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.

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Commentary

Interleukin 6 inhibition in severe COVID-19: Another piece of the puzzle

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More than two years have passed since the beginning of the coronavirus disease 2019 (COVID-19) pandemic. Extensive efforts have been invested into better understanding the pathogenesis of this disease and developing the ideal pharmacological approach [1]. However, severe COVID-19 still remains a therapeutic challenge. Since the very beginning of the pandemic, a detrimental inflammatory response was implicated as the major driver of the significant morbidity and mortality that characterizes patients with critical COVID-19 [2]. As targeted anti-viral medications were lacking, different anti-inflammatory strategies were studied to stop the progression of tissue damage and respiratory failure [3,4]. In light of their remarkable anti-inflammatory properties, monoclonal antibodies targeting interleukin (IL)-6 [5] intuitively posed as agents of choice in these difficult-to-treat patients, also because this cytokine was found to be elevated in patients with severe COVID-19 [1,6]. However, the first studies on monoclonal antibodies blocking the IL-6 pathway, many of which were also published in this Journal, showed mixed results [2,7–9]. Later, the first randomized studies that were designed to address this issue paradoxically contributed to uncertainty: three studies did not find that IL-16 was associated to a significant clinical benefit in patients with variable degrees of disease severity [10–12]. Intriguingly, one study even hinted at a possible ominous effect in terms of survival in patients treated with tocilizumab [13]. On the other hand, the larger RECOVERY trial showed that tocilizumab was able to decrease both mortality and the need for mechanical ventilation in severely ill patients with COVID-19 [14]. As a result of this latter observation, IL-6 blocking agents were approved for the treatment of patients with severe COVID-19 [15]. Differences in study samples, disease severity, and duration of follow-up have been regarded as possibly responsible for such discrepant results. Also, the timing of those treatments with regards to the different clinical phases of COVID-19 might have contributed to make the potential beneficial effects of IL-6 blockade less evident [16–19]. Once these issues were made clear, the need for accurate and comprehensive re-analysis of the generated data became glaring. Indeed, one meta-analysis of randomized clinical trials did show that IL-6 inhibition had, in fact, a beneficial effect on survival in patients with severe COVID-19 [20]. However, this study analyzed aggregate data from each study without considering individual patient information. On the contrary, meta-analyses of raw individual patient data from each analyzed study are more reliable, since different durations of follow-up, sample sizes, and outcomes can be evaluated separately. Hence, more definitive conclusions may be drawn from such studies.

In their work published in this issue of the Journal [21], Tasoudis and colleagues present the first meta-analysis on IL-6 inhibition in COVID-19 based on individual patient data. Tasoudis *et al* retrieved and analyzed data about more than 7,000 individual patients with COVID-19 from nine different randomized clinical trials. The Authors then confirmed the remarkable therapeutic potential of IL-6 inhibition, which was associated with a reduction of mortality that has been estimated to be up to 25%. A 26% reduction of the likelihood of need for mechanical ventilation and a 28% increase in the probability of discharge from hospital were also found in patients treated with monoclonal antibodies targeting IL-6. Furthermore, the Authors found that the beneficial effect of IL-6 inhibition was even more pronounced in those studies in which a greater proportion of patients received corticosteroids as a concomitant medication. Finally, there was a tendency to a greater improvement associated with IL-6 inhibition in older patients with severe COVID-19.

In summary, Tasoudis and colleagues were able to identify by means of their analysis a beneficial impact of pharmacological blockade of IL-6 in patients with COVID-19. Very importantly, this study gives new insights about the apparent discrepancies between the findings of previous clinical trials, as the overall therapeutic effect of IL-6 inhibition is – as highlighted by the elegant design of their meta-analysis – clear-cut.

More than two years since the beginning of the pandemic, the role of

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IL-6 inhibition in severe COVID-19 finally seems to be clearer. The initial findings suggesting this approach as an effective treatment for severe cases of COVID-19 have been – at last – confirmed, and pharmacological blockade of IL-6 now represents a significant therapeutic option in this scenario.

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