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antigen-driven adaptive immune responses supervening on innate immune activation at both these sites might be responsible for different patterns of polymyalgia rheumatica and giant cell arteritis associations, but this remains conjectural, because endogenous autoantigens or foreign triggering antigens have not been defined. We hope that our comparative model, linking age-related changes in the vascular and musculoskeletal system to immune system interactions, will form a preliminary step to further progress in understanding the mechanisms underlying giant cell arteritis, polymyalgia rheumatica, and their striking interrelationship.

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IL-1 and IL-6 inhibition affects the neutralising activity of anti-SARS-CoV-2 antibodies in patients with COVID-19

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Spatiotemporal dynamics of interleukin (IL)-6 expression in lymphoid organs influence the balance between antiviral humoral and cellular adaptive immunity.[1] In particular, cytopathic viruses typically induce IL-6-mediated differentiation of naive CD4$^+$ T cells into follicular helper T-cells, facilitating the production of potent neutralising antibody responses.[1]

SARS-CoV-2 (the causal agent of the COVID-19 pandemic) is a cytopathic virus that can cause a life-threatening pneumonia characterised by a maladaptive inflammatory response whereby higher levels of serum IL-6 correlate with disease severity.[2,3] Notably, patients who have recovered from severe forms of COVID-19 develop the most effective anti-SARS-CoV-2 neutralising antibodies, and convalescent plasma from these individuals is being studied to derive monoclonal antibodies for therapeutic purposes.[4] Yet, treatments that antagonise IL-6 have been repurposed from the beginning of the pandemic and are currently approved for the treatment of inpatients with severe COVID-19.[5]

Given the crucial role of IL-6 in the development of neutralising antiviral humoral immunity, we assessed the titre of anti-SARS-CoV-2 antibodies and their neutralising capacity over time in patients recovered from life-threatening COVID-19 treated with IL-6 inhibitors. 30 patients admitted at San Raffaele Hospital (Milan, Italy) with severe COVID-19 pneumonia with hyperinflammation were studied. Ten patients were treated with local standard of care and ten with the anti-IL-6 receptor monoclonal antibodies sarilumab

(five patients) or tocilizumab (five patients) in addition to standard therapy. Ten patients treated with the IL-1 receptor antagonist anakinra were also studied. All 30 patients have been previously included in larger observational studies on tocilizumab, sarilumab, and anakinra reported elsewhere.[2,3] The current study was approved by the San Raffaele Hospital Ethical Committee (number 34/int/2020) and participants gave written informed consent. Details about study design and treatments are reported in the appendix (pp 1–3). Serum samples obtained before treatment (day 0), at day 30 and at day 60 were tested for anti-receptor-binding domain (RBD) antibodies and for their in vitro neutralising activity against SARS-CoV-2. The three groups of patients were similar in baseline demographic characteristics, laboratory test results, and respiratory parameters (appendix p 4). Anti-RBD antibodies were comparable in all groups at day 0 and at day 30, whereas a lower, yet not statistically significant, median antibody titre was observed at day 60 in patients treated with either IL-1 or IL-6 blockade (figure A). Anti-RBD antibody titre at day 0 did not correlate with respiratory or laboratory parameters associated with disease severity including lymphocyte count, PaO_2/FiO_2 ratio, lactate dehydrogenase, C-reactive protein, ferritin, and IL-6 levels (appendix p 4). Importantly, the neutralising activity of sera from patients treated with IL-1 or IL-6 inhibitors was significantly decreased compared with standard treatment, with 33% lower median neutralisation activity in patients treated with IL-1 inhibitors (50%, compared with 83% in patients treated with standard care) and 39% lower median neutralisation activity in patients treated with IL-6 inhibitors (44%) at day 30. Similarly, at day 60, median neutralisation activity was lower in patients treated with IL-1 inhibitors (32%) and IL-6 inhibitors (33%) compared with standard care (72%; figure B).

See Online for appendix

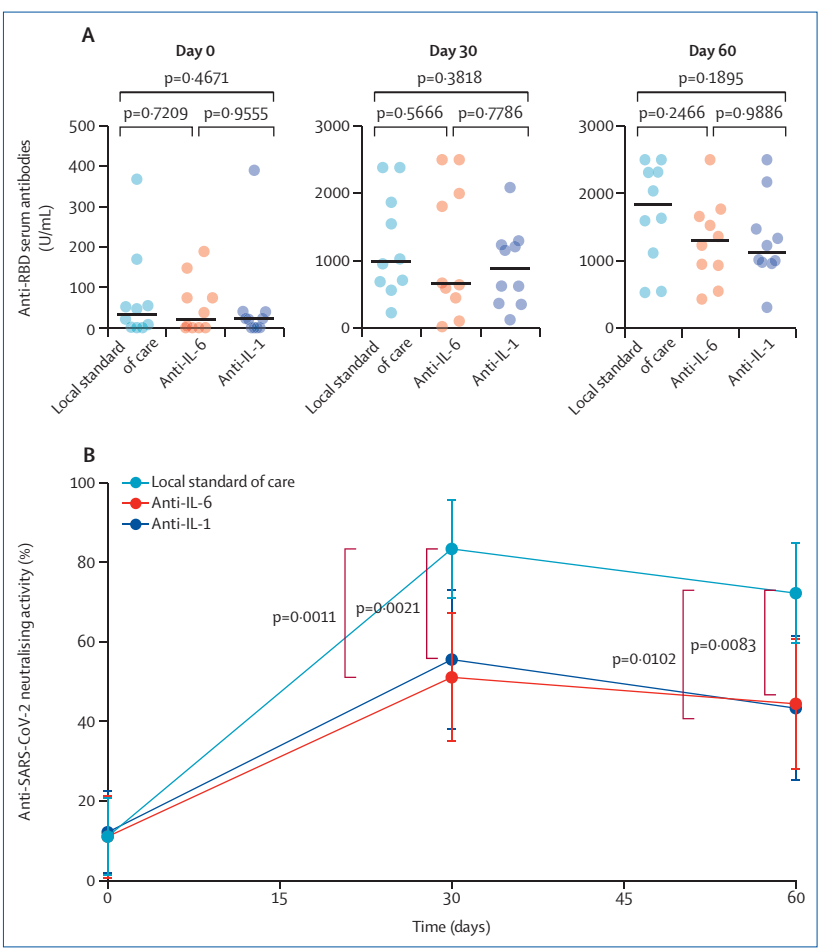

Figure: **Features of anti-SARS-CoV-2 humoral response in patients treated with anti-IL-1 and anti-IL-6 therapies**

(A) Concentration of anti-RBD serum antibodies in patients treated with the local standard of care, anti-IL-6 (sarilumab or tocilizumab), and anti-IL-1 (anakinra). Horizontal lines represents medians of 10 measurements performed in triplicate. (B) In vitro anti-SARS-CoV-2 neutralising activity of sera from patients treated with the local standard of care, IL-1, and IL-6 blocking agents. Neutralising antibody activity was measured at baseline, at day 30, and at day 60. Results are reported as medians and 95% CI of 10 measurements performed in triplicate. RBD=receptor-binding domain.

These results raise three major and previously overlooked practical concerns about the long-term management of patients with COVID-19 treated with cytokine blocking strategies. First, as modelling has shown that the neutralising activity of anti-SARS-CoV-2 antibodies predicts immune protection from symptomatic infection,[6] the significant reductions in neutralising activity observed in our study warrants careful reassessment of the risk of reinfection and of severe disease in patients treated with anti-IL-6 agents. Second, while some national health-care programmes advocate a single dose of vaccine in case of previous SARS-CoV-2 infection, our findings indicate that the effectiveness of one-jab programmes should be carefully ascertained in patients recovered from COVID-19 who received IL-6 inhibitors as part of their anti-inflammatory therapy because this strategy could leave them with suboptimal protection.[7] Finally, our results suggest that these considerations should apply not only to patients treated with IL-6 blocking agents, but also to patients treated with anakinra. IL-1 is a master regulator of the inflammatory cascade upstream of IL-6, and its inhibition might hamper downstream IL-6 release thus preventing full B-cell differentiation and the development of protective humoral immune responses.[1]

Our study has both limitations and strengths. Weaknesses include the small number of patients, patients were not randomly assigned to receive anti-IL-1, anti-IL-6, or standard treatment, and the absence of immunological assays addressing memory T-cell responses over time. Yet, the study cohort was homogeneous and treatment groups were enriched equally for patients with severe COVID-19 with a highly inflamed phenotype and comparable serum IL-6 concentration at baseline. Additionally, the absence of concomitant corticosteroid therapy, the serological assessment performed at regular intervals, and the treatment scheme consistent across groups support the reliability of obtained results. In conclusion, we here show that IL-1 and IL-6 blocking therapies in use for the treatment of patients with severe COVID-19 can affect the neutralising activity of anti-SARS-CoV-2 antibodies. Accordingly, if these findings are confirmed in other cohorts, vaccination strategies should be carefully discussed in patients recovered from COVID-19 after treatment with IL-1 and IL-6 inhibitors and, possibly, implemented with regard to the optimal timing of vaccine administration.

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