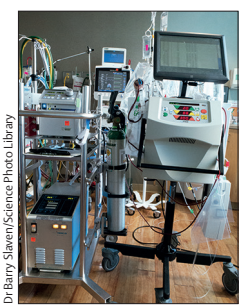
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Baricitinib for patients with severe COVID-19—time to change the standard of care?



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Published Online
February 3, 2022
https://doi.org/10.1016/S2213-2600(22)00021-2

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Mortality is high among patients with severe COVID-19 who require invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).[1,2] Therefore, further specific treatment options for these patients are urgently needed.

Early in the COVID-19 pandemic, Janus kinase (JAK) inhibitors were identified as potential therapeutic agents for the treatment of SARS-CoV-2 infections.[3,4] JAK inhibitors, such as ruxolitinib, fedratinib, and baricitinib, have strong anti-inflammatory properties and are already in clinical use for the treatment of graft-versus-host disease, myelofibrosis, and rheumatoid arthritis.[5–7]

Two large, randomised, controlled trials have assessed the use of baricitinib in hospitalised patients with COVID-19.[8,9] The Second Adaptive COVID-19 Treatment Trial (ACTT-2)[8] showed that administration of baricitinib in combination with remdesivir shortened the time to recovery in hospitalised patients with COVID-19 compared with remdesivir alone. The COV-BARRIER trial[9] did not show a significant benefit of baricitinib plus standard of care compared with placebo plus standard of care in the primary endpoint of disease progression by day 28. Nevertheless, although these were only secondary endpoints, 28-day mortality and 60-day mortality were significantly lower in patients who received baricitinib than in those who received placebo.

However, important questions remain, especially regarding the effect of baricitinib in patients with severe COVID-19 who require IMV or even ECMO. In the ACTT-2 trial, only 111 (11%) of 1033 patients were receiving IMV or ECMO at study inclusion; whereas in the primary COV-BARRIER trial, these severely affected patients were excluded.

In *The Lancet Respiratory Medicine*, E Wesley Ely and colleagues[10] report the findings of an exploratory trial that followed the design of the COV-BARRIER trial and aimed to evaluate the efficacy and safety of baricitinib in addition to standard of care in critically ill hospitalised adults with COVID-19 who were receiving IMV or ECMO. Patients were randomly assigned to receive baricitinib 4 mg (n=51) or matched placebo (n=50) once daily for up to 14 days in addition to standard of care. All-cause mortality by day 28 was significantly lower in patients who received baricitinib than in those who received placebo (20 [39%] of 51 participants died in the baricitinib group *vs* 29 [58%] of 50 in the placebo group; hazard ratio [HR] 0·54 [95% CI 0·31–0·96]; p=0·030); this finding persisted through day 60 (23 events [45%] *vs* 31 [62%]; HR 0·56 [95% CI 0·33–0·97]; p=0·027). The authors concluded that baricitinib might represent a novel option for the reduction of mortality in patients with COVID-19, even in progressed disease stages (ie, when already receiving IMV or ECMO).

Although the assignment of participants to the treatment groups was randomised and masked, the mortality benefit determined in this exploratory trial should be interpreted with caution. Important baseline data for the assessment of disease severity and comparison of the study cohort with other cohorts were not provided, including duration of IMV and ECMO before study inclusion, ventilator settings, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and prognostic scores, such as Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) II, or Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP). Without these supporting data, it cannot be assumed that the study groups were balanced in terms of baseline disease severity and that quality of care was consistent across study locations. Therefore, the results from this study cannot match the level of evidence from a phase 3 randomised, controlled trial with well-defined primary and secondary endpoints, accompanying sample size estimations, and a prespecified statistical analysis plan.

Interestingly, the all-cause mortality by day 60 in the placebo group in this study was high (62%), despite the baseline use of corticosteroids in 44 (88%) of 50 patients in this group.[10] A meta-analysis summarising data from more than 50 000 patients with COVID-19 receiving IMV showed a mortality of only 45%, although a large number of these patients were treated without corticosteroids at the beginning of the pandemic.[1] Furthermore, by contrast with the findings from this trial, in ACTT-2, in the subgroup of patients receiving IMV or ECMO at baseline, who were randomly assigned

to receive baricitinib (n=54) or placebo (n=57) in addition to remdesivir but without corticosteroids, there was no significant difference between the treatment groups with respect to the outcomes of recovery time or survival by day 28.[8] These observations contradict the results of the study by Ely and colleagues. At this time, we can only speculate about the reasons for these conflicting results; possible explanations are a potential influence of the concomitant treatment with remdesivir, the effect of corticosteroids, or any other differences between the groups or the treatments they received.

Taken together, we believe that the level of evidence provided by the results from this study is not sufficient to change standard of care and introduce baricitinib into clinical routine for COVID-19 patients with severe respiratory failure. However, the results of this exploratory trial and the data from COV-BARRIER and ACTT-2 reflect clinical equipoise for the addition of baricitinib to standard of care for patients with severe COVID-19 requiring IMV or ECMO, and provide a sound basis for a well-designed phase 3 trial to confirm these findings.

AS reports research grants and lecture fees from CytoSorbents and lecture fees from Abiomed, outside of the submitted work. RZ reports lecture fees from Novartis, Incyte, and Mallinckrodt, outside of the submitted work.

*Alexander Supady, Robert Zeiser
alexander.supady@uniklinik-freiburg.de

Department of Medicine III, Interdisciplinary Medical Intensive Care (AS) and Department of Medicine I (RZ), Medical Center—University of Freiburg, and Department of Cardiology and Angiology I, Heart Center—University of Freiburg (AS), Faculty of Medicine, University of Freiburg, Freiburg im Breisgau 79106, Germany; Heidelberg Institute of Global Health, University of Heidelberg, Heidelberg, Germany (AS)

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Surgery and uncontrolled chronic rhinosinusitis

Chronic rhinosinusitis with nasal polyps (CRSwNP), an inflammatory condition of the nose and sinuses, is normally treated with topical corticosteroids. Oral corticosteroids can be used in severe cases, but benefits are short lived and side-effects restrict long term use.[1] Surgery is standard of care when medical treatment has not led to adequate control of symptoms.[2] An estimated 24% of patients receiving active treatment for CRSwNP will undergo surgery for their nasal polyps within 10 years.[3] Surgery removes polyp tissue and thus relieves nasal obstruction and sleep disturbance but, more importantly, enlarges the sinus ostia and improves access to topical therapy, thereby improving the effectiveness of topical steroids in controlling other symptoms such as olfactory loss and rhinorrhoea. Postoperative use of topical steroids might reduce the risk of revision surgery but despite this, polyp recurrence has been found in 40% of patients within 18 months of surgery,[4] and 20% will have undergone a revision surgery within 5 years.[5] Surgery is recommended in treatment guidelines[2] and remains commonplace, in part because of the absence of alternative treatment options.

However, there is a paucity of high-quality evidence to support a surgical approach. Surgical trials pose unique challenges, both in design (since it is not possible to mask patients or investigators to treatment assignment, and use of placebos would be unethical) and recruitment (paucity of equipoise among both patients and investigators); hence, observational cohort studies still predominate in the literature. This paucity of evidence has led to questions being raised regarding the appropriateness of offering surgical treatment. For example, surgery for chronic rhinosinusitis has been widely included in the list of procedures included


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Published **Online** January 7, 2022 https://doi.org/10.1016/S2213-2600(21)00490-2

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