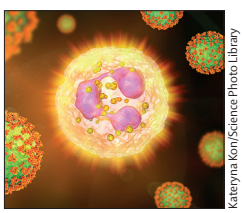
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Is neutrophilic inflammation treatable in COVID-19?



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As the world is entering the third year of the COVID-19 pandemic, the discovery of effective treatments continues to be a global health priority. Despite vaccination success, promising antiviral drugs, and benefits of pharmacological immunomodulation for patients who are hospitalised with severe COVID-19, systemic hyperinflammation currently cannot be fully controlled and remains a major cause of morbidity and mortality.[1]

Neutrophils in people with severe COVID-19 show increased abundance, altered phenotypes, and dysregulated functionality.[2] As first responder innate immune cells, neutrophils release several classes of proteases that are essential for microbe destruction but can also cause collateral tissue damage when neutrophil proteolytic activity becomes excessive. Neutrophil serine proteases, such as neutrophil elastase, proteinase 3, and cathepsin G, have been recognised as such so-called double-edged immune modulators, and elevated concentrations of these markers in the blood and lung fluid are associated with poor outcomes in patients with COVID-19.[3,4] However, no COVID-19 therapies specifically targeting neutrophilic inflammation have been investigated in large-scale clinical trials.

In *The Lancet Respiratory Medicine,* Holly R Keir and colleagues[5] test the hypothesis that blocking activation of multiple neutrophil serine proteases could improve outcomes in patients hospitalised with COVID-19 by limiting the injurious effects of neutrophilic inflammation. In a multicentre, double-blind, randomised, parallel-group, placebo-controlled trial involving 406 patients hospitalised with COVID-19, 192 participants in the intervention group were given brensocatib, an oral inhibitor of dipeptidyl peptidase-1 (DPP-1), which is an enzyme that activates neutrophil serine proteases. Despite encouraging results in a previous phase 2 trial for bronchiectasis,[6] brensocatib was not superior to placebo treatment in patients with COVID-19 infection. In fact, brensocatib therapy was associated with worse clinical status on the 7-point WHO ordinal scale for clinical status (primary outcome; adjusted odds ratio 0·72 [95%CI 0·57–0·92]) and there was no association between treatment with brensocatib and new oxygen use versus placebo (IRR 1·13 [0·73–1·74]) during the 28 day follow-up period. Furthermore, the number of deaths was higher in the brensocatib group (29 [15%] of 190 *vs* 23 [11%] of 214 in the placebo group; adjusted hazard ratio 1·41 [95% CI 1·06–1·88]). In conclusion, despite solid scientific rationale, brensocatib therapy cannot currently be recommended to prevent or treat COVID-19.

The limitations of the study should be considered when evaluating these results. One limitation is that patients at different stages of COVID-19 severity with unknown immune cell profiles were enrolled in the trial, leading to a wide range of clinical heterogeneity. Treatment responses can vary between patients with hypoinflammatory and hyperinflammatory COVID-19 subphenotypes,[7] and anticipated responders to brensocatib are patients with dysregulated neutrophil proteolytic pathways. However, evaluation of these parameters was not incorporated into the trial design. Another limitation is that, although previous work from Chalmers and colleagues[6] supports that oral brensocatib can modulate pulmonary inflammation, it is possible that drug concentrations in the lung were not reached at an early enough timepoint to limit or reverse COVID-19 hyperinflammation. Thus, it cannot be excluded that DPP-1 inhibition might have the potential to help specific patient subgroups when given at the right time.

The negative outcome of this study raises the important question whether targeting neutrophilic inflammation in COVID-19 is a suitable therapeutic strategy at all. Several pharmacological attempts to harness the powerful functions of neutrophils in pneumonia and acute respiratory distress syndrome have been equally disappointing in clinical trials.[8,9] These results are unexpected given that many preclinical and observational studies have conclusively identified neutrophils as central cellular mediators in the pathogenesis of severe lung inflammation, including in SARS-CoV-2 pneumonia.[9,10] Nevertheless, these findings must not discourage additional efforts toward clinical translation of limiting inflammatory tissue damage caused by neutrophils.

One of the lessons of the many trials is that the current understanding of neutrophils in COVID-19 is too simplistic and in-depth knowledge to understand their complex functions is needed. The transcriptional

and functional heterogeneity of neutrophils is increasingly being recognised along with the role of neutrophils in resolving inflammation.[2,10] For therapeutic development, fine-tuning of neutrophil recruitment and responses could be important in balancing protective, reparative, and injurious effects during pulmonary inflammation. Sensitive and rapid point-of-care tests to monitor the inflammatory profiles of patients to guide therapy would be of great use. Measuring the activities of disease-associated immune modulators, such as proteases, might be a step towards personalised and timely therapeutic approaches for COVID-19. Although Keir and colleagues[5] have provided evidence in this trial that broad-spectrum targeting of neutrophil serine proteases is not beneficial for patients with COVID-19, we should remain open-minded that different approaches to precision-target neutrophils might enable improvement of clinical outcomes.

We declare no competing interests.

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