European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Editorial

One year later: The case of tocilizumab in COVID-19

ARTICLE INFO

Keywords
COVID-19
Tocilizumab
Treatment
Randomized-controlled trials

In severe coronavirus disease 2019 (COVID-19) patients, SARS-CoV-2 infection induces a systemic immune activation characterized by an afinalistic release of inflammatory cytokines [1,2]. This dysfunctional response often ends up into a multi-organ damage and can be responsible for a significant, and sometimes irreversible, clinical deterioration [3]. In this scenario, the pro-inflammatory cytokine interleukin (IL)-6 has been universally recognized as a key player [1]. Moreover, its central role in COVID-19 has been further corroborated by the clinical evidence that serum levels of IL-6, and of its surrogate C-reactive protein, correlate with disease severity and patients' outcome [3].

It is then not surprising that pharmacological blockade of IL-6 has become the pivotal focus of the therapeutic strategies since the very start of COVID-19 pandemic. In fact, the *first-in-class* IL-6 receptor antagonist tocilizumab has been the most widely employed and evaluated drug [4,5]. As commonly happens in emergency situations, the first data on the safety and effectiveness of tocilizumab in severe COVID-19 were retrieved from observational retrospective studies, three of which published by this *Journal* [6–8]. However, in these studies, patient populations were quite heterogeneous, and tocilizumab was administered at different dosages and schemes. These limitations prevented from drawing clear conclusions on the role of tocilizumab in the treatment of COVID-19. Nonetheless, the feverish excitement for a possible therapy for COVID-19 paved the way for the design of more rigorous clinical trials. As the world was still holding its breath and the number of COVID-19 victims was worrisomely increasing, scientists and physicians all over the world rushed to perform the best-quality studies, namely randomized placebo-controlled trials (RCTs). Unfortunately, in this rapidly changing landscape of multiple concomitantly running RCTs, trial designs and primary outcomes were hard to be refined and correctly identified. When the results of the first RCTs were published, the efficacy of tocilizumab was questioned [9–13]. Indeed, these trials not only found tocilizumab to have a marginal role in preventing death or the need of invasive mechanical ventilation, but also reported warning signals related to the risk of secondary bacterial infections, especially among critically ill patients. At the same time, British researchers published the first results of the RECOVERY trial, showing that a 10-day course of systemic dexamethasone could significantly reduce 28-day mortality in patients with COVID-19 receiving respiratory support [14]. Consequently, dexamethasone was soon officially approved by most regulatory agencies as a primary treatment for this subgroup of COVID-19 patients.

Nevertheless, the disappointing results of the first RCTs and the significant step forward made with the approval of dexamethasone did not dissuade researchers to carry on other already in progress RCTs and to design new ones to further investigate tocilizumab in COVID-19 treatment. One of these was conducted exploiting the same platform used for the landmark study on dexamethasone and contributed to rehabilitate the role of tocilizumab, as it showed a significant improvement in survival among hypoxic patients with systemic inflammation [15]. Of note, benefits obtained with tocilizumab appeared to be additional to those observed with glucocorticoid treatment.

While the results of these RCTs were progressively disclosed, living systematic literature reviews and meta-analyses were also performed [16]. Under these circumstances (i.e., best data quality available), the favorable position of tocilizumab as a treatment option for COVID-19 patients was consolidated. In a prospective meta-analysis of 27 RCTs including 10,930 patients, the use of IL-6 antagonists appeared to be associated with lower 28-day mortality and lower progression to invasive mechanical ventilation. Even if both tocilizumab and sarilumab (another available IL-6 antagonist) were considered, outcomes were substantially better in the former group. Notably, also in this meta-analysis, the association of IL-6 antagonists with improved outcomes was higher in patients receiving glucocorticoids at baseline. Encouraging results emerged also from a Cochrane Living systematic review, which showed a reduction of all-cause mortality and little or no impact in the outcome of clinical improvement at day 28 in patients treated with tocilizumab [17]. In addition, it is important to underline that both in meta-analyses and in the Cochrane Living systematic review significant concerns related to secondary bacterial infections did not

https://doi.org/10.1016/j.ejim.2021.10.024
Received 10 October 2021; Accepted 18 October 2021
Available online 23 October 2021

emerge. At this point, the arising question is whether, in a real-life setting, there is still a place for tocilizumab for the treatment of hospitalized COVID-19 patients.

In our opinion, the available data point towards an affirmative answer making tocilizumab a valuable treatment option in COVID-19. However, we do also strongly believe that not all patients might equally benefit from tocilizumab (or other immunosuppressive treatments), with probably a greater potential benefit for patients with significantly greater systemic inflammation [18–20]. Consequently, an appropriate patients' selection is of fundamental importance for the final inclusion of tocilizumab in the treatment protocol of COVID-19 patients. Though, patient selection still remains extremely challenging for the physician. Moreover, some specific questions are still unanswered even several months after the first report of tocilizumab in COVID-19: which is the best subgroup of patients to be treated? Should tocilizumab be always combined with steroids or given as a monotherapy? Should tocilizumab be considered only for steroid-refractory patients? Large individual patient data meta-analyses are eagerly craved to get more precise insight about the right place in therapy for IL-6 blockers in COVID-19. Answering to these only partially answered questions will ultimately mitigate the rage of the current storm of tocilizumab clinical trials.

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