Cytokine storm release syndrome and the prospects for immunotherapy with COVID-19, part 4: The role of JAK inhibition

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■ ABSTRACT

This review focuses on an alternative strategy utilizing small molecules to inhibit a key signal-transduction pathway, the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. The JAK-STAT pathway mediates biologic activity for a large number of inflammatory cytokines and mediators.

■ INTRODUCTION

Previous parts of this series focused on the basic immunobiology of severe COVID-19 disease and the role of inflammatory cytokines and their select targeting in an effort to limit respiratory damage, coagulopathy, end-organ failure, and death.1 Figure 1 represents the idealized model in this series, and the current iteration remains relevant, though our granular understanding of immunopathogenesis has progressed. The term “COVID-19 cytokine storm”? still has relevance, though recently some have focused on meaningful quantitative (especially interleukin 6) and qualitative differences between the inflammatory phase of COVID-19 and inflammatory states observed in other relevant disease states such as acute respiratory distress syndrome. Despite such questioning, enthusiasm remains strong for therapeutic strategies that focus on limiting damaging effects of inflammatory mediators on host tissues. Most biologic therapies (ie, targeted therapies) currently under investigation in COVID-19 employ monoclonal antibodies produced by recombinant technology, capable of selectively attacking inflammatory phase 3, one cytokine at a time.

The lead rationale for utilizing JAK inhibitors in COVID-19 is based on an examination of the cytokines already known to be elevated in advanced COVID-19 disease and that act via the JAK-STAT signaling pathways (Table 1).4 This evaluation suggests that a broad-based inhibitory approach may be
beneficial in stage 3 disease (Figure 1). Broad-based inhibition, in contrast to single anti-cytokine based therapies with monoclonal antibodies, is appealing as data supporting the identification of a single cytokine as the clear upstream source of the inflammatory process have been problematic. As proof of concept, the kinase inhibitor, ruxolitinib, has been used successfully to treat refractory cytokine storm in patients with relapsed refractory hemophagocytic lymphohistiocytosis.5

A second rationale for employing JAK inhibition in COVID-19 stems from an analysis using artificial intelligence identifying a role for the JAK1 inhibitor baricitinib in inhibiting relevant inflammatory pathways, but also in providing evidence that the drug was capable of inhibiting other non-JAK kinases (ie, numb associated kinases or NAKs), which appear to be involved in viral entry.6 Thus, if this is true, baricitinib may have a structural and mechanistic advantage over other agents in this class because of its capacity to limit both inflammation and viral propagation. The original theoretical work is now supported by mechanistic ex vivo studies and forms the rationale for the investigation of this agent in randomized trials.7

Collectively, the potential for a broad-based immunosuppressive therapy with some antiviral activity is attractive, and the extensive experience of its use in non-COVID-19 immune diseases has also furthered our understanding of how to balance the benefits and risks when using this class of agents.8

### TABLE 1
Cytokines of interest in COVID-19 involving the JAK-STAT pathway

| Family          | Type I cytokines | Signaling JAKs | Signaling STATs | Hyper-inflammation | Viral clearance | Safety concerns |
|-----------------|------------------|----------------|-----------------|--------------------|----------------|-----------------|
| Common β-χ      | GM-CSF           | JAK2           | 3+5             | X                  |                |                 |
| Common γ-c      | IL-15            | JAK1, JAK3     | 3+5             | X                  |                |                 |
|                 | IL-21            | JAK1, JAK3     | 1+3+5           | X                  |                |                 |
|                 | IL-13            | JAK1, JAK3, TYK2 | 6              | X                  |                |                 |
|                 | IL-4             | JAK1, JAK3     | 6               | X                  |                |                 |
|                 | IL-7             | JAK1, JAK3     | 3+5             | X                  |                |                 |
|                 | IL-9             | JAK1, JAK3     | 1+3+5           | X                  |                |                 |
| Dimeric         | IL-12            | JAK2, TYK2     | 4               | X                  |                |                 |
| gp130           | IL-6             | JAK1, JAK2, TYK2 | 1+3            | X                  |                |                 |
| Hormone-like    | G-CSF            | JAK2           | 5               | X                  |                |                 |
| Type II cytokines |                  |                |                 |                    |                |                 |
| IFN             | IFN α/β          | JAK1, TYK2     | 1+2+3+4+5       | X                  | X              | X               |
|                 | IFN γ            | JAK1, TYK2     | 1               | X                  | X              | X               |
| IL-10           | IL-10            | JAK1, JAK2, TYK2 | 1+3+5          | X                  |                |                 |

G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; JAK = Janus kinase; STAT = signal transducers and activators of transcription; TYK = tyrosine kinase

To date, investigations examining the use of JAK inhibitors in COVID-19 have been limited mostly to case reports and small retrospective series that have been largely positive. Table 2 is a list (as of January 20, 2021) of registered clinical trials on www.clinicaltrials.gov employing currently approved JAK inhibitors; other experimental JAK inhibitors and multiple non-JAK inhibitors are also being currently investigated.9

A few trials with more than 10 patients have been reported and are instructive. The first, an Italian study, employed baricitinib 4 mg per day for 2 weeks in all consecutive COVID-19 hospitalized patients...
Figure 1. Course of COVID-19 infection: A paradigm for therapy.

DAMPs = damage-associated molecular patterns; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IgM = immunoglobulin M; IL-1 = interleukin 1; IL-6 = interleukin 6; PAMPs = pathogen-associated molecular patterns; TNF = tumor necrosis factor.
mg per day for 14 days with dose adjustments for renal or hepatic impairment.\textsuperscript{14}

The basis for this approval was the ACTT-2 study, a randomized controlled trial of baricitinib alone versus baricitinib plus remdesivir in hospitalized patients with COVID-19.\textsuperscript{15} Overall, the effects of this combined regimen were modest with a 1 day shortening of recovery time, median 7 days (95% CI 6–8 days) in the baricitinib arm versus 8 days (95% CI 7–9 days) in the remdesivir-alone arm. The 28 day mortality was 5.1% in the active group versus 7.8% in the control group (Hazard ratio 0.65, 95% CI 0.39–1.09). The relevance of this toxicity to COVID-19 is not apparent, as the mechanisms of maintenance of viral latency to varicella and the integrated host defense against respiratory viral infections are highly different. Still, vigilance for infectious complications is critical in the use of JAK inhibitors in this setting.

A second area of concern is the potential to further increase the risks of hypercoagulable complications, which are already overexpressed in the setting of COVID-19. JAK inhibitors are known to increase the risks of venous thromboembolism in rheumatoid arthritis, though the mechanisms contributing to this phenomenon are unclear. Finally, the clinical application of JAK inhibitors in the setting of COVID-19 also raises concerns regarding off-target effects on integrated antiviral immunity through inhibition of interferon signaling. Type I and III interferon activity is mediated via JAK1, JAK2, and TYK2 and may be vulnerable to off-target effects. This pathway is known to be suppressed in patients with COVID-19, and further suppression could contribute to failure to clear active infection.\textsuperscript{17}

### DOSAGE AND ADMINISTRATION

There are currently 3 approved JAK inhibitors under investigation in COVID-19; their indications, dosing, warnings, and side effects are listed in Table 3. All are orally administered once or twice daily and have narrow therapeutic ranges for dosing. In COVID-19 clinical trials, the doses under investigation are generally within the same range used in immune-mediated diseases, with some provisions for dose escalation as part of the protocol.
LABORATORY MONITORING

When JAK inhibitors are used in COVID-19, careful laboratory monitoring is important, as the drug class has numerous effects on biochemical and hematologic parameters. While there are small differences in adverse effects across agents in this class, presumably reflecting differential JAK selectivity, cytopenias including neutropenia and anemia are often observed. Of note, lymphopenia, observed primarily with tofacitinib, is of concern especially in COVID-19, where this is a biomarker correlated with severe disease. Elevations of liver enzymes and perturbations of serum lipids are of concern but are also infrequent, and functional liver impairment with hyperbilirubinemia is rarely observed. Serum creatinine and creatinine kinase may also be adversely affected, but this is rarely severe.

CONCLUSION

JAK inhibitors are a class of drugs that are growing rapidly for the treatment of a wide variety immune-based diseases; their mechanism of action is broadly immunomodulatory, and some also have antiviral potential. Experience with these drugs in non-COVID-19 settings has informed us of potential safety issues, and this will hopefully allow effective risk-mitigation. Baricitinib is currently approved under an emergency use authorization license, though how it will be positioned relative to current use of dexamethasone remains to be determined. Numerous trials of JAK inhibitors underway should soon provide more meaningful data on potential effects in patients with COVID-19.

DISCLOSURES

Dr. Leonard Calabrese has disclosed financial relationships (consulting, teaching, or speaking) with Abbvie Pharmaceuticals, BMS, Crescendo, GSK, Genentech-Roche, Horizon Pharma, Janssen, Novartis, Pfizer, Regeneron, Sanofi Aventis, and USB. Dr. Cassandra Calabrese has disclosed financial relationships (consulting, teaching, or speaking) with Abbvie and Sanofi-Regeneron.
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