



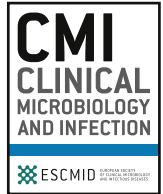
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Commentary

Successful immunomodulators for the treatment of COVID-19 have opened the pathway for comparative trials

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Because coronavirus disease 2019 (COVID-19) became a dominant factor in our daily lives, we have learned a tremendous amount about it through both study and shared experience. Therapies for patients hospitalized for COVID-19 have improved from ineffective shots in the dark, through mildly effective antivirals, to mortality-reducing immunomodulatory therapies [1]. The widely accepted view of COVID-19 as a dual-phase illness with a viral component and an inflammatory component has led to the successful search for immunomodulatory therapies to attenuate host response and improve outcomes [2,3]. As studies have advanced, our standard of care has advanced as well; patients with severe and critical COVID-19 now receive combinations of these corticosteroids with Janus kinase inhibitors or interleukin 6 inhibitors [4–6]. What have largely not occurred thus far are comparative, head-to-head trials to determine which therapies are best. Two comparison trials exist, only one of which is direct. One is the IL-6 inhibitor arm of the REMAP-CAP trial (Randomised, Embedded, Multi-factorial,

Adaptive Platform Trial for Community-Acquired Pneumonia), in which tocilizumab and sarilumab are compared separately to the standard of care [7]. This trial showed improved outcomes in patients with progressive critical COVID-19 receiving tocilizumab or sarilumab with corticosteroids compared with the outcomes in controls, although only 48 patients received sarilumab in the study, whereas 353 patients received tocilizumab [7]. In the other trial, which is available as a preprint, Karampitsakos et al. [8] directly compared tocilizumab to baricitinib in patients with a partial pressure of inhaled oxygen to fraction of inhaled oxygen (PaO₂-to-FiO₂) ratio of <200. This open-label randomized study of 251 patients showed noninferiority of baricitinib to tocilizumab using their criteria (upper bound of the hazard ratio for death or mechanical ventilation not exceeding 1.5) [8].

The paucity of head-to-head trials comparing established treatment options has led different guideline panels to make different recommendations even though informed by a similar body of evidence (Table 1) [4–6]. For example, WHO recommends tocilizumab, baricitinib, or sarilumab, whereas the Infectious Diseases Society of America (IDSA) and the US National Institutes of Health (NIH) both recommend tocilizumab and sarilumab but recognize sarilumab as an alternative when tocilizumab is not available instead of recommending it at the same level [4–6]. These stepped recommendations from IDSA and NIH recognize the lack (at the time) of trials directly comparing these treatments and the limited certainty from indirect comparisons.

In the absence of a robust body of evidence from trials reporting on direct comparisons, in this issue of *Clinical Microbiology and Infection*, Albuquerque et al. [9] propose a Bayesian meta-regression to indirectly assess the efficacy of sarilumab and baricitinib compared with that of tocilizumab [9]. The authors initially conducted several pairwise Bayesian meta-analyses studying the effects of tocilizumab, sarilumab, and baricitinib versus an inactive comparison (i.e. placebo or standard of care) when added to corticosteroid therapy for COVID-19 on 28-day mortality. The meta-regression, based on multiple levels of assumptions, aimed to determine the probabilities of noninferiority of sarilumab and baricitinib to the reference of tocilizumab. The investigators present four models informed by different priors, including using the

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Table 1
Guideline recommendations for interleukin 6 inhibitors and baricitinib for COVID-19 [4–6]

Drug	WHO	Infectious diseases society of America	National institutes of health (United States)
Tocilizumab	Recommended for patients with severe or critical COVID-19	Suggested for patients with progressive severe or critical COVID-19 and elevated markers of inflammation	Recommended for patients with progressive severe or critical COVID-19 and elevated markers of inflammation
Sarilumab	Recommended for patients with severe or critical COVID-19	Suggested for patients with progressive severe or critical COVID-19 and elevated markers of inflammation when tocilizumab is not available	Recommended for patients with progressive severe or critical COVID-19 and elevated markers of inflammation when tocilizumab is not available
Baricitinib	Recommended for patients with severe or critical COVID-19	Suggested for patients with severe COVID-19	Recommended for patients with progressive severe or critical COVID-19 and elevated markers of inflammation

results from two recent head-to-head trials comparing the active treatments. While recognizing wide variability, they concluded that sarilumab and baricitinib may have high probabilities of non-inferiority compared with that of tocilizumab for the treatment of COVID-19, all in combination with corticosteroids. The authors recognized the heterogeneity in the primary meta-analyses because the methods used for this indirect comparison could not completely account for the differences in study populations across different trials, such as age, the severity of disease, circulating variant, etc. Similarly, it is unclear whether the meta-regression considered the certainty of the evidence for the pairwise meta-analyses because this varied across therapies. Although intra-study differences were small, the studies had different inclusion criteria and, resultantly, different proportions of patients requiring intensive respiratory therapy, which indicate the populations in which tocilizumab shows the greatest benefit.

What is a clinician to do with these data? Although it is reassuring that the effectiveness of sarilumab and baricitinib may not be inferior to that of tocilizumab for 28-day mortality, it is still important to take the findings with caution. The interleukin 6 inhibitors in particular have had a difficult road in determining where their utility lies for COVID-19. A quick scan of the meta-analysis shows that there has been no shortage of studies with either tocilizumab or sarilumab. Some of these early studies were underpowered because of low enrollment, low event rates, the inclusion of patients at low risk of poor outcomes, and/or low numbers of patients receiving concomitant corticosteroid therapy, highlighting the importance of pooling the results in a meta-analysis [5]. Many of the studies on both tocilizumab and sarilumab showed no benefit, and it was not until they were studied in critically ill patients receiving corticosteroids that an effect on mortality was observed. The eligibility for inclusion of primary studies is appropriately limited to evaluating patients who received concomitant corticosteroids; however, this comes with the potential for loss of randomization from trials that did not stratify on the basis of the receipt of corticosteroids and lumping patients from the subgroups of earlier studies with the entire populations of later studies. Both of these have the potential for introducing heterogeneity into the analyses owing to changing study characteristics, such as standards of care, recognition of severe disease, and concomitant therapies.

Ultimately, the study is a useful reference but does not supersede the need for direct comparisons and/or fit-for-purpose analyses, such as a network meta-analysis of therapies for patients with severe COVID-19. Separately, there are sufficient data showing the efficacy of both baricitinib and tocilizumab compared with that of the standard of care, and in overlapping levels of severity, both therapies are good options for patients with severe illness. Although studies on baricitinib in populations published earlier in

the pandemic included few patients on mechanical ventilators, an analysis of patients on mechanical ventilators or receiving extracorporeal membrane oxygenation in the COV-BARRIER study showed a reduction in mortality [10]. The data supporting sarilumab are sparser; hence, recommendations by IDSA and NIH guideline panels are measured and these panels recommend sarilumab only when better-studied therapies are not available. In the absence of more robust studies, to recommend it on parity with tocilizumab and baricitinib is premature. As our standards of care for severe COVID-19 have advanced, our standards of evidence should advance as well.

Author contributions

JCG is the lead and corresponding author. JCG wrote the original draft of the article. JCG and RLM reviewed and edited the article.

Transparency declaration

JCG has received royalties for book authorship from Jones and Bartlett Learning; consulting fees from Qpex, Shionogi, Merck, Accelerate Diagnostics, Achaogen, Astellas Pharma, Melinta Therapeutics, Nabriva Therapeutics, Paratek Pharma, scPharmaceuticals, Spero Therapeutics, and Tetrphase Pharmaceuticals; speaker honoraria from Astellas Pharma, Melinta Therapeutics, Merck, and Shionogi; travel support from Merck; and research support from Merck.

R.M. declares that she has no conflicts of interest.

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