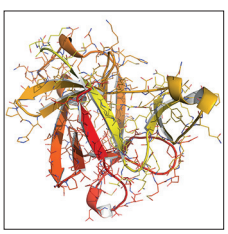
A role for interleukin-1 receptor antagonism in severe COVID-19?



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Early in the COVID-19 pandemic it was noted that a subset of people with severe disease were admitted to hospital with a hyperinflammatory illness.[1] Subsequently, trials investigating immunomodulation as a treatment for severe COVID-19 resulted in dexamethasone becoming standard of care for people admitted to hospital with severe COVID-19 and the interleukin (IL)-6 receptor inhibitor tocilizumab being recommended for people requiring supplemental oxygen and with evidence of a significant inflammatory response.[2] The clinical character, pathophysiology, and phenotype of hyperinflammation in severe COVID-19 is still being elucidated. The hypercytokinaemaia and hyperferritinaemia observed in COVID-19 is modest compared with the prototype cytokine storm syndromes haemophagocytic lymphohistiocytosis and macrophage activation syndrome. Instead, a model of more limited, lung-centric immunothrombogenic inflammatory pathology has been proposed.[3]

Beyond the established role of corticosteroids and tocilizumab in hyperinflammatory COVID-19, the IL-1 pathway is a target of particular interest. NLRP3 inflammasome activation (with increased IL-18 and IL-1β) has been observed in patients with severe or critical COVID-19 pneumonia,[4] and direct mononuclear cell inflammasome activation upon exposure to SARS-CoV-2[5] has also been reported, supporting the concept that IL-1 pathway antagonism may be a tractable target in severe COVID-19. Anakinra is a recombinant IL-1 receptor antagonist inducing both IL-1α and IL-1β blockade that has a key role in the treatment of hyperinflammatory syndromes and reported benefit in patients with septicaemia.[6] The recently published negative canakinumab trial in severe COVID-19[7] cannot be fully extrapolated to anakinra trials as canakinumab selectively blocks IL-1β and therefore might have a different impact on immunothrombosis.

In *The Lancet Rheumatology*, Evdoxia Kyriazopoulou and colleagues[8] present the results of a systematic review and meta-analysis of studies assessing the safety and efficacy of anakinra (compared to standard of care or placebo) in treating people admitted to hospital with COVID-19. With a primary outcome of mortality after 28 days, and a secondary outcome of safety, the authors did a meta-analysis of aggregate data from 1185 patients in nine studies and of individual patient-level data from 895 patients in six studies. Mortality was significantly lower in people treated with anakinra (38 [11%] of 342) than in those receiving standard of care or placebo (137 [25%] of 553; adjusted odds ratio 0·32 [95% CI 0·20–0·51]; p<0·0001). There was no safety signal associated with anakinra, although the dose and route of administration were not included. Other limitations of the present study include the small numbers of patients recruited in the original studies, a predominantly observational methodology of the included studies, and most studies being done before dexamethasone became standard of care in this setting.

Dexamethasone use was not standardised in the studies of anakinra included in this meta-analysis and, based on data from very small numbers of patients, the authors suggest that anakinra was not beneficial above and beyond dexamethasone. By contrast, large trials of tocilizumab and corticosteroids have shown that the addition of IL-6 blockade further improved survival in patients with severe COVID-19.[2] If the absence of additional benefit of anakinra in patients treated with dexamethasone was to be prospectively confirmed, what is the role of this costly and limited-availability drug in a global pandemic? It might be that there is a place for anakinra in specific patient groups to enable steroid-minimised treatment regimens, given the worrying reports of increased complications in people with diabetes treated with dexamethasone and the rise of previously rare infections such as mucormycosis.[9]

The observation by Kyriazopoulou and colleagues[8] that the beneficial effect of anakinra was more pronounced in people with evidence of a significant inflammatory response, defined as a C-reactive protein concentration higher than 100 mg/L, is important. We and others have sought to define the hyperinflammatory response in severe COVID-19 infection by use of simple, widely available clinical measures including, but not limited to, C-reactive protein.[10] Defining the hyperinflammatory phenotype of severe COVID-19 is key in further prospective trials of immunomodulation

therapies. Trial designs need to rest on better evidence of the pathophysiology of severe COVID-19 and ensure stratification by phenotype to select patients who have evidence of hyperinflammation and who are therefore more likely to benefit. Equally, such trial designs need to consider where immunosuppression might plausibly cause harm. For example, it has been postulated that in some patients with severe COVID-19, persistence of viral RNA drives the inflammatory responses,[11] and the host needs a robust immune system to clear the virus and viral products.

The COVID-19 pandemic has shown the importance of multispecialty collaboration. Further prospective trials of IL-1 pathway antagonism are needed, and rheumatologists should be central to the design of such trials to ensure thoughtful stratification of patients to maximise benefit and minimise harm.

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*Rachel S Tattersall, Dennis McGonagle, Jessica J Manson
rachel.tattersall@nhs.net

Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (RST); Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, UK (DM); Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK (JJM)

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