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.

the pivotal cytokines involved. In daily practice, the availability of rapid immune monitoring tests (eg, cytokine multiplex assays) would therefore be of utmost interest.

We declare no competing interests.

See Online for appendix

*Yvan Jamilloux,
Mathieu Gerfaud-Valentin, Pascal Sève
yvan.jamilloux@chu-lyon.fr

Department of Internal Medicine, Hopital de la Croix-Rousse, Hospices Civils de Lyon, F-69004 Lyon, France (YJ, MG-V, PS); and Inserm U1111, CIRI, Université Claude Bernard Lyon 1, Lyon, France (YJ)

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We read with interest the Viewpoint by Puja Mehta and colleagues[1] on the use of intravenous anakinra in secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome (sHLH/MAS), in which they suggest a framework for the management of cytokine storm syndromes.

As clinical immunologists who collaborate daily with intensivists, our primary concern, not unlike that of Mehta and colleagues,[1] is the causal diagnosis of sHLH/MAS. Unlike Mehta and colleagues, however, we find it difficult not to separate subclinical hyperinflammatory states with some macrophage activation syndrome features from macrophage activation syndrome that requires intensive care, because their treatment objectives are simply not the same. A stepwise approach with corticosteroids as first-line therapy would have the added benefit of selecting a second-line treatment on the basis of clinical context and disease severity. We provide a tentative approach to treating sHLH/MAS in the appendix that reflects this philosophy and also incorporates the framework suggested by Mehta and colleagues.

From a purely rheumatological point of view, anakinra seems like an appealing treatment for macrophage activation syndrome triggered by systemic autoimmune or autoinflammatory diseases and even, off label, for highly inflammatory states resulting from infectious triggers.[1] However, systemic autoimmune diseases make up barely a quarter of the overall causes of macrophage activation syndrome.[2] Anakinra is not the best first-line treatment when specific drug combination therapies with sufficiently anti-inflammatory and immunosuppressive effects on cytokine storm are indicated (ie, for lymphoma).

The risk of clinical worsening after immunosuppressive therapy for macrophage activation syndrome caused by parasitic infections must also be emphasised. For instance, in vitro and in vivo findings from a mouse model suggested that NLRP3 inflammasome activation and IL-1β signalling are required for elimination of *Leishmania* infection.[3,4] In the clinic, leishmaniasis-associated macrophage activation syndrome can be fatal, and the risk of death is increased by the inappropriate use of steroids or immunosuppressive agents in patients with undiagnosed parasitic infection. These cases are occasional and are insufficiently described in the literature.[5]

Although we sincerely hope that anti-IL-1 receptor antagonists would provide a survival benefit over current therapeutics (eg, steroids and etoposide), evidence for this benefit is still missing, as Mehta and colleagues themselves point out. For reasons provided earlier, anakinra seems more suited for treating macrophage activation syndrome-associated diseases with systemic autoimmune or autoinflammatory causes, pending increased knowledge of its potential effects on viral infections.

Future clinical trials involving anakinra for the treatment of macrophage activation syndrome need to focus on more specific groups of patients, both in terms of underlying causes of the condition and disease severity.

We declare no competing interests.

*Nihal Martis,
Alexandra Audemard-Verger
martis.n@chu-nice.fr

Medical Intensive Care Unit and Internal Medicine Department, University Hospital of Nice, 06200 Nice, France (NM); Côte d'Azur University, Nice, France (NM); Internal Medicine Department, University Hospital of Tours, Tours, France (AA-V); and University of Tours, Tours, France (AA-V)

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Authors' reply

We appreciate the interest in our Viewpoint[1] on the use of intravenous anakinra in cytokine storm syndromes. Yvan Jamilloux and colleagues contribute to continuing discussions regarding the terminology of hyperinflammatory disorders;[2] we suggest a unifying umbrella term of cytokine storm syndromes. We feel that it is the concept of hyperinflammation

that is crucial; the conditions characterised by hyperinflammation overlap, and we endorse shared clinical and scientific learning.

We agree with Jamilloux and colleagues that a subgroup of patients with severe COVID-19-associated hyperinflammation might benefit from immunomodulation, but we caution against prematurely predicting optimal immunomodulatory therapies on the basis of systemic cytokine concentrations measured from peripheral blood, as local (eg, pulmonary) cytokinaemia might be more informative. The focus on inhibition of IL-6 early in the COVID-19 pandemic might be because of, at least in part, the relative ease of measurement of IL-6 and access to drug supply (tocilizumab is widely available in China), rather than a true hypothesised advantage of blocking IL-6 in preference to a different cytokine.

Nihal Martis and Alexandra Audemard-Verger discuss the timing of intervention (subclinical compared with fulminant hyperinflammatory states) and the relative merits of corticosteroids and anakinra, and suggest that anakinra should be reserved for rheumatic triggers. We have described a potential window of opportunity to reduce the risk of progression and high mortality in cytokine storm syndromes.[3] Although steroid-free treatment regimens are difficult to achieve, we would emphasise the increased risk of infection with high-dose steroids, and the risk of masking signs of infection with IL-6 blockade (suppression of C-reactive protein or fever) as important considerations.

The use of anakinra in cytokine storm syndromes should not be confined to presentations with a rheumatic cause. Of the eight reported cases using intravenous anakinra (at the time of writing the Viewpoint), an equal number of cases had an infectious (three of eight patients) and rheumatological (three of eight patients) cause, and one patient had both an infection and a rheumatological condition (*cytomegalovirus* and vasculitis). As we mention in our Viewpoint, the efficacy of anakinra in non-rheumatic hyperinflammation was shown in post-hoc analyses of bacterial sepsis trials, and data suggest that IL-1 blockade might have a role in the neurotoxicity secondary to chimeric antigen receptor T-cell therapy for refractory leukaemia or lymphoma.

Additionally, cohort studies of 81 patients with severe COVID-19 suggested an efficacy signal with anakinra use.[4,5] Data from controlled trials of anakinra in patients with COVID-19 are eagerly anticipated.

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*Puja Mehta, Randy Q Cron, James Hartwell, *Jessica J Manson, Rachel Tattersall*
jessica.manson@nhs.net

Department of Rheumatology, University College London Hospital, London NW1 2PG, UK (PM, JJM); Centre for Inflammation and Tissue Repair, UCL Respiratory, Division of Medicine, University College London, London, UK (PM); Department of Pediatric Rheumatology, Children's of Alabama, University of Alabama, Birmingham, AL, USA (RQC); Department of Pharmacy, University College London Hospital, London, UK (JH); and Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust and Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK (RT)

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Effect of anakinra in COVID-19

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We read with interest the Article by Giulio Cavalli and colleagues[1] that described the effects of the interleukin-1 receptor antagonist anakinra in patients who were critically ill with COVID-19. The authors reported promising effects of high-dose anakinra treatment, including improvement of respiratory function and better survival compared with a historical control group that received standard treatment. Although these results are encouraging, there are notable differences in patient characteristics between the groups that might have confounded the observed effects.

First, the authors indicate that they studied a group of patients with COVID-19 and hyperinflammation. This makes sense, as anakinra was shown to be effective in patients with sepsis and features of macrophage activation syndrome (MAS) in a post-hoc analysis of a randomised clinical trial done more than two decades ago.[2] MAS is characterised by an excessive inflammatory response, most specifically elevated ferritin concentrations.[3] According to a validated diagnostic score of MAS, a ferritin level higher than 2000 ng/mL increases the probability of MAS.[4] Notably, in the study by Cavalli and colleagues,[1] median ferritin levels were only 1237 ng/mL in the anakinra group compared with 2218 ng/mL in the