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.

Clinical Microbiology and Infection 27 (2021) 1177–1178

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis – Author's reply

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ARTICLE INFO

Article history:
Received 8 February 2021
Received in revised form
20 February 2021
Accepted 25 February 2021
Available online 8 March 2021

Editor: L. Leibovici

To the Editor,

We read with interest the letter by Koeckerling et al. [1] commenting on our meta-analysis on the efficacy and safety of tocilizumab in COVID-19 [2]. Koeckerling et al. [1] discussed the potential effect of immunomodulating therapies including tocilizumab on promoting SARS-CoV-2 evolution. Their argument was based on the observations of prolonged viral replication in severe COVID-19 disease and protracted viral shedding among immunocompromised patients, which could increase mutation rates and chance of emergence of new viral variants. The authors hypothesized that tocilizumab could enhance SARS-CoV-2 evolution by suppressing the immune system through blocking interleukin-6 (IL-6). We applaud the authors for raising this concern; however, we have several points to make in reference to this purported potential risk.

First, the inference that the authors made is an extrapolation from observations in immunocompromised patients. This population represent a chronic and more broad state of suppressed immunity in contrast with the more specific and short-term immunomodulatory effect of tocilizumab in the context of COVID-19 therapy. Further, Koeckerling et al. [1] postulated that IL-6 blockade by tocilizumab may dampen the host's antiviral responses and impair viral clearance. The authors quoted a study by Masiá et al. [3] in support of their hypothesis. In contrast to their claim, this study [3] not only revealed that IL-6 blockade was not associated with delayed viral clearance but also showed higher concentration of antiviral antibodies among tocilizumab-treated individuals [3]. Moreover, Guo et al. [4] reported that tocilizumab therapy was not associated with reduction in cytotoxic $CD8^+$ and plasma B cell and suggested that tocilizumab may further promote the host's adaptive immune response [4]. In another intriguing study, Mazzoni et al. [5] showed that in severe COVID-19 disease, the impaired immune cell cytotoxicity was IL-6 dependent and that tocilizumab therapy restored the cytotoxic properties of the natural killer cells. Likewise, Giamarellos-Bourboulis et al. [6] demonstrated that COVID-19 patients with severe respiratory failure displayed very low expression of HLA-DR and marked reduction in CD4 and CD19 lymphocytes and natural killer cells. Tocilizumab partially restored HLA-DR in *in vitro* experiments [6]. These findings are reassuring that IL-6 blockade as a treatment strategy in severe COVID-19 disease is unlikely to broadly impair the immune response of patients against SARS-CoV-2 infection or cause delayed viral clearance.

Second, the authors correctly discussed the association between prolonged viral shedding and viral evolution in severe COVID-19. Indeed, tocilizumab use in COVID-19 is restricted to this group and several observational studies and randomized trials demonstrated that tocilizumab could lead to a reduction of disease severity in COVID-19 patients [2]. Reduction in disease severity and preservation of adequate immune response associated with tocilizumab therapy may theoretically shorten disease duration, shorten viral replication time and decrease viral mutation rate.

Third, similar to other RNA viruses, SARS-CoV-2 has been shown to have a high mutational rate. Emerging data report worldwide evolutionary changes of the SARS-CoV-2 virus [7–9]. In one study, the rate of SARS-CoV-2 mutation was estimated to be 4.133×10^{-4} substitutions/site/year [8], which is similar to the mutation rate of other

DOIs of original article: https://doi.org/10.1016/j.cmi.2021.01.025, https://doi.org/10.1016/j.cmi.2021.04.019.
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https://doi.org/10.1016/j.cmi.2021.02.024

coronaviruses [10]. Interestingly, the majority of documented SARS-CoV-2 mutations involve G-U and C–U substitutions with nearly 50% of all mutations involving C–U substitutions [10,11]. This type of mutation may represent host driven process through nucleotide deaminases [10,11] such as APOBEC proteins which are cytidine deaminases and represent one type of innate immune response against viruses [12]. This contention is supported by the findings of recent studies by Di Giorgio et al. [13] and Matyášek et al. [14]. APOBEC3 protein family is a target for induction by interferon type-I response and tocilizumab has been shown to upregulate interferon type-I response in rheumatoid arthritis patients [15]. These observations imply that the contribution of tocilizumab treated COVID-19 patients to SARS-CoV-2 evolution is unlikely.

Fourth, immunocompetent humans and animals represent the predominant reservoir for SARS-CoV-2 and could contribute to the ongoing evolution of the virus. For example, it has been well documented that SARS-CoV-2 virus continue to lurk within the gastrointestinal (GI) tract for a long time. In one systematic review, it has been shown that SARS-CoV-2 was detectable in GI tract up to 70 days from symptom onset and up to 33 days after complete clearance from the upper respiratory system [16]. This extrapulmonary SARS-CoV-2 viral reservoir could be a more important source for continuing viral replication and evolution.

In conclusion, the evidence incriminating tocilizumab use in enhancing SARS-CoV-2 evolution is lacking. What potentially poses more risk of SARS-CoV-2 evolution is the ongoing spread of the virus among the chronically immunocompromised population, the indiscriminate use of convalescent plasma therapy [17] and the delay in vaccination worldwide. However, we agree with Koeckerling et al. [1] that ongoing and future studies should explore further whether tocilizumab or other immunomodulators use would have any impact on SARS-CoV-2 evolution.

Transparency declaration

The authors declare that there are no conflicts of interest.

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