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8 **FULL TITLE**
9 Baricitinib: A review of pharmacology, safety and emerging clinical experience in COVID-19

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11 Baricitinib for COVID-19

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29 **CONFLICT OF INTEREST**

30 SCJJ, CLYT and LB have nothing to disclose. LDD has received conference development and
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56 **ABSTRACT**

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

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80 **INTRODUCTION**

81

82 Patients with severe acute respiratory syndrome coronavirus (SARS-CoV)-2 disease, (COVID-19),
83 experience a wide spectrum of clinical manifestations and illness severity.^{1, 2} Although most
84 symptomatic patients have a relatively mild clinical course, approximately 20% require hospitalization
85 and 20% of those hospitalized will be admitted to the intensive care unit (ICU).^{2, 3} In some patients a
86 sudden and rapid clinical deterioration manifesting as acute respiratory distress syndrome and multi-
87 organ failure has been observed around day 7 to 10 of hospitalization.^{1, 4} Interestingly, clinical
88 deterioration often occurs when viral titers are declining leading some to postulate that an over

89 exuberant immune response may be involved in the underlying pathophysiology of organ damage.^{5, 6}
90 This theory is supported by the correlation between COVID-19 complications and elevated levels of
91 acute phase reactants, coagulation abnormalities and hypercytokinemia, reminiscent of cytokine
92 release syndrome.^{4, 5, 7, 8} A number of agents that inhibit one or more components of the pro-
93 inflammatory cascade are now being investigated in clinical trials with hopes that blunting this
94 process may improve clinical outcomes.^{9, 10}

95
96 The use of immunosuppressive drugs during an acute viral illness carries the risk delaying viral
97 clearance and increasing vulnerability to secondary opportunistic infections.^{9, 11} Coupling these drugs
98 with effective antiviral agents, either sequentially or concurrently, may therefore be essential for
99 positive patient outcomes.^{12, 13} Antiviral drug discovery has traditionally focused on designing
100 compounds that target essential viral components, including viral proteases or polymerases.¹⁴ This
101 approach has been successful for chronic viral infections such as HIV and hepatitis C.^{15, 16} However,
102 direct-acting antivirals are typically narrow in spectrum, take years or even decades to develop and
103 may have a low barrier to resistance when used as monotherapy.¹⁴ An alternative approach that
104 may be more suitable for emerging viral pathogens is to repurpose approved drugs that target host
105 functions that viruses rely on.¹⁴ This may drastically reduce the costs and time devoted to early drug
106 discovery and these agents may, in theory, have higher barriers to resistance since most resistance
107 is secondary to mutations in the viral genome.¹⁴

108
109 Baricitinib (C₁₆H₁₇N₇O₂S, formerly LY3009104) is a small molecule reversible Janus-associated
110 kinase (JAK)-inhibitor approved in over 65 countries for the treatment of adults with moderate to
111 severe rheumatoid arthritis (RA).^{1, 5, 17} The JAK/signal transducers and activators of transcription
112 (STAT)-pathway mediates the signaling of multiple cytokines and interrupting this pathway may
113 therefore be an attractive strategy to modulate the immunopathology seen with SARS-CoV-2
114 infection.^{9, 12, 18} Furthermore, many drugs within this class exhibit antiviral effects, albeit often at
115 supra-therapeutic concentrations, by targeting host factors that viruses usurp for cell entry.^{12, 19}
116 Baricitinib has the advantage of providing *in vitro* antiviral activity at concentrations achieved with
117 approved dosing.^{13, 20}

118

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

122

123 **DATA SOURCES**

124

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

134

135 **PHARMACOLOGY AND PHARMACODYNAMICS**

136

137 Basic and translational science have identified a wide array of subcellular pathways that regulate
138 normal and aberrant immune responses.^{18, 21, 22} One of these is the JAK / STAT pathway.^{21, 22} The
139 JAK/STAT pathway mediates signal transduction from extracellular stimuli, including cytokines,
140 growth factors and hormones, to the nuclei of cells.^{21, 22} Baricitinib exerts its anti-inflammatory effects
141 through reversible JAK inhibition, as shown in Figure 1.³ Signaling is initiated when cytokines bind to
142 their receptor on the cell membrane.²² This results in conformational changes that trigger activation
143 of associated JAK complexes. JAK activation in turn leads to autophosphorylation and subsequent
144 increased JAK kinase activity as well as phosphorylation of the intracellular portion of their cognate
145 receptors.²² Receptor phosphorylation creates a docking site for signaling molecules especially
146 members of the STAT family.²² Once docked to the receptor, STAT molecules are also
147 phosphorylated by JAKs. The phosphorylated STATs are then released from the receptor, form
148 homo- or hetero-dimers through reciprocal interactions with their newly phosphorylated tyrosine
149 domains, and translocate to the cell nucleus where they bind to specific DNA sequences to activate
150 target gene transcription.²²

151

152 The JAK family is comprised of 4 cytoplasmic protein tyrosine kinases: JAK1, JAK 2, JAK3 and
153 tyrosine kinase 2 (TYK2).^{21, 22} Cytokine receptors recruit 2 of the 4 JAKs to the intracellular domain of
154 the signaling complex (i.e. JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/TYK2, Figure 1).¹⁸ Inhibition
155 of one or both JAK monomers associated with the cytokine receptor is typically sufficient to interrupt
156 signal transduction.⁴ JAK1, JAK2 and TYK2 are expressed throughout the human body whereas
157 JAK3 is primarily expressed by hematopoietic cells in the bone marrow. ^{4, 21} The various JAK
158 complexes mediate distinct cytokine signaling pathways. For example, innate antiviral responses via
159 type I interferon (IFN) are mediated by JAK1/TYK2 and IFN-gamma signaling is mediated by
160 JAK1/JAK2.^{4, 18, 23} IL-6, which has emerged as a strong predictor of poor outcomes in COVID-19,
161 transduces signaling via complexes of JAK1, JAK2 and TYK2.^{8, 9}

162

163 Baricitinib was designed to selectively inhibit JAK1 and JAK2 with less potency for JAK3. It has been
164 postulated that sparing JAK3 could reduce the immunosuppression associated with pan-JAK
165 inhibition. ^{1, 4} However as presented in Table 1, baricitinib's purported selectivity is only evident in
166 cell-free assays but not recapitulated in cell-based assays.⁴ Baricitinib 50% inhibitory concentrations
167 (IC₅₀) for JAK complexes that mediate signaling for a wide variety of cytokines implicated in COVID-
168 19 immunopathology generally fall below the free C_{max} values achieved with approved dosing (Tables
169 1 and 2).^{1, 3, 4, 13}

170

171 **ANTIVIRAL ACTIVITY**

172

173 Baricitinib may also have antiviral activity. ^{12, 13, 24} It's potential antiviral activity was identified by
174 searching a large repository of structured medical and drug information extracted using machine
175 learning (Benevolent^{AI}, London, England). Nearly 50 currently approved drugs for variety of
176 indications from oncology to auto-immune disorders were identified by this approach as inhibitors of
177 host enzymes involved in regulating intracellular viral trafficking. Only baricitinib however showed
178 inhibitory activity at clinically achievable serum concentrations.

179

180 Many viruses gain entry into human cells by hijacking host-derived membrane trafficking processes;
181 one of the most well studied, is clathrin-mediated endocytosis.^{25, 26} Clathrin is an endocytic coat
182 protein that clusters on the inner leaflet of the plasma membrane to form the initial spherical cage-

183 like vesicle structure involved in endocytosis.²⁶ Viral internalization via clathrin-mediated endocytosis
184 is shown in Figure 2. The process is initiated when the virus binds to the host cell surface receptor
185 (angiotensin-converting enzyme 2 (ACE2) in the case of SARS-CoV-2).^{25, 27} Receptor binding leads
186 to activation of 2 host-derived kinases, AP2-associated protein kinase 1 (AAK1) and cyclin G-
187 associated kinase (GAK).^{25, 28} AAK1 and GAK in turn phosphorylate and activate key host proteins
188 called adaptor protein complexes (APs).^{25, 28} Activated APs bind to the cytoplasmic tail of the cell-
189 surface receptors and recruit clathrins to assemble into a cage-like structure in preparation for
190 endocytosis.^{25, 28} Next, the cell surface receptor with bound virus is invaginated into the cage-like
191 structure which pinches off and traffics the virus and associated APs in early endosomes.^{25, 28} In
192 addition to clathrin recruitment, APs also interact with the cargo (in this case the virus) to facilitate
193 intracellular transport and regulate *trans*-Golgi network trafficking involved in subsequent stages of
194 the viral lifecycle.^{25, 28}

195
196 Baricitinib has been shown to inhibit AAK1 and, to a lesser degree, GAK (Table 1) and may thereby
197 impede viral cell entry and internal transport.^{12, 13} It is uncertain if compounds need to inhibit both
198 AAK1 and GAK to block SARS-CoV-2 viral cell entry although in murine infection models the
199 combination of both sunitinib (an anticancer drug that inhibits AAK1) and erlotinib (an anticancer drug
200 that inhibits GAK) was required to protect mice from lethal Ebola and dengue virus challenges.^{19, 28} It
201 should also be pointed out that, SARS-CoV-1 uses several different endocytic pathways for viral
202 entry^{25, 29} and if this is also true for SARS-CoV-2, baricitinib's inhibition of clathrin-mediated
203 endocytosis could be circumvented by use of an alternative pathway.

204
205 An additional antiviral mechanism related to baricitinib's inhibitory effect on IFN signaling has been
206 proposed.²⁴ As noted above, IFN responses are essential host antiviral defenses but recent work has
207 revealed that type I IFN and to a lesser extent type II IFN up-regulate ACE2 expression in multiple
208 human cell lines including upper airway epithelial cells and primary bronchial cells.³⁰ Suppressing
209 type I IFN antiviral response could, in theory, decrease ACE2 expression and thereby interfere with
210 the ability of SARS-CoV-2 to infect neighboring cells.³⁰ However, ACE2 is also counter-regulatory to
211 the renin-angiotensin-aldosterone-system (RAAS) and has a protective effect against RAAS-related
212 organ damage, including acute lung injury.³¹ One of SARS-CoV-2's key virulence factors is its ability
213 to down-regulate ACE2 expression after cell entry, thereby thwarting ACE2 lung protective effects.³¹
214 It is conceivable that baricitinib's suppression of type I IFN signaling could amplify ACE2 down-

215 regulation, further diminishing its protective effects. The net effect of IFN suppression (beneficial
216 versus detrimental) in the setting of COVID-19 might depend on the underlying immune status of the
217 patient and the stage of infection.³⁰

218

219 **PHARMACOKINETICS**

220

221 Table 2 summarizes pertinent baricitinib PK parameters which were derived from single and multiple-
222 dose studies in healthy adult volunteers and RA patients.^{1, 3, 32} After oral administration baricitinib is
223 rapidly absorbed reaching peak plasma concentrations within 60 minutes.^{1, 3} The absolute
224 bioavailability is 79% and food has minimal impact on PK parameters.^{1, 3} Baricitinib exhibits linear
225 dose proportional PK following single oral doses between 1 mg and 20 mg with minimal
226 accumulation for up to 28 days.^{3, 32} Both C_{max} and area under the concentration time curve over 24
227 hours (AUC_{24}) values increase approximately 60% and 75% in patients with RA compared to healthy
228 subjects, respectively and inter-individual variability is higher in RA patients.^{1, 3} Exposure is also
229 increased greater than 2-fold in those with moderate to severe renal impairment and end stage renal
230 disease (ESRD). Exposure in patients with COVID-19 or other acute viral infections has not been
231 reported at this time (acute infection at baseline was a contraindication for all RA clinical trials).² As
232 shown in Table 1 and 2, baricitinib free C_{max} values with 4 mg once daily dosing exceed IC_{50} values
233 for inhibition of cytokine-induced JAK/STAT signaling in cell-free and cell-based assays and
234 concentrations also exceed the dissociation constant (K_d) for AAK1 but supratherapeutic levels may
235 be required to inhibit GAK.^{1, 4, 13} Additionally, PK modeling of 4mg once daily dosing showed that
236 there is a 12 hour window when baricitinib serum levels fall below IC_{50} values for JAK complexes.¹
237 The clinical implications of this in the setting of COVID-19-related cytokine storm are unclear.

238

239 Plasma protein binding for baricitinib is 50% and is not concentration dependent. The mean volume
240 of distribution is 1.1 L/kg, suggesting moderate distribution into tissues.^{1, 3} Epithelial lining fluid
241 concentrations have not been reported.

242

243 Baricitinib is primarily cleared by renal elimination through both filtration and active secretion.^{1, 3}
244 Approximately 75% is excreted in the urine (69% unchanged) and 20% in the feces (15%
245 unchanged).^{1, 3} The half-life is 6 to 9 hours in healthy volunteers but increases to 12 hours in RA
246 patients and 19 hours in subjects with severe renal impairment or ESRD.^{1, 3} Baricitinib is effectively

247 dialyzed with a mean clearance by hemodialysis of 6 L/h.³ The impact of continuous renal
248 replacement therapy and extracorporeal membrane oxygenation on baricitinib PK have not been
249 described at this time. In population PK analyses, body weight did not have a clinically meaningful
250 impact on baricitinib clearance, however obese RA patients have been reported to have lower
251 response rates.^{3,33} As discussed in the DRUG INTERACTIONS section, baricitinib is a substrate of
252 several drug transporters which impact absorption, distribution and elimination.³

253
254 Only a small fraction (6%) of baricitinib is metabolized, predominantly by CYP3A4, and there is no
255 clinically relevant difference in baricitinib exposure in patients with moderate hepatic function (Child-
256 Pugh B).³

257
258 Baricitinib PK has been evaluated in a small number of pediatric patients (n=18, mean age 12.5
259 years, weight 9.2 kg – 84.3 kg) who received the drug through a compassionate use program for rare
260 Mendelian autoinflammatory diseases.³⁴ Weight and renal function significantly influenced volume of
261 distribution and clearance respectively, suggesting the need for weight and renal function based
262 dosing. Importantly the half-life of baricitinib was significantly shorter in children, especially among
263 those weighing less than 40 kg, and the authors of this study recommended twice daily to four times
264 daily dosing in children depending on renal function.³⁴

265
266 PK parameters in pregnant or breastfeeding women have not been reported at this time. It is not
267 known if baricitinib crosses the placenta in humans. Skeletal malformations and developmental
268 toxicity have been observed in the offspring of pregnant rats exposed to supra-therapeutic doses of
269 baricitinib.⁴ Effects on fertility in animals have been inconsistent.⁴

270 271 **DRUG-DRUG INTERACTIONS**

272
273 Baricitinib is not an inhibitor or inducer of CYP450 enzymes or drug transporters (P-glycoprotein,
274 BCRP, OATP1B1, OATP1B3, OCT 1-3, MATE-1, MATE2-K) at clinically relevant concentrations.^{1,3}
275 Although a small fraction (6%) of baricitinib is metabolized by CYP3A4, co-administration with
276 ketoconazole (a strong CYP3A4 inhibitor) or rifampin (a strong CYP3A4 inducer) did not have a
277 clinically meaningful impact on baricitinib PK.^{1,3}

278

279 As noted in the PK section, baricitinib is a substrate of several drug transporters (P-glycoprotein,
280 BCRP, MATE2-K, OAT3).^{1,3} Co-administration with cyclosporine (P-glycoprotein inhibitor) did not
281 result in clinically relevant changes to baricitinib PK however, co-administration with probenecid (a
282 strong OAT3 inhibitor) lead to decreased renal clearance and a ~2-fold increase in AUC.^{1,3} Dose
283 reduction is recommended in patients taking strong OAT3-inhibitors (see DOSAGE AND
284 ADMINISTRATION section).^{1,3} Based on PK modeling, less potent OAT3 inhibitors such as
285 ibuprofen and diclofenac are expected to have minimal impact on baricitinib PK.³ Studies examining
286 the impact of BCRP or MATEK-2 inhibitors have not been reported at this time. Increased gastric pH
287 and the use of proton-pump inhibitors does not alter overall exposure to baricitinib although the time
288 to peak plasma concentrations was prolonged to 2 hours with concomitant administration of
289 omeprazole.³ No signal of QT_c interval prolongation has been observed with baricitinib doses up to
290 40 mg in healthy volunteers.^{2,34}

291

292 **CLINICAL EXPERIENCE FOR COVID-19**

293

294 Baricitinib is under investigation in multiple ongoing clinical studies (Table 3), including the second
295 iteration of the National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19
296 Treatment Trial (ACTT-2).²⁷⁻²⁹ ACTT-2 is an adaptive, randomized, double-blind, active-controlled
297 multinational study.^{27,29} Hospitalized patients with laboratory confirmed SARS-CoV-2 infection and
298 one of the following are eligible for enrolment: infiltrates on chest imaging, an oxygen saturation ≤
299 94% on room air, need for supplemental oxygen or need for mechanical ventilation.²⁹ The primary
300 endpoint is time to recovery within 28 days after randomization using a 3-point ordinal scale.²⁹ In the
301 first iteration of the study (ACTT-1), patients were randomized to the antiviral drug, remdesivir, or
302 placebo.³³ Preliminary results were recently published after enrolling over 1000 patients: the median
303 time to recovery was significantly shorter in the remdesivir group (11 days vs. 15 days, hazard ratio
304 1.32; 95% confidence interval 1.12 – 1.55).³³ Moving forward in ACTT-2, all patients will receive
305 remdesivir and additionally be randomized to baricitinib 4 mg daily or placebo for up to 14 days.²⁷

306 The off-label use of baricitinib in patients with COVID-19 was recently reported in a small before-after
307 study of patients at centers in the Northern Italian province of Prato.³⁵ This study included
308 consecutive patients hospitalized between March 16 and 30, 2020 with moderate COVID-19 defined
309 as a positive SAR-CoV-2 real-time polymerase chain reaction (RT-PCR) nasopharyngeal or

310 oropharyngeal swab, evidence of pneumonia on chest imaging and 3 of fever, cough, myalgia or
311 fatigue. Patients (n=12) were treated with lopinavir/ritonavir (250 mg twice daily) plus baricitinib (4 mg
312 daily) for 14 days. Those with thrombophlebitis, latent tuberculosis and pregnant or breastfeeding
313 women were excluded. An equal number of patients with moderate COVID-19 admitted in the week
314 preceding this period served as the control group. All patients in the control group received
315 lopinavir/ritonavir (250 mg twice daily) plus hydroxychloroquine (400 mg daily) for 14 days.³⁵

316 Overall, recorded demographics, comorbidities and baseline signs and symptoms were similar in the
317 2 groups.³⁵ The median oxygen saturation was 91-92% and none of the patients resided in the ICU
318 at enrolment. At 2 weeks, most clinical and laboratory parameters had normalized in the baricitinib
319 group, no patients required ICU admission and 7 (58%) were discharged home. In the control group,
320 there was no significant improvement in most clinical and laboratory parameters, 4 (33%) required
321 ICU admission and 1 (8%) was discharged home. With regards to safety, no new bacterial, viral or
322 opportunistic infections were reported in either group. Baricitinib (and lopinavir/ritonavir) was stopped
323 in 1 patient after 10 days due to increased transaminases.³⁵ Platelets increased from a median of
324 $203 \times 10^9/L$ at baseline to $354 \times 10^9/L$ at day 14 in patients who received baricitinib ($p = 0.018$).
325 There was no change in platelets over 2 weeks in the control group (see SAFETY section for further
326 discussion on increased platelets associated with baricitinib).³⁵

327 The authors of this report rightly acknowledge its main weaknesses including the lack of a
328 randomized control group and the small sample size.³⁵ The use of a historical control group in an
329 emerging infectious disease is fraught with limitations due to rapidly evolving knowledge and patterns
330 of care. In addition, the use of concomitant antiviral and adjunctive agents complicates interpretation.
331 The small sample size and short duration of follow-up do not allow a meaningful assessment of
332 safety. Finally, although the authors report that antibiotics were only used when bacterial infection
333 was suspected, it is unclear if any were in fact administered; this information is important when
334 interpreting rates of secondary infections.

335

336 SAFETY

337

338 Pooled data from 3492 baricitinib exposed patients (7860 patient-years) enrolled in Phase 2 and 3
339 RA clinical trials together with long-term extensions of these studies in the baricitinib development

340 program has been used to characterize baricitinib's safety profile.^{2, 23} One caveat to these analyses is
341 that patients in the placebo or baricitinib 2 mg/day arms of many studies were allowed to crossover
342 to the 4 mg/day group after week 16 which complicates interpretation and raises the possibility that
343 some risks in the 4 mg/day group may be overestimated. Furthermore, as discussed below, although
344 many adverse effects appeared to be dose related, far fewer patients were exposed to 2 mg/day so
345 there is more uncertainty in relative risk estimates. In ongoing COVID-19 studies, the duration of
346 baricitinib therapy is typically 7 to 14 days. Safety data by contrast is derived from patients who
347 received baricitinib for months and many adverse effects manifested after prolonged exposures.
348 Finally, all trials excluded patients with acute infections at baseline limiting generalizability for
349 COVID-19 patients.

350
351 The most common side effects with baricitinib are upper respiratory tract infection (14-22%),
352 headache (11-24%) and nasopharyngitis (11-18%).² In addition, dose-related changes in multiple
353 laboratory parameters have been observed in patients treated with baricitinib.^{2, 23} Many of these have
354 been reported with other JAK-inhibitors and include rapid and sustained decreases in neutrophil and
355 lymphocyte counts, decreases in hemoglobin, small increases in creatinine (< 0.1 mg/dL), increases
356 in lipid parameters, elevations in liver enzymes and bilirubin and increases in creatine
357 phosphokinase (CPK).^{18, 36} Decreases in lymphocyte counts have been associated with higher rates
358 of treatment emergent infections among RA patients in clinical trials.^{2, 34} Lymphopenia is one of the
359 most prominent laboratory abnormalities in COVID-19 patients and lower lymphocyte counts have
360 been associated with more severe disease.^{37, 38} In addition to being quantitatively reduced,
361 lymphocytes from SARS-CoV-2 infected patients also show functional exhaustion and decreased
362 functional diversity.³⁹ The consequences of exacerbating this immunophenotype with baricitinib
363 requires further study.

364
365 The significance of modest increases in lipid parameters has been difficult to predict; major cardiac
366 events have occurred in a small number of patients in RA trials, most commonly in extension phases
367 after week 52 but a clear a link with lipid parameters has not been reported. Patients with preexisting
368 cardiovascular diseases are at increased risk of the most severe COVID-19 complications.^{32, 40}
369 Furthermore, myocardial injury has been observed in nearly 30% of hospitalized patients with
370 COVID-19 and is significantly associated with higher short term mortality.^{32, 40} However, in this

371 setting, the underlying pathogenesis of myocardial injury may be related to the pro-inflammatory
372 response to infection⁴⁰ and countering this with baricitinib could conceivably be protective.

373

374 Although increases in liver enzymes and bilirubin have been reported with baricitinib, no cases of
375 liver injury satisfying Hy's law have occurred.^{2, 34} Thirteen patients were withdrawn from studies due
376 to liver function test abnormalities (vs. 1 withdrawal with placebo) and patients with transaminase
377 elevations at baseline (> 1.5 x the upper limit of normal) have been excluded from all studies.^{2, 34}
378 Many patients who experienced liver function test abnormalities were receiving concomitant
379 hepatotoxic drugs (i.e. methotrexate or isoniazid). In case series, between 2% and 11% of patients
380 with COVID-19 had chronic liver comorbidities and 14% to 53% had elevated transaminases during
381 the course of the disease (reviewed in⁴⁰). Furthermore, higher rates of liver dysfunction have been
382 correlated with more severe COVID-19.⁴⁰ Hepatotoxic drug effects may be difficult to detect in these
383 circumstances and clinicians may need to maintain a high index of suspicion.

384

385 In the clinical trials program, CPK elevations were not associated with muscle pain or
386 rhabdomyolysis.^{2, 34} However, a recent report describes 2 RA patients who developed unexplained
387 lower and/or upper extremity muscle pain and joint swelling coupled with moderate CPK elevations
388 following the initiation of baricitinib.⁴¹ In both cases, clinical and biochemical resolution occurred
389 rapidly following baricitinib discontinuation.⁴¹ The mechanism behind baricitinib-associated CPK
390 elevations has not been widely studied although experimental evidence supports the theory that
391 certain pro-inflammatory cytokines may block differentiation of myoblasts into mature myocytes.⁴²
392 CPK increases observed with JAK-inhibitors may therefore represent recovery of muscle
393 development and CPK expression.⁴²

394 Increased CPK is correlated has been with mortality in COVID-19⁴ and rhabdomyolysis has been
395 reported as a late complication.¹⁷ The interaction between possible baricitinib-associated CPK
396 elevations and those secondary to COVID-19 requires further study.

397

398 Increased platelet counts is a unique baricitinib effect and has not been observed with other JAK-
399 inhibitors.^{2, 36, 43} In fact, small decreases in platelets and occasional thrombocytopenia occur 2 other
400 JAK-inhibitors, tofacitinib and upadacitinib.^{36, 43} With baricitinib, platelet counts increase rapidly after
401 initiation and peak around week 2 (mean increase $50 \times 10^9/L$).^{2, 23} Thereafter they decline and
402 stabilize but remain above placebo and comparators for the duration of therapy. Thrombocytosis

403 appears to be dose related but still occurs with the 2 mg/day dose. No clear temporal or quantitative
404 association between platelet increases and thromboembolic events (discussed below) has been
405 established.^{2, 23} The etiology is not known although the prevailing theory, based on animal
406 experiments, implicates selective JAK2 inhibition in increased circulating thrombopoietin (TPO, the
407 hormone that stimulates megakaryopoiesis and platelet production) levels. TPO signals are
408 transduced by JAK2. Knockout of the *Jak2* gene in hematopoietic stem cells (HSCs) results in
409 thrombocytopenia in mice.⁴⁴ In contrast deletion of *Jak2* or the TPO receptor gene in
410 megakaryocytes and mature platelets results in thrombocytosis.^{23, 45, 46} Megakaryocytes and mature
411 platelets are responsible for internalizing and degrading circulating TPO by a JAK2 dependent
412 mechanism.^{23, 45, 46} Thus it is possible that predominant JAK2 inhibition at the level of
413 megakaryocytes and mature platelets may lead to increased circulating TPO resulting in the
414 increased platelet counts seen with baricitinib. JAK-inhibitors that are less selective for JAK2 may act
415 mainly on JAK2 signaling at the level of HSCs to decrease platelet production.²³ Early case series
416 from Wuhan, China suggested thrombocytopenia was a prominent feature of severe COVID-19.⁴⁷
417 For unclear reasons, later studies and those from other regions have shown normal or even elevated
418 platelet counts in COVID-19 patients.^{48, 49} The impact of thrombocytosis secondary to baricitinib in
419 the setting of the COVID-19 coagulopathy is difficult to predict.

420
421 Besides common side effects and changes in laboratory parameters, baricitinib has been associated
422 with serious adverse effects including infections, thrombosis, malignancy, gastrointestinal
423 perforations, and major cardiovascular events.^{2, 23} Adverse effects of particular relevance to COVID-
424 19 patients are infection and thrombosis and are expanded upon below.

425
426 Overall the incidence of serious and opportunistic infections in RA patients treated with JAK-
427 inhibitors is comparable to other biological DMARDs, however the risk of viral infections, specifically
428 herpes zoster virus (HZV) reactivation, appears to be higher with JAK-inhibitors.²³ HZV reactivation
429 rates are approximately 1.5 to 2-fold higher among RA patients taking JAK-inhibitors (3.2 – 4.0 cases
430 / 100 patient years) compared to the general RA population.^{2, 11, 23} Other factors associated with
431 decreased cell-mediated immunity, such as older age and concomitant steroid use, amplify this
432 risk.²³ The incidence of HZV and other infections were numerically higher with baricitinib 4mg/day
433 versus 2 mg/day.²³ Type I IFNs orchestrate a critical antiviral defense via the JAK/STAT pathway and
434 their inhibition by baricitinib is thought to be responsible for HSV reactivation.^{9, 23} Critically ill patients

435 with COVID-19 demonstrate an impaired type I IFN response and the degree of impairment has
436 been correlated with higher viral loads and poor outcomes.^{50, 51} Interestingly, type I IFN deficiency
437 was associated with an exacerbated inflammatory response with markedly elevated levels of IL-6
438 and tumor necrosis factor (TNF)- α . These data suggest timing of baricitinib initiation may be
439 important to both avoid amplifying impaired innate immunity and suppress a harmful
440 hyperinflammatory response. An additional concern with baricitinib use in COVID-19 is its inhibition
441 of signaling from mediators of immune restoration (i.e. IL-2 and IL-7) which may make patients more
442 vulnerable to nosocomial infections.⁹ Although rates of co- or secondary infections in COVID-19
443 patients have been low,^{52, 53} little is known about incidence with the use of immunosuppressive
444 drugs.

445
446 With regards to thrombosis, there was a numerical imbalance in both arterial and venous
447 thromboembolic events (VTE) not favoring baricitinib treated patients in pooled safety data, primarily
448 with 4 mg/day.^{2, 34} Five VTEs occurred in patients receiving baricitinib 4 mg/day during the first 16
449 weeks of therapy (compared to zero in the baricitinib 2 mg/day and placebo groups) and additional
450 events continued to accumulate in both the 4 mg/day and 2 mg/day groups with extended follow-up.
451 In total 39 VTE have been reported with baricitinib in the clinical trials program (34 at 4 mg/day and 5
452 at 2 mg/day) compared to none with placebo (VTE incidence rates 0.6 / 100 patient year and 0.4 /
453 100 patient year for 4 mg/day and 2 mg/day, respectively). Twenty-nine arterial thrombotic events
454 have also been reported in patients who received baricitinib (incidence rates 0.5 / 100 patient year
455 and 0.3 / 100 patient year for 4 mg/day and 2 mg/day respectively) versus 1 event with placebo.^{2, 34} It
456 should be noted that in population-based observational studies, VTE rates among individuals with
457 RA on DMARDs range from 0.68 to 1.63 /100 patient years, in line with what was observed in the
458 baricitinib RCTs, however differences in study designs and patient populations make such
459 comparisons problematic.^{2, 34} Furthermore, an increased incidence of thromboembolic events was
460 also recently reported with higher doses of tofacitinib, another JAK-inhibitor used for RA.⁵⁴
461 Thrombotic events and other dose-related adverse effects coupled with the absence of a clear
462 efficacy benefit in RA with the 4 mg/day versus 2 mg/day dose were the primary reasons behind the
463 FDA's failure to approve the manufacturer's first submission in 2017.^{2, 34} Baricitinib was approved one
464 year later but only at the lower 2 mg/day dose.^{2, 34} Health Canada has similarly only approved the 2
465 mg/day dose.¹⁷ Four mg/day has been approved in some European and Asian countries however.¹
466 (see DOSAGE AND ADMINISTRATION section).

467

468 The coagulation system is closely linked to inflammation through the innate immune system and
469 patients with COVID-19 appear to have an increased proclivity towards immunothrombosis.^{49, 55}

470 Common coagulation abnormalities include elevations in D-dimer and fibrinogen and prolonged
471 prothrombin time.^{49, 55} Published series also describe what appears to be a higher than expected

472 incidence of VTE.^{49, 55} Baricitinib's inhibition of inflammatory mediators that also drive

473 immunothrombosis could have collateral benefits of reducing hypercoagulability; it is equally

474 plausible however that baricitinib's pro-thrombotic tendencies could be detrimental. Moving forward,

475 thorough baseline risk assessment and use of the minimally effect dose will be important in

476 minimizing iatrogenic harm. Suggested monitoring parameters for patients receiving baricitinib are

477 shown in Table 4.

478

479 **DOSAGE AND ADMINISTRATION**

480

481 When used for RA, baricitinib is taken once daily by mouth with or without food. The recommended

482 starting dose in Europe is 4 mg/day with the option to decrease to 2 mg/day when RA signs and

483 symptoms are controlled.¹ In Canada and US, only 2 mg/day is approved.^{2, 17} As shown in Table 3,

484 both 2 mg/day and 4 mg/day are being tested in clinical trials. Recommendations for dosage

485 reductions vary by country. The EMA recommends a 50% dose reduction in the following patients:

486 age \geq 75 years, a history of chronic or recurrent infections, creatinine clearance (CrCl) between 30

487 mL/min and 60 mL/min, and concomitant use of a strong OAT3-inhibitor.¹ According to current

488 prescribing information, baricitinib should not be initiated and therapy should be interrupted for the

489 following laboratory parameters: absolute lymphocyte count $< 0.5 \times 10^9/L$, absolute neutrophil count

490 $< 1 \times 10^9/L$ and hemoglobin < 8 g/mL.^{1, 2, 17} Baricitinib is contraindicated in patients with CrCl < 30

491 mL/min.^{1, 2, 17} Baricitinib is only available as a film-coated, immediate release tablet.¹ There is no

492 published data on the stability and bioavailability of crushed/dissolved tablets or extemporaneously

493 compounded suspensions at this time.

494

495 **DISCUSSION**

496

497 A growing body of evidence suggests that the host immune response to SARS-Cov-2 infection may

498 be critically import in determining outcomes.^{8, 37-39, 47, 50} This has bolstered enthusiasm about

499 treatment strategies aimed at attenuating both pathogen virulence and the pro-inflammatory
500 phenotype seen in the many critically ill patients with COVID-19.^{5, 9, 12, 13, 20, 56} As detailed in this
501 review, baricitinib pairs immunosuppressive properties with antiviral activity making it a logical
502 candidate for further evaluation in COVID-19 clinical trials.^{9, 12, 13, 20}

503

504 It is unlikely that a single treatment strategy will help all patients with COVID-19 or have the same
505 effect in an individual patient as illness evolves over time. For many years, an uncontrolled pro-
506 inflammatory response was thought to be the driver of poor outcomes in sepsis.^{57, 58} On the basis of
507 this theory and supportive pre-clinical data, multiple immunosuppressive agents were investigated in
508 sepsis but with uniformly disappointing results.⁵⁷⁻⁶² We now know that anti-inflammatory mediators,
509 which invoke a state of immunoparalysis, also contribute to poor outcomes by impairing the host's
510 ability to clear infection and increasing vulnerability to secondary opportunistic infections.⁵⁷ Our
511 understanding of the pathogenesis of and immune response to COVID-19 is rapidly evolving and,
512 like sepsis, relative immunodeficiency also appears to be at play.^{9, 37, 39, 50} At this time we do not have
513 a reliable way to gauge whether the over-ruling response is pro or anti-inflammatory and this
514 complicates deployment of immunosuppressive drugs like baricitinib. If given to the wrong patient
515 (i.e. a patient with a predominantly immunosuppressed phenotype) or at the wrong time during the
516 illness, these drugs could cause harm by inhibiting the cytokines required for viral clearance (type-I
517 IFNs) or immune restoration (IL-2, IL-7).

518

519 Baricitinib's associated with thromboembolic events is equally concerning in the context of treating
520 patients with COVID-19. Markers of systemic coagulation activation have been widely reported in
521 patients with COVID-19 and a more pronounced prothrombotic state has been correlated with a
522 more severe disease course and poor outcomes.^{4, 47, 48} These patients also have multiple thrombotic
523 risk factors related to critical illness and the supportive care they receive. The ability to detect a
524 thrombotic safety signal related to baricitinib may be challenging in patients with COVID-19 since
525 pulmonary embolism symptoms overlap with symptoms of COVID-19 and imaging may not be
526 feasible.

527

528 **CONCLUSIONS**

529

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

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Table 1: Anti-inflammatory and antiviral activity of baricitinib (adapted from ^{4, 13, 20})

JAK enzymes (cell-free)	Baricitinib mean IC₅₀ (nM)	JAK enzyme pair (cell-based)^a	Baricitinib mean IC₅₀ (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_d (nM)	NAK enzymes (cell-based)^b	Baricitinib K_d (nM)
AAK1	17	AAK1	34
GAK	136	GAK	272

a. Across multiple cell-types including B-cells, CD⁴⁺ T-cells, CD⁸⁺ T-cells, Natural killer cells and monocytes

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

AAK1: AP2-associated protein kinase 1; GAK: cyclin G-associated kinase; JAK: Janus-associated kinase; NAK: numb-associated kinase; TYK2: tyrosine kinase 2

Table 2: Pharmacokinetic parameters of baricitinib 4 mg orally once daily (adapted from ^{1,3})

Parameter	Value	
C _{max, ss} ^a	Total	Free
	53.4 ng/mL 143.8 nM ^b	26.7 ng/mL 71.9 nM ^b
C _{min, ss} ^a	Total	Free
	6.9 ng/mL 18.6 nM ^b	3.5 ng/mL 9.3 nM ^b
AUC ₂₄ ^a	477.6 ng*h/mL 1285.9 nM ^b	
Bioavailability	79%	
V _d	75.7 L	
Free fraction	50%	
T _{1/2}		
Healthy subjects	6 – 9 hours	
RA patients	12 hours	
a. Concentrations from studies in patients with RA		

b. Calculated based on molecular mass 371.42¹

AUC: area under the concentration time curve; $C_{max, ss}$: 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

Table 3: Ongoing clinical studies registered on ClinicalTrials.gov of baricitinib for COVID-19 (adapted from ^{27, 54})

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"> • Remdesivir IV 200 mg day 1 then 100 mg days 2 – 10 x 10 days PLUS one of: • Baricitinib 4 mg PO OD x 14 days • Placebo x 14 days 	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"> • Baricitinib 2 mg PO OD x 14 days 	USA	Grade 3 or 4 adverse events	80	University of Colorado
NCT04390464	Randomized, multicenter, parallel assignment, open label	<ul style="list-style-type: none"> • Baricitinib 4 mg PO OD x 14 days • Ravulizumab IV (weight-based dosing) on day 1 • Standard of care 	UK	Time to composite endpoint 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	<ul style="list-style-type: none"> • Baricitinib • Anakinra 	Spain	All-cause mortality	576	Complejo Hospitalario Universitario de

	cohort study					Albacete
NCT04346147	Randomized, single-center, parallel assignment, open-label	<ul style="list-style-type: none"> Hydroxychloroquine 200 mg PO BID x 7 days PLUS one of: <ul style="list-style-type: none"> Baricitinib 4 mg PO OD x 7 days Lopinavir/ritonavir 200/50 mg PO OD x 7 days Imatinib 400 mg PO OD x 7 days 	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"> Lopinavir/ritonavir 200/50 mg PO OD x 7 days PLUS Baricitinib 4 mg PO OD x 14 days 	Italy	ICU transfer	200	Hospital of Prato

		<ul style="list-style-type: none"> • Antiviral and/or hydroxychloroquine 				
NCT04373044	Prospective, single-arm, two-center, open-label	<ul style="list-style-type: none"> • Baricitinib 4 mg PO OD x 14 days PLUS one of the following at the treating physician's discretion: • Hydroxychloroquine Lopinavir/ritonavir • Remdesivir (doses not reported) 	USA	Death or mechanical ventilation at day 14	59	University of Southern California
NCT04321993	Non-randomized, multi-center, parallel	<ul style="list-style-type: none"> • Baricitinib 2 mg PO OD x 10 days Hydroxychloroquine 400 mg PO BID x 	Canada	Clinical improvement on 7-point ordinal scale at day 15	1000	Lisa Barrett

	assignment, open label	<p>10 days</p> <ul style="list-style-type: none"> Lopinavir/ritonavir 500/100 mg PO BID x 10 days 				
NCT04345289	Adaptive, multicenter, randomized, double-blind, placebo- controlled	<ul style="list-style-type: none"> Baricitinib 4 mg PO OD x 7 days Convalescent plasma 600 mL IV x 1 dose Sarilumab 200 mg SC x 1 dose Hydroxychloroquine 600 mg PO OD x 7 days Placebo 	Denmark	All-cause mortality of need for mechanical ventilation at day 28	1500	Thomas Benfield
<p>BID: twice daily; CV: cardiovascular; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IV: intravenous; OD: once daily; PO: orally; SC: subcutaneous; UK: United Kingdom; USA: United States of America</p>						

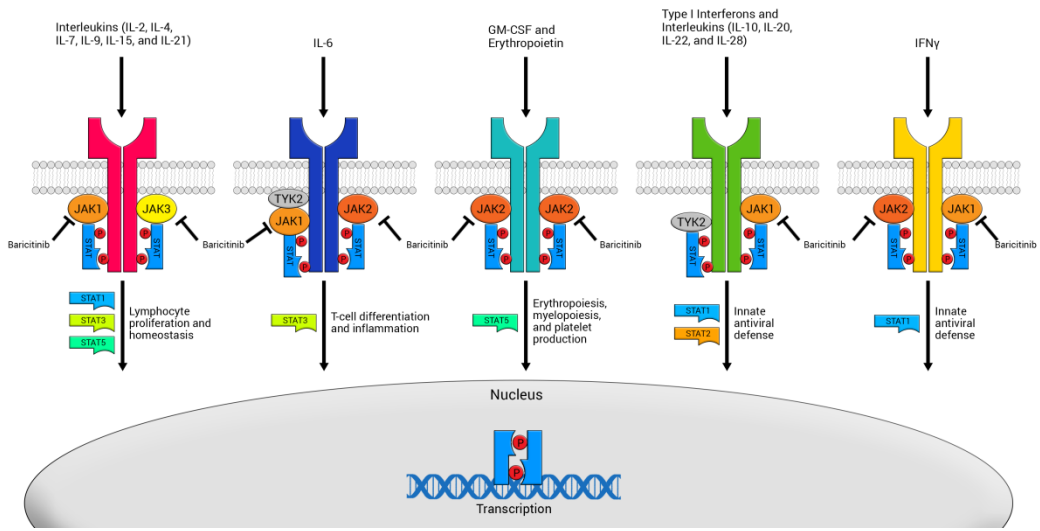
Table 4: Laboratory and clinical monitoring parameters while receiving baricitinib^{10, 43, 63, 64}

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

a. When used for RA it is recommended to interrupt therapy when the absolute lymphocyte count falls below 500 cells/mm³

- b. When used for RA it is recommended to interrupt therapy when the absolute neutrophil count falls below 1000 cells/mm³
- c. When used for RA it is recommended to interrupt therapy when hemoglobin falls below 8 g/dL

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



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