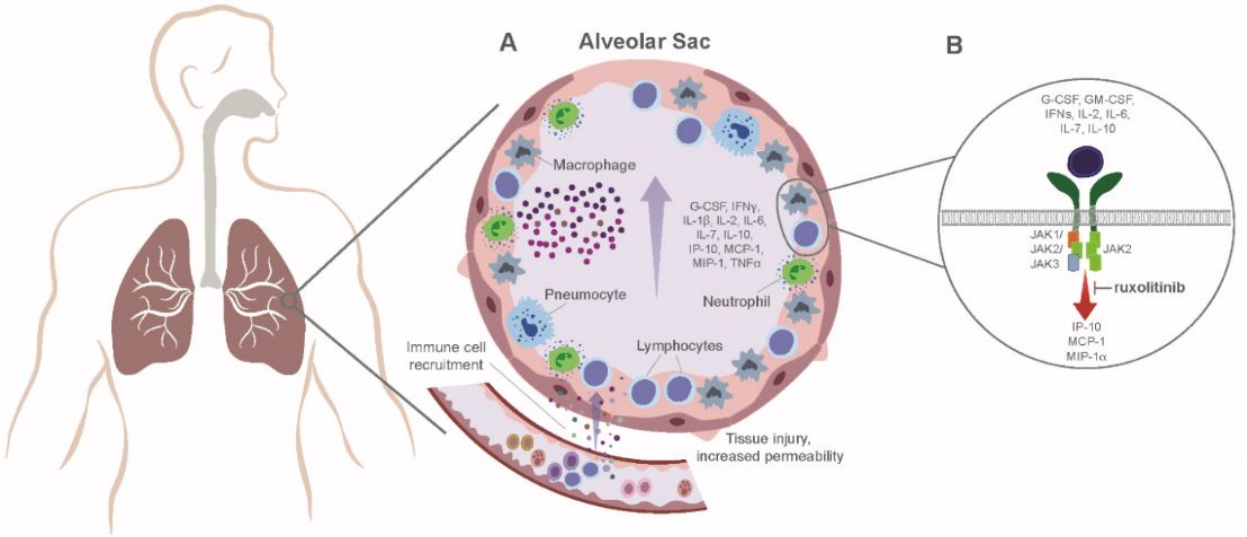
Fig. 1. Pathophysiology of impact of severe COVID-19 infection on lung alveoli. **A.** Activation of immune response to SARS-CoV-2 infection of lung cells leads to hyperproliferation of cytokines (cytokine storm); massive infiltration by immune cells follows, resulting in tissue injury and decreased lung function. **B.** Implicated cytokines are dependent on JAK signaling; ruxolitinib is a potent and selective inhibitor of JAK1 and JAK2 and could mitigate the hyperinflammatory state.

COVID-19, coronavirus disease 2019; CSF, colony stimulating factor; GM, granulocyte-macrophage; IFN, interferon; IL, interleukin; IP, interferon-gamma induced protein; JAK, Janus kinase; MCP, monocyte chemotactic protein; MIP, microphage inflammatory protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.



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Several cytokines implicated in the COVID-19–associated cytokine storm signal predominantly through a key cellular pathway, the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. Interleukin (IL)-2, IL-6, IL-7, IL-10, interferon gamma (IFN-γ), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are dependent on JAK1, JAK2, or both.[5,6] Additionally, IFN-γ–induced protein 10 (IP-10/CXCL10), monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein (MIP)-1α are dependent on IFN-γ. The convergence of signaling of multiple pro-inflammatory cytokines on the JAK/STAT pathway suggests that its inhibition could mitigate the hyperinflammatory state associated with severe COVID-19 (Figure 1B).

Ruxolitinib (INCB018424, INC424) is a selective inhibitor of JAK1 and JAK2 approved globally for the treatment of select patients with myelofibrosis (MF), polycythemia vera (PV), and steroid-refractory acute graft-versus-host disease (SR-aGVHD).[7,8] Evidence from preclinical models as well as clinical data in these and other disease states (e.g., cytokine release syndrome, hemophagocytic lymphohistiocytosis [HLH]) has shown that ruxolitinib treatment results in reduction in pro-inflammatory cytokine levels and improvement in related symptoms.[9–11]

Mechanistic and evidentiary support for the effect of ruxolitinib on the hyperinflammatory state led a number of independent teams across the world to test its use in patients with COVID-19–

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associated cytokine storm. In a small randomized trial of 43 patients in Wuhan, China, 22 patients were assigned to receive ruxolitinib plus standard of care (SoC), and 21 to placebo plus SoC.[12] The primary endpoint was time to clinical improvement (2-point improvement), as measured on a 7-point ordinal scale. Although not statistically significant, patients treated with ruxolitinib had a numerically shorter time to clinical improvement compared with controls (median 12 vs 15 days). At day 14, 90% of evaluable patients treated with ruxolitinib showed significant improvement in chest computed tomography (CT) scans compared with 62% of patients in the placebo group ($P = 0.0495$). In addition, cytokine levels decreased more in the ruxolitinib group than in the control group. Among patients with fever, more rapid fever reduction (within two days) was observed with ruxolitinib than placebo (four to five days). Furthermore, no patient receiving ruxolitinib deteriorated or died, whereas four patients in the placebo group experienced clinical deterioration, and three died due to respiratory failure. The median time to virus clearance was similar between patients receiving ruxolitinib and those in the placebo group (13 vs 12 days), and there was no significant difference in viral load between treatment groups at discharge ($P = 0.6$).

Although the patient populations are small, findings from the Wuhan study, combined with favorable outcomes in a retrospective chart review and case reports,[6,13] provide early clinical support for ruxolitinib as treatment for COVID-19–associated cytokine storm. Larger, well-controlled trials are needed to fully elucidate the efficacy and safety of ruxolitinib in these patients. Here we describe the designs of three ongoing clinical trials to assess ruxolitinib in patients with COVID-19–associated cytokine storm.

Methods

Ruxolitinib is being explored for treatment of COVID-19–associated cytokine storm in two phase 3 clinical trials (RUXCOVID and 369-DEVENT) and provided to patients ineligible for these trials through an Expanded Access Program (EAP) in the United States. Each of these three studies was designed and will be implemented, executed, and reported in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles outlined in the Declaration of Helsinki. Eligible patients may be included in a study only after providing Institutional Review Board/Independent Ethics Committee–approved informed consent. Patient or guardian/health proxy must provide informed consent prior to any study assessment; in the case of health proxy consent, the patient must be informed to the extent possible given their understanding.

RUXCOVID

RUXCOVID is a phase 3 randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of ruxolitinib in patients with COVID-19 pneumonia. Eligible patients are aged ≥12 years with confirmed SARS-CoV-2 infection and hospitalized or to be hospitalized with COVID-19 disease. Eligible patients must also meet ≥1 of the following criteria: pulmonary infiltrates (chest X-ray or CT scan), respiratory frequency ≥30/minutes, requiring supplemental oxygen, oxygen saturation ≤94% on room air, or arterial oxygen partial pressure (PaO_2)/fraction of inspired oxygen (FiO_2) <300 mmHg. Patients will be excluded if they have severely impaired renal function, other uncontrolled infections, current or history of active tuberculosis infection; are intubated or in an intensive care unit (ICU) for COVID-19 prior to screening; are currently intubated or intubated between screening and randomization; are in ICU

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at time of randomization; have evidence of liver cirrhosis; or have platelet count <50 × 10^9/L at screening.

Approximately 402 patients will be randomized (2:1, stratified by region) to receive oral ruxolitinib 5 mg twice daily (BID) or oral matching-image placebo for 14 days (or via nasogastric tube in patients unable to ingest tablets). Dose reductions/interruptions are permitted. An additional 14 days of randomized study treatment may be given at the discretion of the investigator if the patient has not experienced clinical improvement and the potential benefit outweighs the potential risk. SoC treatment will be allowed according to investigator's clinical judgement (e.g., supportive care, antiviral treatments, systemic corticosteroids, anticoagulants). Prohibited concomitant medications include other JAK inhibitors, aspirin doses >150 mg/day, and fluconazole >200 mg/day. Patients may discontinue treatment due to unacceptable toxicity or disease progression, or at the discretion of the investigator or patient. The overall study period is 29 days.

The primary study endpoint, clinical failure, is a composite efficacy endpoint defined as death, respiratory failure requiring mechanical ventilation, or ICU care by day 29. Secondary endpoints, assessed on day 15 and/or day 29, include clinical status (assessed on a nine-point ordinal scale); mortality rate; proportion of patients requiring mechanical ventilation; duration of hospitalization; time either to first of discharge or to a National Early Warning Score 2 (NEWS2) score of ≤2 (uninfected or not in hospital or ready for hospital discharge) maintained for 24 hours; change from baseline in SpO_2/FiO_2 ratio; proportion of patients with no oxygen therapy; and treatment-related adverse events (TRAEs), serious adverse events (SAEs), and changes in laboratory parameters and vital signs. Exploratory study endpoints include time to independence from noninvasive ventilation; time to independence from oxygen therapy; duration of ICU stay; duration of supplemental oxygen; duration of invasive mechanical ventilation; proportion of patients requiring treatment with tocilizumab, canakinumab, sarilumab, or anakinra; changes in serum ferritin, CRP, D-dimer, procalcitonin, and IL-6; and change in circulating inflammatory biomarkers or other molecular signatures related to COVID-19 disease biology.

This trial is a global collaboration between Incyte and Novartis, with sites recruiting in the United States, Germany, Italy, Russia, Spain, and the United Kingdom at the time of this writing. The estimated primary completion date is October 12, 2020.

369-DEVENT

369-DEVENT is a phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of ruxolitinib in patients with COVID-19–associated ARDS who require mechanical ventilation. Eligible patients are aged ≥12 years with confirmed SARS-CoV-2 infection (within two weeks of randomization), and are intubated and receiving mechanical ventilation due to COVID-19–associated ARDS. Patients must have a PaO_2/FiO_2 of ≤300 mmHg within 6 hours of randomization and have lung imaging (chest X-ray or CT scan) showing bilateral or diffuse pulmonary infiltrates. Patients will be excluded if they have severely impaired renal function; have other active uncontrolled infection including known active tuberculosis infection; are unlikely to survive for >24 hours from randomization; are currently receiving extracorporeal membrane oxygenation; are sharing a ventilator or coventilating with another patient; have evidence of liver cirrhosis; or have platelet count <50 × 10^9/L at screening. Patients are not permitted to have received treatment with anti–IL-6, IL-6R, IL-1RA, IL-1β, or GM-CSF

antagonists, or a Bruton's tyrosine kinase (BTK) inhibitor, within seven days of randomization or treatment with a JAK inhibitor within 30 days of randomization.

Approximately 500 patients will be randomized 2:2:1 (stratified by ARDS severity) to receive ruxolitinib 5 mg BID, ruxolitinib 15 mg BID, or matching placebo for 14 days. Dose reductions/interruptions are permitted. Study treatment can continue for an additional 14 days at the investigator's discretion. Medication will be provided through an enteric feeding tube after suspension in water. Patients who are extubated during the study may receive oral study treatment. All patients are eligible for SoC therapy according to the investigator's clinical judgement (e.g., supportive care, antiviral treatments). Treatment with concomitant JAK inhibitor or IL-6, IL-6R, IL-1RA, IL-1β, or GM-CSF antibodies; any investigational medication except antivirals being used to treat SARS-CoV-2 infection or ARDS; or aspirin >150 mg/day is not permitted. Patients may be discontinued early from treatment due to unacceptable toxicity, progression/worsening of COVID-19 ARDS, resolution/improvement of COVID-19 symptoms, and/or at the discretion of the investigator or patient. The overall study period is 29 days.

The primary study endpoint is the proportion of patients who die from any cause through day 29. Secondary endpoints include the number of ventilator-free days, ICU-free days, supplemental oxygen–free days, vasopressor-free days, and hospital-free days by day 29; clinical status (assessed on a nine-point ordinal scale) on days 15 and 29; change from baseline to days 3, 5, 8, 11, 15, and 29 in sequential organ failure assessment score; and TRAEs and SAEs, including clinically significant changes in laboratory parameters and vital signs. Exploratory study endpoints include proportion of patients requiring treatment with IL-6, IL-6R, IL-1RA, IL-1β, GM-CSF, and BTK- or JAK-directed therapies by days 15 and 29; change from baseline to days 15 and 29 in serum ferritin, CRP, D-dimer, procalcitonin, and IL-6; and change from baseline to days 15 and 29 in viral load and anti–SARS-CoV-2 antibody titer.

This US-only trial is open to recruitment and has an estimated primary completion date of July 29, 2020.

Expanded Access Program

In addition to the phase 3 clinical studies, an open-label EAP has been initiated in the United States to provide ruxolitinib for the emergency treatment of cytokine storm due to COVID-19. The protocol allows eligible patients with severe COVID-19–associated cytokine storm to receive ruxolitinib while it is being investigated for this indication. To qualify for this EAP, patients must be aged ≥12 years with confirmed SARS-CoV-2 infection or clinical diagnosis of COVID-19 if testing is not available, and must be unable to participate in other clinical trials of ruxolitinib in COVID-19. Patients must have disease severity making them eligible for hospitalization, with physician-determined evidence of cytokine storm, manifesting as respiratory rate >24 breaths/minute, SpO_2 <90% on ambient air, need for medical ventilation, ARDS, and/or multiple organ failure. Patients will be excluded if they have platelet counts $<50 \times 10^9$/L or inadequate liver function (alanine aminotransferase >4 × upper limit of normal [ULN] or direct bilirubin 4 × ULN and considered to be due to underlying liver dysfunction).

Ruxolitinib is recommended for oral use, but can be administered through a nasogastric tube for patients unable to ingest tablets. The recommended dose of ruxolitinib is 5 mg BID in most patients. Dose reductions/interruptions are permitted. For patients with moderate renal impairment or any degree of hepatic impairment and platelet counts between 50 and 100×10^9/L,

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the recommended dose is 5 mg once daily. For patients on dialysis, ruxolitinib should be administered after the dialysis session. Treatment will be given for seven days, and can be extended to a maximum of 14 days if the treating physician believes that clinical benefit is observed and treatment withdrawal criteria have not been met. Patients can receive or continue any concomitant medication (except aspirin >125 mg/day or any other JAK inhibitor), including anti-infective medications for COVID-19. Patients who require concomitant treatment with strong CYP3A inhibitors or anticoagulant/antiplatelet medications should be closely monitored.

The primary objective of this program is to provide ruxolitinib for the treatment of cytokine storm due to COVID-19 in the United States. The secondary objective is to monitor the safety (SAEs) in this setting. The total number of patients and investigational sites is not prospectively defined.

Discussion

Encouraging results have been observed in small, single-site studies of ruxolitinib for COVID-19–associated cytokine storm. These initial positive results with ruxolitinib, coupled with the biologic rationale of JAK inhibition to ameliorate the hyperinflammatory response in this condition, led to the initiation of these large phase 3 trials, the EAP in the United States and similar Managed Access Programs globally. It is anticipated that the phase 3 trials will reach their primary completion dates this summer/fall.

Based on the data from >10,000 patients treated with ruxolitinib in clinical programs for other conditions that exhibit a hyperinflammatory state similar to COVID-19 (i.e., MF, SR-aGVHD, and HLH), the primary clinical risk has been myelosuppression, which can result in anemia, thrombocytopenia, and increased infection. Cytopenias observed in patients with MF treated with ruxolitinib were dose-dependent and reversible. As COVID-19 is not a disease of the bone marrow, it is hypothesized that the myelosuppressive effects will be less pronounced in these patients. In support of this, low levels of hematologic toxicity were noted in the randomized trial conducted in Wuhan, China with a ruxolitinib dose of 5 mg BID; grade 3–4 lymphopenia occurred in one patient in each treatment group, and there were no grade 3–4 anemia, neutropenia, or thrombocytopenia events in the ruxolitinib group.[12]

In patients with MF and PV, ruxolitinib treatment has been associated with reactivation of herpes zoster virus, and increases in hepatitis B viral load in patients with chronic hepatitis B infections. This has led to discussion of the possibility that ruxolitinib could lead to an increase in COVID-19 viral load or decrease virus clearance. Given the low dose (≤5 mg BID in all but the most severe ventilated patients) and short course of therapy in these COVID-19 trials (seven to 14 days, with possible extension of 14 days), the anticipated risk of viral titer increase or reactivation of COVID-19 is considered to be minimal. In line with this expectation, patients in the Wuhan study who received ruxolitinib had a similar median time of virus clearance as the patients in the control group and a similar viral load at discharge. Interestingly, the mean peak level of SARS-CoV-2–specific IgM antibodies was higher in the ruxolitinib group than in the control group, while there was no between-group difference in IgG antibodies.

Public Health Implications

Ruxolitinib is not approved by the US Food and Drug Administration for use in patients with COVID-19. Insights gained from the large trials described herein may inform the optimal timing

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of treatment initiation and clinical characteristics of patients most likely to respond. A recently proposed staging system of COVID-19 includes three escalating stages of infection: stage I, early infection; stage II, pulmonary phase without (IIA) and with (IIB) hypoxia; and stage III, hyperinflammation phase.[14] Treatment of the first stage is primarily for symptomatic relief; however, an antiviral agent that demonstrates efficacy could provide some benefit during this early infection phase marked by mild symptoms and leukopenia. During the second stage, patients develop a viral pneumonia and bilateral infiltrates or ground glass opacities on imaging, while the immune response begins to switch from primarily viral response to primarily host inflammatory response. Patients in the second stage may experience hypoxia ($PaO_2/FiO_2 \leq 300$ mmHg), which may serve as a warning sign of impending deterioration and need for ventilation; during stage II, most patients would need to be hospitalized. Patients may still be treated with antiviral therapies, and could also begin careful use of corticosteroids or immunosuppressive agents upon development of hypoxia. The third stage is marked by extrapulmonary systemic hyperinflammation syndrome, with elevated markers of systemic inflammation. Multiorgan failure would manifest during this stage, and treatment with immunomodulatory agents to reduce inflammation would be appropriate. As prognosis is poor in patients with stage III disease, limiting progression from stage IIB or rapidly recognizing and treating the systemic inflammation in stage III disease could help to reduce mortality. Importantly, RUXCOVID, 369-DEVENT, and the EAP described herein are investigating ruxolitinib in patients with stage IIB or III COVID-19 infection. Hopefully, these trials will provide insights into which clinical markers will be most useful in determining the ideal timing of treatment initiation to control the host inflammatory response while minimizing adverse events.

RUXCOVID and 369-DEVENT will provide insight into the efficacy and safety of ruxolitinib in hospitalized patients prior to or during ventilator use. In these studies, ruxolitinib can be administered orally or via nasogastric tube, as required given the patient's ventilator status. If the phase 3 trials are successful, ruxolitinib may improve outcomes for patients—fewer or shorter intubations, more rapid recovery, and/or fewer deaths—and also lessen the burden on the health care system by reducing the number of patients requiring the most resource-intensive inpatient treatments.

About Incyte

Incyte is a Wilmington, Delaware-based, global biopharmaceutical company focused on finding solutions for serious unmet medical needs through the discovery, development, and commercialization of novel medicines. Since 2002, Incyte has remained committed to the relentless pursuit of science that can improve the lives of patients and make a difference in health care. Incyte is advancing a diversified portfolio of clinical candidates across indications in Oncology and Inflammation & Autoimmunity. For additional information on Incyte, please visit Incyte.com and follow @Incyte.

Incyte is providing ruxolitinib cost-free to patients with COVID-19. Questions or inquiries regarding RUXCOVID, 369-DEVENT, or the EAP should be made to U.S. Medical Information, 1-888-4MED-INFO (1-855-463-3463); medinfo@incyte.com.

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Declaration of interests

PBL, SY, PAS, and PKS are employed by and hold stock/shares in Incyte Corporation. BAK is employed by and holds stock/shares in Novartis Pharmaceuticals Corporation.

Contributors

All authors have made substantial contributions to the drafting the article or revising it critically for important intellectual content, and provided final approval of the version to be submitted.

References

1. Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... Zhong, N. S., & the China Medical Treatment Expert Group for Covid-19. (2020, April 30). Clinical characteristics of coronavirus disease 2019 in China. *The New England Journal of Medicine, 382*(18), 1708–1720. PubMed
2. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., . . . Cao, B. (2020, February 15). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497–506. PubMed https://doi.org/10.1016/S0140-6736(20)30183-5
3. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., . . . Wang, F. S. (2020, April). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory Medicine*, *8*(4), 420–422. PubMed https://doi.org/10.1016/S2213-2600(20)30076-X
4. McGonagle, D., Sharif, K., O'Regan, A., & Bridgewood, C. (2020, June). The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmunity Reviews*, *19*(6), 102537. PubMed https://doi.org/10.1016/j.autrev.2020.102537
5. Stark, G. R., Cheon, H., & Wang, Y. (2018, January 2). Responses to cytokines and interferons that depend upon JAKs and STATs. *Cold Spring Harbor Perspectives in Biology*, *10*(1), a028555. PubMed https://doi.org/10.1101/cshperspect.a028555
6. Won, C., Damsky, W., Singh, I., Joseph, P., Chichra, A., Oakland, H., . . . Chun, H. (2020, May 20). HiJAKing the SARS-CoV-2 cytokinopathy: Janus kinase inhibitors for moderate to severe COVID-19. Retrieved from https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3606658
7. Incyte Corporation. (2019, May). Jakafi (ruxolitinib) [package insert]. Wilmington, DE.
8. Novartis Pharma AG. (2019, May). Jakavi (ruxolitinib) tablets [EU summary of product characteristics]. Basel, Switzerland.
9. Ahmed, A., Merrill, S. A., Alsawah, F., Bockenstedt, P., Campagnaro, E., Devata, S., . . . Wilcox, R. A. (2019, December). Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: An open-label, single-centre, pilot trial. *The Lancet. Haematology*, *6*(12), e630–e637. PubMed https://doi.org/10.1016/S2352-3026(19)30156-5
10. Quintás-Cardama, A., Vaddi, K., Liu, P., Manshouri, T., Li, J., Scherle, P. A., . . . Verstovsek, S. (2010, April 15). Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: Therapeutic implications for the treatment of myeloproliferative

neoplasms. *Blood*, *115*(15), 3109–3117. PubMed https://doi.org/10.1182/blood-2009-04-214957

11. Verstovsek, S., Kantarjian, H., Mesa, R. A., Pardanani, A. D., Cortes-Franco, J., Thomas, D. A., . . . Tefferi, A. (2010, September 16). Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *The New England Journal of Medicine*, *363*(12), 1117–1127. PubMed https://doi.org/10.1056/NEJMoa1002028
12. Cao, Y., Wei, J., Zou, L., Jiang, T., Wang, G., Chen, L., . . . Zhou, J. (2020, July). Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *The Journal of Allergy and Clinical Immunology*, *146*(1), 137–146.e3. PubMed https://doi.org/10.1016/j.jaci.2020.05.019
13. La Rosée, F., Bremer, H. C., Gehrke, I., Kehr, A., Hochhaus, A., Birndt, S., . . . La Rosée, P. (2020, July). The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia*, *34*(7), 1805–1815. PubMed https://doi.org/10.1038/s41375-020-0891-0
14. Siddiqi, H. K., & Mehra, M. R. (2020, May). COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart and Lung Transplant*, *39*(5), 405–407. PubMed https://doi.org/10.1016/j.healun.2020.03.012