

## Should baricitinib be used for COVID-19?

*This clinical evidence summary outlines existing evidence on the use of baricitinib as a potential treatment for patients with COVID-19. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.*

### Background

Baricitinib is a Janus-associated kinase inhibitor (JAK inhibitor) acting against JAK1 and JAK2. It is currently approved by regulatory agencies (including US FDA, EMA and HSA) to treat rheumatoid arthritis.

Artificial intelligence has identified a group of drugs (including baricitinib) that could inhibit receptor-mediated endocytosis, which is the mechanism that most viruses use to enter cells.<sup>1,2</sup> A known regulator of endocytosis is the adaptor-associated protein kinase-1 (AAK1) and disruption of this regulator may interrupt the passage of the virus into cells and the intracellular assembly of virus particles. Baricitinib has shown particularly high affinity for AAK1 and also binds cyclin G-associated kinase (GAK) another regulator of endocytosis.<sup>1,2</sup> Further, there is growing interest in using baricitinib in combination with direct-acting antivirals, including lopinavir, ritonavir and remdesivir, since it has minimal interaction with the relevant cytochrome P450 drug-metabolising enzyme.<sup>1,2</sup> However, there are also concerns with its use as baricitinib can inhibit a variety of inflammatory cytokines including interferon- $\alpha$ , which plays an important role in curbing virus activity.<sup>3,4</sup>

While other JAK inhibitors such as ruxolitinib and fedratinib may also have activity against COVID-19, the predicted unbound plasma exposure required to inhibit receptor mediated endocytosis with these treatments greatly exceeds their tolerated doses. Therefore, they are unlikely to be suitable for patients with COVID-19 to reduce viral infectivity.<sup>2</sup>

Recently, online news articles have listed JAK inhibitors, such as baricitinib, as potential COVID-19 treatment options.<sup>5,6</sup>

### Clinical evidence

Published evidence for the use of baricitinib to treat COVID-19 is limited. In a single arm study of 12 patients with moderate COVID-19 pneumonia treated with baricitinib and lopinavir/ritonavir (NCT04358614), all clinical and respiratory function parameters significantly improved both at week 1 and week 2 compared with baseline. When compared with a cohort previously treated with standard of care (lopinavir/ritonavir and hydroxychloroquine), the group administered baricitinib had fewer ICU transfers (0% versus 33%) and a higher discharge rate at week 2 (58% versus 8%). No infections, cardiovascular, or haematological adverse events occurred after two weeks of treatment.<sup>7,8</sup>

In clinical trials when used for the treatment of rheumatoid arthritis (with a median treatment duration of two years) the most significant side effect reported was a small increase in upper respiratory infection and severe infections such as herpes zoster. Haematological abnormalities such as low absolute neutrophil count, absolute lymphocyte count, and haemoglobin level were also reported in less than 1% of patients treated with baricitinib in the clinical trials. As the use of baricitinib for COVID-19 is expected to be short-term, and the risk of infection is low, baricitinib is considered to have a relatively acceptable side-effect profile.<sup>2,9</sup>

Several other international trials of baricitinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future (Table 1).

**Table 1: Studies registered internationally for baricitinib in patients with COVID-19**

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
NCT04320277 <sup>10</sup>	SC*, OL, phIII, cross-over	Baricitinib + ritonavir	Antiviral and/or hydroxychloroquine	June 2020
NCT04321993 <sup>11</sup>	OL, phII, non-randomised parallel assignment	Baricitinib Other arms: Lopinavir/ritonavir Hydroxychloroquine Sarilumab	Standard of care	February 2022
NCT04340232 <sup>12</sup>	SC <sup>^</sup> , OL, phII/phIII, single arm	Baricitinib	-	August 2020
NCT04346147 <sup>13</sup> EudraCT 2020-001321-31 <sup>14</sup>	SC <sup>#</sup> , OL, phII, randomised, parallel assignment	Baricitinib + hydroxychloroquine Other arms: Lopinavir/ritonavir + hydroxychloroquine, Imatinib + hydroxychloroquine	-	August 2020
NCT04345289 <sup>15</sup> EudraCT 2020-001367-88 <sup>16</sup>	MC, DB, phIII, randomised	Baricitinib Other arms: convalescent plasma, sarilumab, hydroxychloroquine	Injective placebo, oral placebo	June 2021
NCT04358614 <sup>17</sup>	SC*, OL, single arm	Baricitinib + lopinavir/ritonavir	Standard of care (lopinavir/ritonavir and hydroxychloroquine)	Completed (April 2020)
NCT04373044 <sup>18</sup>	MC <sup>^</sup> , OL, phII, single arm	Baricitinib + hydroxychloroquine or lopinavir/ritonavir or remdesivir	-	May 2021
NCT04362943 <sup>19</sup>	SC <sup>#</sup> , retrospective cohort study	Baricitinib Other arms: Anakinra	-	May 2020
NCT04365764 <sup>20</sup> EudraCT 2020-001246-18 <sup>21</sup>	MC <sup>Ω</sup> , observational, case-control study	Various treatments including baricitinib	-	May 2020
NCT04390464 <sup>22</sup> EudraCT 2020-001354-22 <sup>23</sup> (TACTIC-R) <sup>24</sup>	MC <sup>α</sup> , OL, phIV, randomised	Baricitinib Other arms: Ravulizumab	Standard of care	May 2021
NCT04401579 <sup>25</sup> EudraCT 2020-001052-18 <sup>26</sup> Adaptive COVID-19 Treatment Trial (ACTT) 2 <sup>27</sup>	MC, DB, phIII, randomised	Baricitinib + remdesivir	Placebo + remdesivir	August 2023
NCT04399798 (BREATH) <sup>28</sup>	SC*, phII, single arm	Baricitinib	-	September 2020
NCT04393051 <sup>29</sup>	MC*, OL, phII, randomised	Baricitinib + standard of care	Standard of care	June 2020
NCT04366206 <sup>30</sup>	MC <sup>α</sup> , cohort study	Various treatments including baricitinib	-	July 2020
NCT04421027 <sup>31</sup> (COV-BARRIER)	MC, DB, phIII, randomized	Baricitinib + background therapy	Placebo + background therapy	September 2020

Abbreviations: DB, double blind; MC, multicentre; NA, not available; OL, open label, phII, phase II; phIII, phase III; phIV: phase IV; SC, single centre.

\* Italy ^USA # Spain Ω France α UK

## Recommendations from professional bodies

The World Health Organization (WHO) has yet to recommend any specific medicine to prevent or treat COVID-19.<sup>32</sup>

The National Institutes of Health (NIH, USA) does not recommend the use of baricitinib outside of a trial setting.<sup>33</sup> The National Centre for Infectious Diseases of Singapore (NCID) also do not recommend routine use of baricitinib; however, the NCID states that the use of immunomodulators may be considered in select patients with cytokine storm/hyperinflammation, and after careful discussion with multi-disciplinary input (rheumatology-allergy-immunology, infectious diseases, intensive care specialists).<sup>34</sup>

Interim clinical guidance from the Centers for Disease Control and Prevention (CDC, USA) on the management of coronavirus, guidelines on management of critically ill adults with COVID-19 from the European Society of Intensive Care Medicine and the Society of Critical Care Medicine and the seventh edition of the Chinese National Health Commission (NHC) Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment do not specifically refer to baricitinib.<sup>35-37</sup>

## Conclusion

Current evidence on the efficacy and safety of baricitinib for treating COVID-19 infection is limited. No firm scientific conclusion can be made, although the drug appears to be relatively safe and well tolerated when used for rheumatoid arthritis. Several ongoing studies of baricitinib for COVID-19 are likely to report results in the months ahead, and their findings will determine whether baricitinib should be used more widely in this setting.

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