The conundrum of COVID-19 treatment targets: the close correlation with rheumatology. Response to: 'Management of rheumatic diseases in the time of covid-19 pandemic: perspectives of rheumatology pracitioners from India' by Gupta *et al* and 'Antirheumatic agents in covid-19: is IL-6 the right target?' by Capeechi *et al*

We thank Capecchi *et al*[1] for their comment on our paper. The authors suggested that interleukin 6 (IL-6) represents the key cytokine responsible for the majority of pulmonary and cardiovascular complications of COVID-19. Similarly, we have received a comment from Gupta *et al*[2] who reported the management of rheumatological treatments during COVID-19 pandemic among practitioners in India, revealing that choices were apparently made according to the beliefs on the possible relationships between drug mechanism of action and effect on the viral infection. Both correspondence comments highlighted some striking similarities with changes seen in rheumatological conditions such as the systemic effects of chronic inflammation in rheumatoid arthritis, or laboratory findings resembling macrophage activation syndrome, and argued on the potential applications of rheumatological targeted therapies in this new context, especially on the central role of IL-6 inhibitors. Gupta *et al* also reported that approximately half of the practitioners would reduce the use of biological disease modifying antirheumatic drugs or defer specific drugs such as rituximab or cyclophosphamide.[2] As reported in our previous paper,[3] although caution is warranted, we believe that preventive insufficient treatment of rheumatological conditions would expose patients to the risk of severe morbidity and mortality connected to the underlying disease. Moreover, uncontrolled disease activity would further increase the risk of infection in these patients, and expose them to an additional burden of inflammation with the possible consequences described by Capecchi *et al*,[1] and possible confounding of the clinical picture with challenging management issues. Nevertheless, we acknowledge that more evidence is needed to guide decisions in the treatment of susceptible immunocompromised patients during the ongoing COVID-19 outbreak. Indeed, the molecular and immunological response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not yet been fully elucidated. It is hypothesised that the disease is characterised by different stages.[4] An initial viral phase which would possibly benefit from direct antiviral agents, but also from immunoadjuvant drugs such as type 1 interferon,[5] could then shift towards a gradual, individual-based, host-dependent excessive inflammatory response, probably more susceptible to immunosuppressive treatments, such as IL-6 inhibitors or other targeted drugs.[6] Nevertheless, this is most certainly an oversimplification of the immunopathological changes occurring during SARS-CoV-2 infection, and it is unlikely that the complexity of acute inflammation which progresses through the cellular crosstalk, immune system activation, metabolic changes and coagulation activation may be fully tackled by blocking a singular cytokine target. Moreover, identifying the correct timing to shift the treatment strategy according to the different biological stages of a scarcely known viral disease is particularly challenging. Preliminary, uncontrolled clinical studies have supported a role of IL-6 inhibition in some patients with severe COVID-19.[7 8] Nonetheless, definitive evidence should be awaited from the ongoing randomised controlled trials being conducted on this and other rheumatological targeted drugs. As further high-quality evidence on the nature of SARS-CoV-2 and its immunomodulatory treatment accumulates, there will also be more information to support rheumatologists in the management of their patients receiving chronic treatments, often including the same agents now being tested for COVID-19.

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