

## REVIEW OF THERAPEUTICS

## Baricitinib: A Review of Pharmacology, Safety, and Emerging Clinical Experience in COVID-19

Sarah C.J. Jorgensen<sup>1\*</sup>  Christopher L.Y. Tse,<sup>2</sup> Lisa Burry,<sup>1,2</sup> and Linda D. Dresser<sup>2,3</sup><sup>1</sup>Department of Pharmacy, Sinai Health System, Toronto, Ontario, Canada; <sup>2</sup>Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; <sup>3</sup>Antimicrobial Stewardship Program, University Health Network, Toronto, Ontario, Canada

A hyperinflammatory response to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, reminiscent of cytokine release syndrome, has been implicated in the pathophysiology of acute respiratory distress syndrome and organ damage in patients with coronavirus disease 2019 (COVID-19). Agents that inhibit components of the pro-inflammatory cascade have garnered interest as potential treatment options with hopes that dampening the proinflammatory process may improve clinical outcomes. Baricitinib is a reversible Janus-associated kinase (JAK)-inhibitor that interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology. It may also have antiviral effects by targeting host factors that viruses rely for cell entry and by suppressing type I interferon driven angiotensin-converting-enzyme-2 upregulation. However, baricitinib's immunosuppressive effects may be detrimental during acute viral infections by delaying viral clearance and increasing vulnerability to secondary opportunistic infections. The lack of reliable biomarkers to monitor patients' immune status as illness evolves complicates deployment of immunosuppressive drugs like baricitinib. Furthermore, baricitinib carries the risk of increased thromboembolic events, which is concerning given the proclivity towards a hypercoagulable state in patients with COVID-19. In this article, we review available data on baricitinib with an emphasis on immunosuppressive and antiviral pharmacology, pharmacokinetics, safety, and current progress in COVID-19 clinical trials.

**KEY WORDS** baricitinib, Janus-associated kinase inhibitor, JAK-inhibitor, COVID-19, SARS-CoV-2, severe acute respiratory syndrome.

(Pharmacotherapy 2020;40(8):843–856) doi: 10.1002/phar.2438

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV)-2 disease, coronavirus disease 2019 (COVID-19), experience a wide spectrum of clinical manifestations and illness severity.<sup>1,2</sup> Although most

symptomatic patients have a relatively mild clinical course, ~20% require hospitalization and 20% of those hospitalized will be admitted to the intensive care unit (ICU).<sup>2,3</sup> In some patients, a sudden and rapid clinical deterioration manifesting as acute respiratory distress syndrome and multiorgan failure has been observed around day 7–10 of hospitalization.<sup>1,4</sup> Interestingly, clinical deterioration often occurs when viral titers are declining leading some to postulate that an over exuberant immune response may be involved in the underlying pathophysiology of organ damage.<sup>5,6</sup> This theory is supported by the correlation between COVID-19 complications and elevated levels of acute

---

Conflict of interest: SCJJ, CLYT, and LB have nothing to disclose. LDD has received conference development and administration support from Avir Pharma, Sunovion, and Merck unrelated to this work.

Funding: No funding was received for this work.

\*Address for correspondence: Sarah C.J. Jorgensen, Department of Pharmacy, Sinai Health System, 600 University Ave., Toronto, ON, Canada M5G1X5; e-mail: sarah.jorgensen@sinaihealth.ca

© 2020 Pharmacotherapy Publications, Inc

phase reactants, coagulation abnormalities, and hypercytokinemia, reminiscent of cytokine release syndrome.<sup>4,5,7,8</sup> A number of agents that inhibit one or more components of the proinflammatory cascade are now being investigated in clinical trials with hopes that blunting this process may improve clinical outcomes.<sup>9,10</sup>

The use of immunosuppressive drugs during an acute viral illness carries the risk of delaying viral clearance and increasing vulnerability to secondary opportunistic infections.<sup>9,11</sup> Coupling these drugs with effective antiviral agents, either sequentially or concurrently, may therefore be essential for positive patient outcomes.<sup>12,13</sup> Antiviral drug discovery has traditionally focused on designing compounds that target essential viral components, including viral proteases or polymerases.<sup>14</sup> This approach has been successful for chronic viral infections, such as HIV and hepatitis C.<sup>15,16</sup> However, direct-acting antivirals are typically narrow in spectrum, take years or even decades to develop, and may have a low barrier to resistance when used as monotherapy.<sup>14</sup> An alternative approach that may be more suitable for emerging viral pathogens is to repurpose approved drugs that target host functions that viruses rely on.<sup>14</sup> This may drastically reduce the costs and time devoted to early drug discovery and these agents may, in theory, have higher barriers to resistance because most resistance is secondary to mutations in the viral genome.<sup>14</sup>

Baricitinib ( $C_{16}H_{17}N_7O_2S$ , formerly LY3009104) is a small molecule reversible Janus-associated kinase (JAK)-inhibitor approved in over 65 countries for the treatment of adults with moderate to severe rheumatoid arthritis (RA).<sup>1,5,17</sup> The JAK/signal transducers and activators of transcription (STAT)-pathway mediates the signaling of multiple cytokines and interrupting this pathway may, therefore, be an attractive strategy to modulate the immunopathology seen with SARS-CoV-2 infection.<sup>9,12,18</sup> Furthermore, many drugs within this class exhibit antiviral effects, albeit often at supratherapeutic concentrations, by targeting host factors that viruses usurp for cell entry.<sup>12,19</sup> Baricitinib has the advantage of providing *in vitro* antiviral activity at concentrations achieved with approved dosing.<sup>13,20</sup>

The purpose of this article is to review available data on baricitinib with an emphasis on immunosuppressive and antiviral pharmacology, pharmacokinetics (PKs), safety, and current progress in COVID-19 clinical trials.

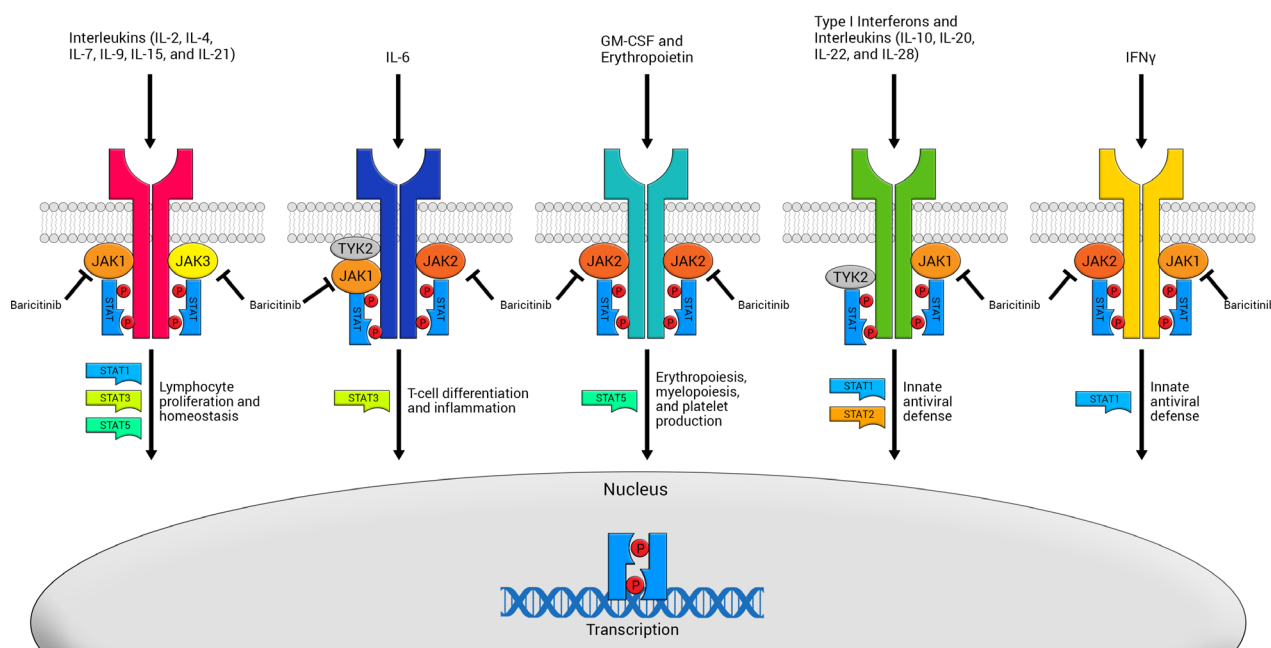
## Data Sources

A literature search of PubMed was conducted on May 10, 2020, and updated on May 22, 2020, using various combinations of the search terms “baricitinib,” “LY3009104,” “Janus-associated kinase inhibitors,” “safety,” “adverse effects,” “infection,” “thrombosis,” “coronavirus,” “COVID-19,” and “severe acute respiratory syndrome coronavirus (SARS-CoV)-2.” Results were limited to English language articles. Articles were selected based on their relevance to baricitinib’s use in COVID-19, pharmacology, PK, and safety. The reference lists of relevant articles were examined to identify sources not captured in the electronic literature search. Additional data were obtained from ClinicalTrials.gov, bioRxiv, medRxiv, the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA) drug approval documents.

## Pharmacology and Pharmacodynamics

Basic and translational science have identified a wide array of subcellular pathways that regulate normal and aberrant immune responses.<sup>18,21,22</sup> One of these is the JAK/STAT pathway.<sup>21,22</sup> The JAK/STAT pathway mediates signal transduction from extracellular stimuli, including cytokines, growth factors, and hormones, to the nuclei of cells.<sup>21,22</sup> Baricitinib exerts its antiinflammatory effects through reversible JAK inhibition, as shown in Figure 1. Signaling is initiated when cytokines bind to their receptor on the cell membrane.<sup>22</sup> This results in conformational changes that trigger activation of associated JAK complexes. JAK activation, in turn, leads to autophosphorylation and subsequent increased JAK kinase activity as well as phosphorylation of the intracellular portion of their cognate receptors.<sup>22</sup> Receptor phosphorylation creates a docking site for signaling molecules especially members of the STAT family.<sup>22</sup> Once docked to the receptor, STAT molecules are also phosphorylated by JAKs. The phosphorylated STATs are then released from the receptor, form homo-dimers or hetero-dimers through reciprocal interactions with their newly phosphorylated tyrosine domains, and translocate to the cell nucleus where they bind to specific DNA sequences to activate target gene transcription.<sup>22</sup>

The JAK family is comprised of four cytoplasmic protein tyrosine kinases: JAK1, JAK 2, JAK3, and tyrosine kinase 2 (TYK2).<sup>21,22</sup>



**Figure 1.** Janus-associated kinase/signal transducers and activators of transcription (JAK/STAT) pathway showing baricitinib inhibition of JAK complexes. GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN $\gamma$  = interferon gamma. [Color figure can be viewed at wileyonlinelibrary.com]

Cytokine receptors recruit two of the four JAKs to the intracellular domain of the signaling complex (i.e., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, and JAK2/TYK2; Figure 1).<sup>18</sup> Inhibition of one or both JAK monomers associated with the cytokine receptor is typically sufficient to interrupt signal transduction.<sup>24</sup> JAK1, JAK2, and TYK2 are expressed throughout the human body, whereas JAK3 is primarily expressed by hematopoietic cells in the bone marrow.<sup>21,24</sup> The various JAK complexes mediate distinct cytokine signaling pathways. For example, innate antiviral responses via type I interferon (IFN) are mediated by JAK1/TYK2 and IFN-gamma signaling is mediated by JAK1/JAK2.<sup>18,23,24</sup> Interleukin (IL)-6, which has emerged as a strong predictor of poor outcomes in COVID-19, transduces signaling via complexes of JAK1, JAK2, and TYK2.<sup>8,9</sup>

Baricitinib was designed to selectively inhibit JAK1 and JAK2 with less potency for JAK3. It has been postulated that sparing JAK3 could reduce the immunosuppression associated with pan-JAK inhibition.<sup>24,25</sup> However, as presented in Table 1, baricitinib's purported selectivity is only evident in cell-free assays but not recapitulated in cell-based assays.<sup>24</sup> Baricitinib 50% inhibitory concentrations (IC<sub>50</sub>) for JAK complexes that mediate signaling for a wide variety of cytokines implicated in COVID-19 immunopathology generally fall below the free

**Table 1.** Antiinflammatory and Antiviral Activity of Baricitinib (adapted from references 13,20,24)

JAK enzymes, cell-free	Baricitinib mean IC <sub>50</sub> , nM	JAK enzyme pair, cell-based <sup>a</sup>	Baricitinib mean IC <sub>50</sub> , nM
JAK1	5.9	JAK1/JAK2	32.8
JAK2	5.7	JAK1/JAK3	55.4
JAK3	> 400	JAK1/TYK2	71.6
TYK2	53	JAK2/TYK2	69.0

NAK enzymes, cell-free	Baricitinib K <sub>d</sub> , nM	NAK enzymes, cell-based <sup>b</sup>	Baricitinib K <sub>d</sub> , nM
AAK1	17	AAK1	34
GAK	136	GAK	272

AAK1 = AP2-associated protein kinase 1; GAK = cyclin G-associated kinase; IC<sub>50</sub> = 50% inhibitory concentrations; JAK = Janus-associated kinase; K<sub>d</sub> = dissociation constant; NAK = numb-associated kinase; TYK2 = tyrosine kinase 2.

<sup>a</sup>Across multiple cell-types, including B cells, CD<sup>4+</sup> T cells, CD<sup>8+</sup> T cells, Natural killer cells, and monocytes.

<sup>b</sup>Not directly measure; calculated based on ratio of cell-based to cell-free inhibition of JAK enzymes.<sup>13</sup>

maximum plasma drug concentration (C<sub>max</sub>) values achieved with approved dosing (Tables 1 and 2).<sup>13,24,25,26</sup>

### Antiviral Activity

Baricitinib may also have antiviral activity.<sup>12,13,27</sup> Its potential antiviral activity was

**Table 2. Pharmacokinetic Parameters of Baricitinib 4 mg Orally Once Daily (Adapted from references 1,3,25,26)**

Parameter	Value	
$C_{\max,ss}^a$	Total	Free
	53.4 ng/ml	26.7 ng/ml
	143.8 nM <sup>b</sup>	71.9 nM <sup>b</sup>
$C_{\min,ss}^a$	Total	Free
	6.9 ng/ml	3.5 ng/ml
	18.6 nM <sup>b</sup>	9.3 nM <sup>b</sup>
$AUC_{24}^a$	477.6 ng*hr/ml	
	1285.9 nM <sup>b</sup>	
Bioavailability	79%	
$V_d$	75.7 L	
Free fraction	50%	
$T_{1/2}$	Healthy subjects	6–9 hrs
	Patients with RA	hrs

$AUC_{24}$  = area under the concentration time curve over 24 hours;  $C_{\max,ss}$  = maximal concentration at steady state;  $C_{\min,ss}$  = minimum concentration at steady state; JAK = Janus-associated kinase; RA = rheumatoid arthritis;  $T_{1/2}$  = half-life;  $V_d$  = volume of distribution.

<sup>a</sup>Concentrations from studies in patients with RA.

<sup>b</sup>Calculated based on molecular mass 371.42.<sup>1</sup>

identified by searching a large repository of structured medical and drug information extracted using machine learning (Benevolent<sup>AI</sup>, London, UK). Nearly 50 currently approved drugs for a variety of indications from oncology to autoimmune disorders were identified by this approach as inhibitors of host enzymes involved in regulating intracellular viral trafficking. Only baricitinib, however, showed inhibitory activity at clinically achievable serum concentrations.

Many viruses gain entry into human cells by hijacking host-derived membrane trafficking processes; one of the most well studied is clathrin-mediated endocytosis.<sup>28,29</sup> Clathrin is an endocytic coat protein that clusters on the inner leaflet of the plasma membrane to form the initial spherical cage-like vesicle structure involved in endocytosis.<sup>29</sup> Viral internalization via clathrin-mediated endocytosis is shown in Figure 2. The process is initiated when the virus binds to the host cell surface receptor (angiotensin-converting enzyme 2 [ACE2] in the case of SARS-CoV-2).<sup>28,30</sup> Receptor binding leads to activation of two host-derived kinases, AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK).<sup>28,31</sup> AAK1 and GAK, in turn, phosphorylate and activate key host proteins called adaptor protein (AP) complexes.<sup>28,31</sup> Activated APs bind to the cytoplasmic tail of the cell-surface receptors and recruit clathrins to assemble into a cage-like structure in preparation for endocytosis.<sup>28,31</sup> Next, the cell surface receptor with bound virus is invaginated into the cage-like structure, which pinches off and traffics the virus and associated

APs in early endosomes.<sup>28,31</sup> In addition to clathrin recruitment, APs also interact with the cargo (in this case, the virus) to facilitate intracellular transport and regulate trans-Golgi network trafficking involved in subsequent stages of the viral lifecycle.<sup>28,31</sup>

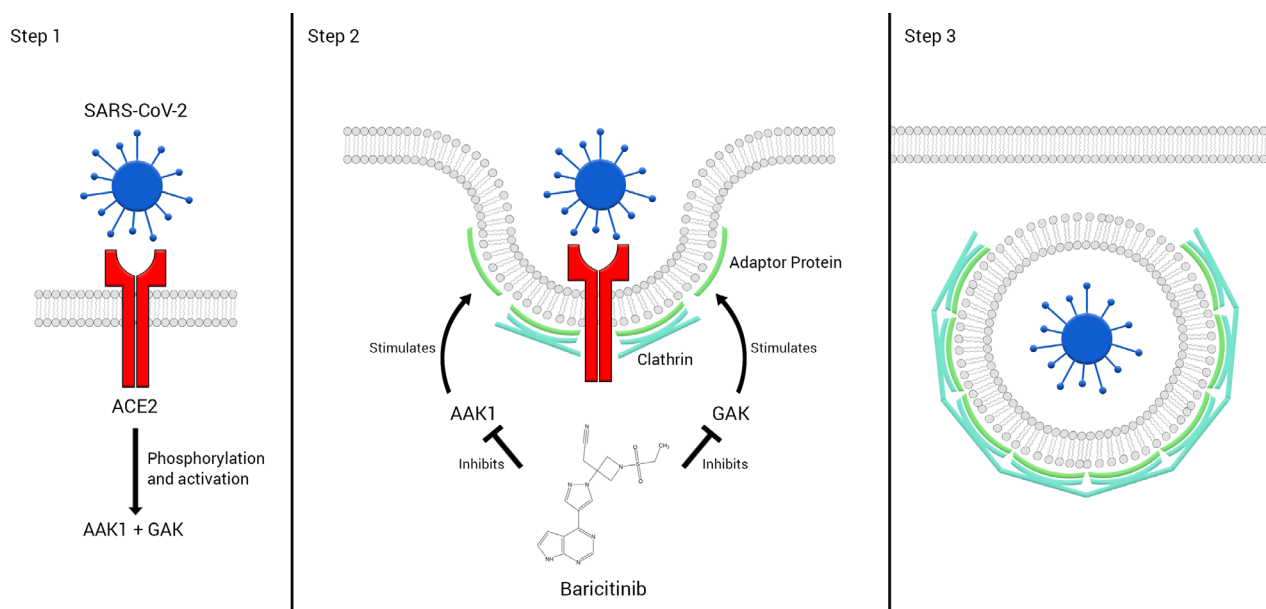
Baricitinib has been shown to inhibit AAK1 and, to a lesser degree, GAK (Table 1) and may thereby impede viral cell entry and internal transport.<sup>12,13</sup> It is uncertain if compounds need to inhibit both AAK1 and GAK to block SARS-CoV-2 viral cell entry, although in murine infection models the combination of both sunitinib (an anticancer drug that inhibits AAK1) and erlotinib (an anticancer drug that inhibits GAK) was required to protect mice from lethal Ebola and dengue virus challenges.<sup>19,31</sup> It should also be pointed out that SARS-CoV-1 uses several different endocytic pathways for viral entry<sup>28,32</sup> and if this is also true for SARS-CoV-2, baricitinib's inhibition of clathrin-mediated endocytosis could be circumvented by use of an alternative pathway.

An additional antiviral mechanism related to baricitinib's inhibitory effect on IFN signaling has been proposed.<sup>27</sup> As noted above, IFN responses are essential host antiviral defenses but recent work has revealed that type I IFN and to a lesser extent type II IFN upregulate ACE2 expression in multiple human cell lines, including upper airway epithelial cells and primary bronchial cells.<sup>33</sup> Suppressing type I IFN antiviral response could, in theory, decrease ACE2 expression and thereby interfere with the ability of SARS-CoV-2 to infect neighboring cells.<sup>33</sup> However, ACE2 is also counter-regulatory to the renin-angiotensin-aldosterone system (RAAS) and has a protective effect against RAAS-related organ damage, including acute lung injury.<sup>34</sup> One of SARS-CoV-2's key virulence factors is its ability to downregulate ACE2 expression after cell entry, thereby thwarting ACE2 lung-protective effects.<sup>34</sup> It is conceivable that baricitinib's suppression of type I IFN signaling could amplify ACE2 downregulation, further diminishing its protective effects. The net effect of IFN suppression (beneficial vs. detrimental) in the setting of COVID-19 might depend on the underlying immune status of the patient and the stage of infection.<sup>33</sup>

### Pharmacokinetics

Table 2 summarizes pertinent baricitinib PK parameters, which were derived from single and multiple-dose studies in healthy adult volunteers





**Figure 2.** Baricitinib inhibition of viral endocytosis. AAK1 = AP2-associated protein kinase 1; ACE2 = angiotensin-converting enzyme 2; GAK = G-associated kinase; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

and patients with RA.<sup>25,26,35</sup> After oral administration, baricitinib is rapidly absorbed reaching peak plasma concentrations within 60 minutes.<sup>25,26</sup> The absolute bioavailability is 79% and food has minimal impact on PK parameters.<sup>25,26</sup> Baricitinib exhibits linear dose proportional PK after single oral doses between 1 mg and 20 mg with minimal accumulation for up to 28 days.<sup>26,35</sup> Both  $C_{max}$  and area under the concentration time curve over 24 hours ( $AUC_{24}$ ) values increase ~60% and 75% in patients with RA compared with healthy subjects, respectively, and interindividual variability is higher in patients with RA.<sup>25,26</sup> Exposure is also increased greater than 2-fold in those with moderate to severe renal impairment and end-stage renal disease (ESRD). Exposure in patients with COVID-19 or other acute viral infections has not been reported at this time (acute infection at baseline was a contraindication for all RA clinical trials).<sup>10</sup> As shown in Tables 1 and 2, baricitinib free  $C_{max}$  values with 4 mg once daily dosing exceed  $IC_{50}$  values for inhibition of cytokine-induced JAK/STAT signaling in cell-free and cell-based assays and concentrations also exceed the dissociation constant ( $K_d$ ) for AAK1 but supratherapeutic levels may be required to inhibit GAK.<sup>13,24,25</sup> Additionally, PK modeling of 4 mg once daily dosing showed that there is a 12-hour window when baricitinib serum levels fall below  $IC_{50}$  values for JAK complexes.<sup>25</sup> The

clinical implications of this in the setting of COVID-19-related cytokine storm are unclear.

Plasma protein binding for baricitinib is 50% and is not concentration dependent. The mean volume of distribution is 1.1 L/kg, suggesting moderate distribution into tissues.<sup>25,26</sup> Epithelial lining fluid concentrations have not been reported.

Baricitinib is primarily cleared by renal elimination through both filtration and active secretion.<sup>25,26</sup> Approximately 75% is excreted in the urine (69% unchanged) and 20% in the feces (15% unchanged).<sup>25,26</sup> The half-life is 6–9 hours in healthy volunteers but increases to 12 hours in patients with RA and 19 hours in subjects with severe renal impairment or ESRD.<sup>25,26</sup> Baricitinib is effectively dialyzed with a mean clearance by hemodialysis of 6 L/h.<sup>26</sup> The impact of continuous renal replacement therapy and extracorporeal membrane oxygenation on baricitinib PK has not been described at this time. In population PK analyses, body weight did not have a clinically meaningful impact on baricitinib clearance, however, obese patients with RA have been reported to have lower response rates.<sup>3,26,36,37</sup> As discussed in the Drug Interactions section, baricitinib is a substrate of several drug transporters that impact absorption, distribution, and elimination.<sup>26</sup>

Only a small fraction (6%) of baricitinib is metabolized, predominantly by CYP3A4, and

there is no clinically relevant difference in baricitinib exposure in patients with moderate hepatic function (Child-Pugh B).<sup>26</sup>

Baricitinib PK has been evaluated in a small number of pediatric patients (n=18, mean age 12.5 years, weight 9.2–84.3 kg) who received the drug through a compassionate use program for rare Mendelian autoinflammatory diseases.<sup>38</sup> Weight and renal function significantly influenced volume of distribution and clearance, respectively, suggesting the need for weight and renal function based dosing. Importantly the half-life of baricitinib was significantly shorter in children, especially among those weighing less than 40 kg, and the authors of this study recommended twice daily to four times daily dosing in children depending on renal function.<sup>38</sup>

Pharmacokinetics parameters in pregnant or breastfeeding women have not been reported at this time. It is not known if baricitinib crosses the placenta in humans. Skeletal malformations and developmental toxicity have been observed in the offspring of pregnant rats exposed to supratherapeutic doses of baricitinib.<sup>24</sup> Effects on fertility in animals have been inconsistent.<sup>24</sup>

### Drug-drug interactions

Baricitinib is not an inhibitor or inducer of CYP450 enzymes or drug transporters (P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT 1–3, MATE-1, and MATE2-K) at clinically relevant concentrations.<sup>25,26</sup> Although a small fraction (6%) of baricitinib is metabolized by CYP3A4, co-administration with ketoconazole (a strong CYP3A4 inhibitor) or rifampin (a strong CYP3A4 inducer) did not have a clinically meaningful impact on baricitinib PK.<sup>25,26</sup>

As noted in the PK section, baricitinib is a substrate of several drug transporters (P-glycoprotein, BCRP, MATE2-K, and OAT3).<sup>25,26</sup> Co-administration with cyclosporine (P-glycoprotein inhibitor) did not result in clinically relevant changes to baricitinib PK, however, co-administration with probenecid (a strong OAT3 inhibitor) led to decreased renal clearance and an ~2-fold increase in AUC.<sup>25,26</sup> Dose reduction is recommended in patients taking strong OAT3-inhibitors (see Section Dosage and Administration).<sup>25,26</sup> Based on PK modeling, less potent OAT3 inhibitors, such as ibuprofen and diclofenac, are expected to have minimal impact on baricitinib PK.<sup>26</sup> Studies examining the impact of BCRP or MATEK-2 inhibitors have not been reported at this time. Increased gastric pH and

the use of proton-pump inhibitors do not alter overall exposure to baricitinib although the time to peak plasma concentrations was prolonged to 2 hours with concomitant administration of omeprazole.<sup>26</sup> No signal of rate-corrected QT (QTc) interval prolongation has been observed with baricitinib doses up to 40 mg in healthy volunteers.<sup>38,39</sup>

### Clinical Experience for COVID-19

Baricitinib is under investigation in multiple ongoing clinical studies (Table 3), including the second iteration of the National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT-2).<sup>40,41</sup> ACTT-2 is an adaptive, randomized, double-blind, active-controlled multinational study.<sup>41</sup> Hospitalized patients with laboratory-confirmed SARS-CoV-2 infection and one of the following are eligible for enrollment: infiltrates on chest imaging, an oxygen saturation less than or equal to 94% on room air, need for supplemental oxygen, or need for mechanical ventilation.<sup>41</sup> The primary end point is time to recovery within 28 days after randomization using a 3-point ordinal scale.<sup>41</sup> In the first iteration of the study (ACTT-1), patients were randomized to the antiviral drug, remdesivir, or placebo.<sup>36</sup> Preliminary results were recently published after enrolling over 1000 patients: the median time to recovery was significantly shorter in the remdesivir group (11 days vs 15 days, hazard ratio 1.32; 95% confidence interval 1.12–1.55).<sup>36</sup> Moving forward in ACTT-2, all patients will receive remdesivir and additionally be randomized to baricitinib 4 mg daily or placebo for up to 14 days.<sup>41</sup>

The off-label use of baricitinib in patients with COVID-19 was recently reported in a small before and after study of patients at centers in the Northern Italian province of Prato.<sup>42</sup> This study included consecutive patients hospitalized between March 16 and 30, 2020 with moderate COVID-19 defined as a positive SAR-CoV-2 real-time polymerase chain reaction (RT-PCR) nasopharyngeal or oropharyngeal swab, evidence of pneumonia on chest imaging, and fever, cough, myalgia, or fatigue. Patients (n=12) were treated with lopinavir/ritonavir (250 mg twice daily) plus baricitinib (4 mg daily) for 14 days. Those with thrombophlebitis, latent tuberculosis, and pregnant or breastfeeding women were excluded. An equal number of patients with moderate COVID-19 admitted in the week preceding this period served as the control group.

Table 3. Ongoing Clinical Studies registered on ClinicalTrials.gov of Baricitinib for COVID-19 (adapted from references 40,41)

ClinicalTrials.gov identifier	Study design	Intervention/treatment of interest	Location	Primary outcome	Target sample size	Sponsor
NCT04280705	Adaptive, randomized, multicenter, double-blind, placebo-controlled	<ul style="list-style-type: none"> <li>• Remdesivir i.v. 200 mg day 1 then 100 mg days 2–10 × 10 days PLUS one of:</li> <li>• Baricitinib 4 mg p.o. o.d. × 14 days</li> <li>• Placebo × 14 days</li> </ul>	Multinational	Time to recovery through day 29 according to 3-point ordinal scale	1000	National Institute of Allergy and Infectious Diseases (NIAID)
NCT04340232	Prospective, single-arm, single-center, open-label	<ul style="list-style-type: none"> <li>• Baricitinib 2 mg p.o. o.d. × 14 days</li> </ul>	USA	Grade 3 or 4 adverse events	80	University of Colorado
NCT04390464	Randomized, multicenter, parallel assignment, open-label	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg p.o. o.d. × 14 days</li> <li>• Ravulizumab IV (weight-based dosing) on day 1</li> <li>• Standard of care</li> </ul>	UK	Time to composite end point up to day 14 defined as 1 of: death, mechanical ventilation, ECMO, CV support, or renal failure	1167	Cambridge University Hospitals NHS Foundation Trust
NCT04362943	Retrospective, observational, single-center cohort study	<ul style="list-style-type: none"> <li>• <del>Baricitinib</del></li> </ul>	Spain	All-cause mortality	576	Complejo Hospitalario
Universitario de Albacete NCT04346147	Randomized, single-center, parallel assignment, open-label	<ul style="list-style-type: none"> <li>• Hydroxychloroquine 200 mg p.o. b.i.d. × 7 days PLUS one of:</li> <li>• Baricitinib 4 mg p.o. o.d. × 7 days</li> <li>• Lopinavir/ritonavir 200/50 mg p.o. o.d. × 7 days</li> <li>• Imatinib 400 mg p.o. o.d. × 7 days</li> </ul>	Spain	Time to clinical improvement on 7-point ordinal scale	165	Hospital
Universitario de Fuenlabrada NCT04320277	Non-randomized, before-after, single-center	<ul style="list-style-type: none"> <li>• Lopinavir/ritonavir 200/50 mg p.o. o.d. × 7 days PLUS</li> <li>• Baricitinib 4 mg p.o. o.d. × 14 days</li> <li>• Antiviral and/or hydroxychloroquine</li> </ul>	Italy	ICU transfer	200	Hospital of Prato
NCT04373044	Prospective, single-arm, two-center, open-label	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg p.o. o.d. × 14 days PLUS one of the following at the treating physician's discretion:</li> <li>• Hydroxychloroquine lopinavir/ritonavir</li> <li>• Remdesivir (doses not reported)</li> </ul>	USA	Death or mechanical ventilation at day 14	59	University of Southern California

(continued)

Table 3 (continued)

ClinicalTrials.gov identifier	Study design	Intervention/treatment of interest	Location	Primary outcome	Target sample size	Sponsor
NCT04321993	Nonrandomized, multicenter, parallel assignment, open-label	<ul style="list-style-type: none"> <li>• Baricitinib 2 mg p.o. o.d. × 10 days</li> <li>• Hydroxychloroquine 400 mg p.o. b.i.d. × 10 days</li> <li>• Lopinavir/ritonavir 500/100 mg p.o. b.i.d. × 10 days</li> </ul>	Canada	Clinical improvement on 7-point ordinal scale at day 15	1000	Lisa Barrett
NCT04345289	Adaptive, multicenter, randomized, double-blind, placebo-controlled	<ul style="list-style-type: none"> <li>• Baricitinib 4 mg p.o. o.d. × 7 days</li> <li>• Convalescent plasma 600 ml i.v. × 1 dose</li> <li>• Sarilumab 200 mg s.c. × 1 dose</li> <li>• Hydroxychloroquine 600 mg p.o. o.d. × 7 days</li> <li>• Placebo</li> </ul>	Denmark	All-cause mortality of need for mechanical ventilation at day 28	1500	Thomas Benfield

COVID-19 = coronavirus disease 2019; CV = cardiovascular; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; UK = United Kingdom; USA = United States of America.

All patients in the control group received lopinavir/ritonavir (250 mg twice daily) plus hydroxychloroquine (400 mg daily) for 14 days.<sup>42</sup>

Overall, recorded demographics, comorbidities, and baseline signs and symptoms were similar in the two groups.<sup>42</sup> The median oxygen saturation was 91–92% and none of the patients resided in the ICU at enrollment. At 2 weeks, most clinical and laboratory parameters had normalized in the baricitinib group, no patients required ICU admission, and 7 patients (58%) were discharged home. In the control group, there was no significant improvement in most clinical and laboratory parameters, four patients (33%) required ICU admission, and one (8%) was discharged home. With regard to safety, no new bacterial, viral, or opportunistic infections were reported in either group. Baricitinib (and lopinavir/ritonavir) was stopped in 1 patient after 10 days due to increased transaminases.<sup>42</sup> Platelets increased from a median of  $203 \times 10^9/L$  at baseline to  $354 \times 10^9/L$  at day 14 in patients who received baricitinib ( $p=0.018$ ). There was no change in platelets over 2 weeks in the control group (see Safety section for further discussion on increased platelets associated with baricitinib).<sup>42</sup>

The authors of this report rightly acknowledge its main weaknesses, including the lack of a randomized control group and the small sample

size.<sup>42</sup> The use of a historical control group in an emerging infectious disease is fraught with limitations due to rapidly evolving knowledge and patterns of care. In addition, the use of concomitant antiviral and adjunctive agents complicates interpretation. The small sample size and short duration of follow-up do not allow a meaningful assessment of safety. Finally, although the authors report that antibiotics were only used when bacterial infection was suspected, it is unclear if any were in fact administered; this information is important when interpreting rates of secondary infections.

### Safety

Pooled data from 3492 baricitinib exposed patients (7860 patient-years) enrolled in phase II and III RA clinical trials together with long-term extensions of these studies in the baricitinib development program has been used to characterize baricitinib's safety profile.<sup>10,23</sup> One caveat to these analyses is that patients in the placebo or baricitinib 2 mg/day arms of many studies were allowed to crossover to the 4 mg/day group after week 16, which complicates interpretation and raises the possibility that some risks in the 4 mg/day group may be overestimated. Furthermore, as discussed below, although many adverse effects appeared to be dose related, far



fewer patients were exposed to 2 mg/day so there is more uncertainty in relative risk estimates. In ongoing COVID-19 studies, the duration of baricitinib therapy is typically 7–14 days. Safety data by contrast is derived from patients who received baricitinib for months and many adverse effects manifested after prolonged exposures. Finally, all trials excluded patients with acute infections at baseline limiting generalizability for patients with COVID-19.

The most common side effects with baricitinib are upper respiratory tract infection (14–22%), headache (11–24%), and nasopharyngitis (11–18%).<sup>10</sup> In addition, dose-related changes in multiple laboratory parameters have been observed in patients treated with baricitinib.<sup>10,39</sup> Many of these have been reported with other JAK-inhibitors and include rapid and sustained decreases in neutrophil and lymphocyte counts, decreases in hemoglobin, small increases in creatinine (< 0.1 mg/dl), increases in lipid parameters, elevations in liver enzymes and bilirubin, and increases in creatine phosphokinase (CPK).<sup>18,43</sup> Decreases in lymphocyte counts have been associated with higher rates of treatment-emergent infections among patients with RA in clinical trials.<sup>10,39</sup> Lymphopenia is one of the most prominent laboratory abnormalities in patients with COVID-19 and lower lymphocyte counts have been associated with more severe disease.<sup>44,45</sup> In addition to being quantitatively reduced, lymphocytes from patients infected with SARS-CoV-2 also show functional exhaustion and decreased functional diversity.<sup>46</sup> The consequences of exacerbating this immunophenotype with baricitinib require further study.

The significance of modest increases in lipid parameters has been difficult to predict; major cardiac events have occurred in a small number of patients in RA trials, most commonly in extension phases after week 52 but a clear link with lipid parameters has not been reported. Patients with preexisting cardiovascular diseases are at increased risk of the most severe COVID-19 complications.<sup>47</sup> Furthermore, myocardial injury has been observed in nearly 30% of hospitalized patients with COVID-19 and is significantly associated with higher short-term mortality.<sup>47</sup> However, in this setting, the underlying pathogenesis of myocardial injury may be related to the proinflammatory response to infection<sup>47</sup> and countering this with baricitinib could conceivably be protective.

Although increases in liver enzymes and bilirubin have been reported with baricitinib, no

cases of liver injury satisfying Hy's law have occurred.<sup>10,39</sup> Thirteen patients were withdrawn from studies due to liver function test abnormalities (vs one withdrawal with placebo) and patients with transaminase elevations at baseline ( $> 1.5 \times$  the upper limit of normal) have been excluded from all studies.<sup>10,39</sup> Many patients who experienced liver function test abnormalities were receiving concomitant hepatotoxic drugs (i.e., methotrexate or isoniazid). In case series, between 2% and 11% of patients with COVID-19 had chronic liver comorbidities and 14–53% had elevated transaminases during the course of the disease (reviewed in ref. 47). Furthermore, higher rates of liver dysfunction have been correlated with more severe COVID-19.<sup>47</sup> Hepatotoxic drug effects may be difficult to detect in these circumstances and clinicians may need to maintain a high index of suspicion.

In the clinical trials program, CPK elevations were not associated with muscle pain or rhabdomyolysis.<sup>10,39</sup> However, a recent report describes two patients with RA who developed unexplained lower and/or upper extremity muscle pain and joint swelling coupled with moderate CPK elevations after the initiation of baricitinib.<sup>48</sup> In both cases, clinical and biochemical resolution occurred rapidly after baricitinib discontinuation.<sup>48</sup> The mechanism behind baricitinib-associated CPK elevations has not been widely studied, although experimental evidence supports the theory that certain proinflammatory cytokines may block differentiation of myoblasts into mature myocytes.<sup>49</sup> CPK increases observed with JAK inhibitors may, therefore, represent recovery of muscle development and CPK expression.<sup>49</sup>

Increased CPK is correlated has been with mortality in COVID-19<sup>4</sup> and rhabdomyolysis has been reported as a late complication.<sup>17</sup> The interaction between possible baricitinib-associated CPK elevations and those secondary to COVID-19 requires further study.

Increased platelet counts is a unique baricitinib effect and has not been observed with other JAK-inhibitors.<sup>10,50,51</sup>

In fact, small decreases in platelets and occasional thrombocytopenia occur with two other JAK-inhibitors, tofacitinib and upadacitinib.<sup>50,51</sup> With baricitinib, platelet counts increase rapidly after initiation and peak around week 2 (mean increase  $50 \times 10^9/L$ ).<sup>10,39</sup> Thereafter, they decline and stabilize but remain above placebo and comparators for the duration of therapy. Thrombocytosis appears to be dose related but

still occurs with the 2 mg/day dose. No clear temporal or quantitative association between platelet increases and thromboembolic events (discussed below) has been established.<sup>10,39</sup> The etiology is not known, although the prevailing theory, based on animal experiments, implicates selective JAK2 inhibition in increased circulating thrombopoietin (TPO, the hormone that stimulates megakaryopoiesis and platelet production) levels. TPO signals are transduced by JAK2. Knockout of the *Jak2* gene in hematopoietic stem cells (HSCs) results in thrombocytopenia in mice.<sup>52</sup> In contrast, deletion of *Jak2* or the TPO receptor gene in megakaryocytes and mature platelets results in thrombocytosis.<sup>23,53,54</sup> Megakaryocytes and mature platelets are responsible for internalizing and degrading circulating TPO by a JAK2 dependent mechanism.<sup>23,53,54</sup> Thus, it is possible that predominant JAK2 inhibition at the level of megakaryocytes and mature platelets may lead to increased circulating TPO resulting in the increased platelet counts seen with baricitinib. JAK-inhibitors that are less selective for JAK2 may act mainly on JAK2 signaling at the level of HSCs to decrease platelet production.<sup>23</sup> Early case series from Wuhan, China, suggested thrombocytopenia was a prominent feature of severe COVID-19.<sup>55</sup> For unclear reasons, later studies and those from other regions have shown normal or even elevated platelet counts in patients with COVID-19.<sup>56,57</sup> The impact of thrombocytosis secondary to baricitinib in the setting the COVID-19 coagulopathy is difficult to predict.

Besides common side effects and changes in laboratory parameters, baricitinib has been associated with serious adverse effects, including infections, thrombosis, malignancy, gastrointestinal perforations, and major cardiovascular events.<sup>10,23</sup> Adverse effects of particular relevance to patients with COVID-19 are infection and thrombosis and are expanded upon below.

Overall, the incidence of serious and opportunistic infections in patients with RA treated with JAK-inhibitors is comparable to other biological disease-modifying antirheumatic drugs (DMARDs), however, the risk of viral infections, specifically herpes zoster virus (HZV) reactivation, appears to be higher with JAK-inhibitors.<sup>23</sup> HZV reactivation rates are ~1.5–2-fold higher among patients with RA taking JAK-inhibitors (3.2–4.0 cases/100 patient-years) compared with the general RA population.<sup>10,23,39</sup> Other factors associated with decreased cell-mediated immunity, such as older age and concomitant steroid

use, amplify this risk.<sup>23</sup> The incidence of HZV and other infections were numerically higher with baricitinib 4 mg/day versus 2 mg/day.<sup>10,23,39</sup> Type I IFNs orchestrate a critical antiviral defense via the JAK/STAT pathway and their inhibition by baricitinib is thought to be responsible for HSV reactivation.<sup>9,23</sup> Critically ill patients with COVID-19 demonstrate an impaired type I IFN response and the degree of impairment has been correlated with higher viral loads and poor outcomes.<sup>58,59</sup> Interestingly, type I IFN deficiency was associated with an exacerbated inflammatory response with markedly elevated levels of IL-6 and tumor necrosis factor (TNF)- $\alpha$ . These data suggest timing of baricitinib initiation may be important to both avoid amplifying impaired innate immunity and suppress a harmful hyperinflammatory response. An additional concern with baricitinib use in COVID-19 is its inhibition of signaling from mediators of immune restoration (i.e., IL-2 and IL-7), which may make patients more vulnerable to nosocomial infections.<sup>9</sup> Although rates of coinfections or secondary infections in patients with COVID-19 have been low,<sup>60,61</sup> little is known about incidence with the use of immunosuppressive drugs.

With regard to thrombosis, there was a numerical imbalance in both arterial and venous thromboembolic events (VTEs) not favoring baricitinib-treated patients in pooled safety data, primarily with 4 mg/day.<sup>10,39</sup> Five VTEs occurred in patients receiving baricitinib 4 mg/day during the first 16 weeks of therapy (compared with zero in the baricitinib 2 mg/day and placebo groups) and additional events continued to accumulate in both the 4 mg/day and 2 mg/day groups with extended follow-up. In total, 39 VTEs have been reported with baricitinib in the clinical trials program (34 at 4 mg/day and 5 at 2 mg/day) compared with none with placebo (VTE incidence rates 0.6/100 patient-year and 0.4/100 patient-year for 4 mg/day and 2 mg/day, respectively). Twenty-nine arterial thrombotic events have also been reported in patients who received baricitinib (incidence rates 0.5/100 patient-year and 0.3/100 patient-year for 4 mg/day and 2 mg/day, respectively) versus 1 event with placebo.<sup>10,39</sup> It should be noted that in population-based observational studies, VTE rates among individuals with RA on DMARDs range from 0.68 to 1.63/100 patient-years, in line with what was observed in the baricitinib RCTs, however, differences in study designs and patient populations make such comparisons

problematic.<sup>10,39</sup> Furthermore, an increased incidence of thromboembolic events was also recently reported with higher doses of tofacitinib, another JAK-inhibitor used for RA.<sup>62</sup> Thrombotic events and other dose-related adverse effects coupled with the absence of a clear efficacy benefit in RA with the 4 mg/day versus 2 mg/day dose were the primary reasons behind the FDA's failure to approve the manufacturer's first submission in 2017.<sup>10,39</sup> Baricitinib was approved 1 year later but only at the lower 2 mg/day dose.<sup>10,39</sup> Health Canada has similarly only approved the 2 mg/day dose.<sup>63</sup> Four mg/day has been approved in some European and Asian countries, however<sup>25</sup> (see Dosage and Administration Section).

The coagulation system is closely linked to inflammation through the innate immune system and patients with COVID-19 appear to have an increased proclivity toward immunothrombosis.<sup>57,64</sup> Common coagulation abnormalities include elevations in D-dimer and fibrinogen and prolonged prothrombin time.<sup>57,64</sup> Published series also describe what appears to be a higher than expected incidence of VTE.<sup>57,64</sup> Baricitinib's inhibition of inflammatory mediators that also drive immunothrombosis could have collateral benefits of reducing hypercoagulability; it is equally plausible however that baricitinib's prothrombotic tendencies could be detrimental. Moving forward, thorough baseline risk assessment and use of the minimally effect dose will be important in minimizing iatrogenic harm. Suggested monitoring parameters for patients receiving baricitinib are shown in Table 4.

### Dosage and Administration

When used for RA, baricitinib is taken once daily by mouth with or without food. The recommended starting dose in Europe is 4 mg/day with the option to decrease to 2 mg/day when RA signs and symptoms are controlled.<sup>25</sup> In Canada and the United States, only 2 mg/day is approved.<sup>10,63</sup> As shown in Table 3, both 2 mg/day and 4 mg/day are being tested in clinical trials. Recommendations for dosage reductions vary by country. The EMA recommends a 50% dose reduction in the following patients: age greater than or equal to 75 years, a history of chronic or recurrent infections, creatinine clearance (CrCl) between 30 ml/min and 60 ml/min, and concomitant use of a strong OAT3-inhibitor.<sup>25</sup> According to current prescribing information, baricitinib should not be initiated and

therapy should be interrupted for the following laboratory parameters: absolute lymphocyte count less than  $0.5 \times 10^9/L$ , absolute neutrophil count less than  $1 \times 10^9/L$ , and hemoglobin less than 8 g/ml.<sup>1,2,17</sup> Baricitinib is contraindicated in patients with CrCl less than 30 ml/min.<sup>10,25,63</sup> Baricitinib is only available as a film-coated, immediate release tablet.<sup>1</sup> There is no published data on the stability and bioavailability of crushed/dissolved tablets or extemporaneously compounded suspensions at this time.

### Discussion

A growing body of evidence suggests that the host immune response to SARS-Cov-2 infection may be critically important in determining outcomes.<sup>8,44-46,55,58</sup> This has bolstered enthusiasm about treatment strategies aimed at attenuating both pathogen virulence and the proinflammatory phenotype seen in the many critically ill patients with COVID-19.<sup>5,9,12,13,20,65</sup> As detailed in this review, baricitinib pairs immunosuppressive properties with antiviral activity making it a logical candidate for further evaluation in COVID-19 clinical trials.<sup>9,12,13,20</sup>

It is unlikely that a single treatment strategy will help all patients with COVID-19 or have the same effect in an individual patient as illness evolves over time. For many years, an uncontrolled proinflammatory response was thought to be the driver of poor outcomes in sepsis.<sup>66,67</sup> On

**Table 4. Laboratory and Clinical Monitoring Parameters While Receiving Baricitinib (adapted from references 10,25,26,39)**

- 
- Serum creatinine
  - Absolute lymphocyte count<sup>a</sup>
  - Absolute neutrophil count<sup>b</sup>
  - Hemoglobin<sup>c</sup>
  - Platelets
  - ALT
  - AST
  - Bilirubin
  - CPK
  - LDL/HDL (if prolonged use)
  - Signs and symptoms of infection
  - Signs and symptoms of thromboembolic events
- 

ALT = alanine aminotransferase; AST = aspartate transaminase; CPK = creatine phosphokinase; HDL = high density lipoprotein; LDL = low density lipoprotein.

<sup>a</sup>When used for rheumatoid arthritis it is recommended to interrupt therapy when the absolute lymphocyte count falls below 500 cells/mm<sup>3</sup>.

<sup>b</sup>When used for rheumatoid arthritis it is recommended to interrupt therapy when the absolute neutrophil count falls below 1000 cells/mm<sup>3</sup>.

<sup>c</sup>When used for rheumatoid arthritis it is recommended to interrupt therapy when hemoglobin falls below 8 g/dl.

the basis of this theory and supportive preclinical data, multiple immunosuppressive agents were investigated in sepsis but with uniformly disappointing results.<sup>66–71</sup> We now know that antiinflammatory mediators, which invoke a state of immunoparalysis, also contribute to poor outcomes by impairing the host's ability to clear infection and increasing vulnerability to secondary opportunistic infections.<sup>66</sup> Our understanding of the pathogenesis of and immune response to COVID-19 is rapidly evolving and, like sepsis, relative immunodeficiency also appears to be at play.<sup>9,44,46,58</sup> At this time, we do not have a reliable way to gauge whether the overruling response is pro or antiinflammatory and this complicates deployment of immunosuppressive drugs like baricitinib. If given to the wrong patient (i.e., a patient with a predominantly immunosuppressed phenotype) or at the wrong time during the illness, these drugs could cause harm by inhibiting the cytokines required for viral clearance (type-I IFNs) or immune restoration (IL-2 and IL-7).

Baricitinib's association with thromboembolic events is equally concerning in the context of treating patients with COVID-19. Markers of systemic coagulation activation have been widely reported in patients with COVID-19 and a more pronounced prothrombotic state has been correlated with a more severe disease course and poor outcomes.<sup>4,55,56</sup> These patients also have multiple thrombotic risk factors related to critical illness and the supportive care they receive. The ability to detect a thrombotic safety signal related to baricitinib may be challenging in patients with COVID-19 because pulmonary embolism symptoms overlap with symptoms of COVID-19 and imaging may not be feasible.

## Conclusions

This review highlights the current challenges faced when balancing potential risks and benefits of immunotherapies for patients with COVID-19. Moving forward, it is incumbent on researchers to develop and validate reliable tools to classify and monitor the overall immune status of patients with COVID-19 to help guide appropriate use of drugs like baricitinib.

## References

- Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;323:1574.

- Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect* 2020;80:656–665.
- Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–62.
- Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395(10229):1033–34.
- Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;361(9371):1767–72.
- Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130(5):2620–29.
- McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020;19(6):102537.
- Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev* 2020;19(7):102567.
- Center for Drug Evaluation and Research. US Food and Drug Administration. Medical review baricitinib. NDA 207-924. Apr. 2017. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/207924Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000MedR.pdf). Accessed May 12, 2020.
- Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: far-away, so close!. *Autoimmun Rev* 2020;5:102523.
- Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020;10223:e30–1.
- Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020;4:400–2.
- Kumar N, Sharma S, Kumar R, et al. Host-directed antiviral therapy. *Clin Microbiol Rev* 2020;33(3):e00168-19
- Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* 2013;12:e81355.
- Burstow NJ, Mohamed Z, Gomaa AI, et al. Hepatitis C treatment: where are we now? *Int J Gen Med* 2017;10:39–52.
- Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19. *Emerg Infect Dis* 2020;26(7):1618–20.
- Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology (Oxford)* 2019;58(Suppl\_1):i43–54.
- Pu SY, Xiao F, Schor S, et al. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. *Antiviral Res* 2018;155:67–75.
- Richardson PJ, Corbellino M, Stebbing J. Baricitinib for COVID-19: a suitable treatment? – Authors' reply. *Lancet Infect Dis*. Online ahead of print. 2020;S1473-3099(20)30270-X. [https://doi.org/10.1016/S1473-3099\(20\)30270-X](https://doi.org/10.1016/S1473-3099(20)30270-X).
- Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. *Immunol Rev* 2009;1:273–87.
- Liu KD, Gaffen SL, Goldsmith MA. JAK/STAT signaling by cytokine receptors. *Curr Opin Immunol* 1998;3:271–8.
- Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol* 2017;5:320.
- Center for Drug Evaluation and Research. US Food and Drug Administration. Pharmacology review baricitinib. NDA 207-924. Apr. 2017. [https://www.accessdata.fda.gov/drugsatfda\\_doc](https://www.accessdata.fda.gov/drugsatfda_doc)



- s/nda/2018/207924Orig1s000PharmR.pdf. Accessed 12 May 2020.
25. Committee for Medicinal Products for Human Use. European Medicines Agency. Assessment report Olumiant (baricitinib). EMAE/H/C/004085/0000. 15 Dec. 2016. Available from [https://www.ema.europa.eu/en/documents/assessment-report/olumiant-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/olumiant-epar-public-assessment-report_en.pdf). Accessed May 12, 2020.
  26. Center for Drug Evaluation and Research. US Food and Drug Administration. Clinical pharmacology and biopharmaceutics review baricitinib. NDA 207-924. Apr. 2017. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/207924Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000ClinPharmR.pdf). Accessed 12 May 2020.
  27. Spinelli FR, Conti F, Gadina M. Hijacking SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. *Sci Immunol* 2020;5(47):eabc5367.
  28. Inoue Y, Tanaka N, Tanaka Y, et al. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. *J Virol* 2007;16:8722–9.
  29. Kaksonen M, Roux A. Mechanisms of clathrin-mediated endocytosis. *Nat Rev Mol Cell Biol* 2018;5:313–26.
  30. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271–80.e8.
  31. Bekerman E, Neveu G, Shulla A, et al. Anticancer kinase inhibitors impair intracellular viral trafficking and exert broad-spectrum antiviral effects. *J Clin Invest* 2017;4:1338–52.
  32. Wang H, Yang P, Liu K, et al. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. *Cell Res* 2008;2:290–301.
  33. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 2020;181:1016–35.e19.
  34. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;17:1653–59.
  35. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol* 2014;12:1354–61.
  36. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 – preliminary report. *N Engl J Med* 2020;NEJMoa2007764. Online ahead of print. <https://doi.org/10.1056/NEJMoa2007764>.
  37. Meißner Y, Baganz S, Schneider M. Baricitinib and tofacitinib in real life – does obesity impact response to janus kinase inhibitor therapy in rheumatoid arthritis? [abstract]. *Arthritis Rheumatol* 2018;70(suppl 10). <https://acrabstracts.org/abstract/baricitinib-and-tofacitinib-in-real-life-does-obesity-impact-response-to-janus-kinase-inhibitor-therapy-in-rheumatoid-arthritis/>. Accessed May 12, 2020.
  38. Kim H, Brooks KM, Tang CC, et al. Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLE and SAVI patients. *Clin Pharmacol Ther* 2018;2:364–73.
  39. Arthritis Advisory Committee Meeting FDA Briefing Document. NDA 207924. Baricitinib Janus Kinase (JAK) inhibitor for RA. Eli Lilly and Company (Lilly). 23 April 2018. Available from <https://www.fda.gov/media/112372/download>. Accessed May 15, 2020.
  40. ClinicalTrials.gov. Available from <https://clinicaltrials.gov/ct2/results?cond=COVID&term=baricitinib&cntry=&state=&city=&dist=>. Accessed May 18, 2020.
  41. National Institutes of Health. US Department of Health and Human Services. News release. NIH clinical trial testing antiviral remdesivir plus anti-inflammatory drug baricitinib for COVID-19 begins. 8 May 2020. <https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-antiviral-remdesivir-plus-anti-inflammatory-drug-baricitinib-covid-19-begins>. Accessed 26 May 2020.
  42. Cantini F, Niccoli L, Matarrese D, Nicastrì E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. *J Infect* 2020;Online ahead of print : S0163-4453(20)30228-0.<https://doi.org/10.1016/j.jinf.2020.04.017>.
  43. Vyas D, O'Dell KM, Bandy JL, Boyce EG. Tofacitinib: the First Janus Kinase (JAK) inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother* 2013;11:1524–31.
  44. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020 Mar 12;ciaa248. Online ahead of print. <https://doi.org/10.1093/cid/ciaa248>.
  45. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061.
  46. Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020;5:533–35.
  47. Guo TFan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; e201017. Online ahead of print. <https://doi.org/10.1001/jamacardio.2020.1017>.
  48. Anjara P, Jiang M, Mundae M. Symptomatic elevation creatine kinase following treatment of rheumatoid arthritis with baricitinib. *Clin Rheumatol* 2020;2:613–14.
  49. Queeney K, Housley W, Sokolov J, Long A. Elucidating the mechanism underlying creatine phosphokinase upregulation with upadacitinib. Annual European Congress of Rheumatology, EULAR 2019, Madrid, 12–15 June 2019. FRIO131. <https://doi.org/10.1136/annrheumdis-2019-eular.7509>.
  50. Center for Drug Evaluation and Research. US Food and Drug Administration. Medical review tofacitinib. NDA 203-214. Aug. 2012. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/203214Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203214Orig1s000MedR.pdf). Accessed 15 May 2020.
  51. Center for Drug Evaluation and Research. US Food and Drug Administration. Clinical review upadacitinib. NDA 211-675. Dec. 2019. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2019/211675Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211675Orig1s000MedR.pdf). Accessed 15 May 2020.
  52. Grisouard J, Hao-Shen H, Dirnhofer S, Wagner KU, Skoda RC. Selective deletion of Jak2 in adult mouse hematopoietic cells leads to lethal anemia and thrombocytopenia. *Haematologica* 2014;4:e52–4.
  53. Meyer SC, Keller MD, Woods BA, et al. Genetic studies reveal an unexpected negative regulatory role for Jak2 in thrombopoiesis. *Blood* 2014;14:2280–4.
  54. Ng AP, Kauppi M, Metcalf D, et al. Mpl expression on megakaryocytes and platelets is dispensable for thrombopoiesis but essential to prevent myeloproliferation. *Proc Natl Acad Sci USA* 2014;16:5884–9.
  55. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;4:844–47.
  56. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis* 2020;1–4.
  57. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020;18(7):1738–42. Epub 2020 Jun 24. <https://doi.org/10.1111/jth.14850>.
  58. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. medRxiv 2020;2020.04.19.20068015.
  59. Trouillet-Assant S, Viel S, Gaymard A, et al. Type I IFN immunoprofiling in COVID-19 patients. *J Allergy Clin Immunol* 2020;146(1):206–208.e2. <https://doi.org/10.1016/j.jaci.2020.04.029>.
  60. Rawson TM, Moore LSPZhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* 2020; ciaa530. Online ahead of print. <https://doi.org/10.1093/cid/ciaa530>.
  61. Sepulveda J, Westblade LF, Whittier S, et al. Bacteremia and blood culture utilization during COVID-19 surge in New York City. *J Clin Microbiol* 2020 May 13;JCM.00875-20. Online ahead of print. <https://doi.org/10.1128/JCM.00875-20>.



62. Vallejo-Yague E, Weiler S, Micheroli R, Burden AM. Thromboembolic safety reporting of tofacitinib and baricitinib: An analysis of the WHO VigiBase. Online ahead of print. *Drug Saf*. 2020 Jun 12; Online ahead of print. <https://doi.org/10.1007/s40264-020-00958-9>.
63. Product monograph Olumiant (baricitinib) tablets. Eli Lilly Canada Inc. April 2020. <http://pi.lilly.com/ca/olumiant-ca-pm.pdf>. Accessed 15 May 2020.
64. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost* 2020;18(7):1559–1561.
65. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020 Apr 13. Online ahead of print. <https://doi.org/10.1001/jama.2020.6019>.
66. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis* 2013;3:260–8.
67. Kox WJ, Volk T, Kox SN, Volk HD. Immunomodulatory therapies in sepsis. *Intensive Care Med* 2000;S124–8.
68. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012;22:2055–64.
69. Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. *Lancet* 1998;351(9107):929–33.
70. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995;8:1430–9.
71. Dhainaut JF, Vincent JL, Richard C, et al. CDP571, a humanized antibody to human tumor necrosis factor-alpha: safety, pharmacokinetics, immune response, and influence of the antibody on cytokine concentrations in patients with septic shock. CPD571 Sepsis Study Group. *Crit Care Med* 1995;9:1461–9.