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LETTER TO THE EDITOR

Authors' Reply to Chia Siang Kow et al.: Comment on: 'Should We Interfere with the Interleukin-6 Receptor During COVID-19: What Do We Know So Far?'

Alexia Plocque[1] · **Francois Philippart**[2,3]

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Dear Editor

We do thank Dr. Chia Siang Kow and his colleagues for their very interesting comment about the unknown and delayed potential complications associated with the inhibition of interleukin (IL)-6 receptors [1]. As we emphasised in our review [2] safety of tocilizumab and sarilumab still remains a major concern as very few data are currently available. As well as the described potential risk of secondary infections, the alteration of immune response is associated with many other concerns that have been weakly studied to date.

First, IL-6 limits tissue degradation during the inflammatory response [3, 4]. Inhibition of signal transduction by gp130 protein leads to impaired regeneration of the digestive mucosa [3, 5], the impermeability of which is altered in the context of the systemic inflammatory response of infectious origin, favouring the translocation of microbial structures, which may, in turn, perpetuate the systemic inflammatory state [5–8]. These elements lead to a hypothetical risk of mucosal complications and a risk of the perpetuation of the inflammatory response.

Second, the theoretical risk of upper gastrointestinal bleeding is all the more important to consider since patients with COVID-19 frequently receive corticosteroid therapy and anticoagulant therapy. Furthermore, by inhibiting the effect of IL-6 in the liver, tocilizumab would correct the inhibition of CYP3A4, CYP2C9, and CYP2C19, the latter playing a central role in the degradation of inhibiting the therapeutic effect of proton pump inhibitors. More generally, the pharmacokinetics of treatments is considerably altered in ICU patients and would be further disrupted by the inhibition of IL-6 pathway [8]. This seems to be particularly true for statins, the anti-inflammatory effect of which has long been shown to be of interest in COVID-19 [9].

Third, among hypothetical long-term complications, peripheral neuropathy would also be noticeable [10] and may contribute to the broad long COVID pattern. No data are available to date concerning such a neuropathy during COVID-19.

Finally, there is a theoretical risk of altering the efficacy of immune checkpoint inhibitors during tumour disease management [11].

However, the specific involvement of IL-6 among a broad spectrum of proinflammatory mediators in the occurrence of long COVID needs to be confirmed. As intensity of the inflammatory response and endothelial alteration [12] are associated with a blood-brain-barrier disruption during the acute infection [13–15], many cytokines and other mediators may contribute to the long-term neurophysiological alterations observed during the so-called "long COVID". In the same way, the local inflammatory response may significantly contribute to the observed neurological cognitive impairment [15].

In this context, trying to inhibit systemic IL-6 could be questionable for at least two reasons: blockade of the large amount of IL-6 circulating molecules during the acute phase of inflammatory response would be very challenging and targeting a single mediator before collecting precise and relevant data on long-COVID physiopathology would expose

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✉ Francois Philippart
fphilippart@ghpsj.fr

[1] Department of Haematology, Hôpital Necker-Enfants Malades, Assistance-Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France

[2] Medical and Surgical Intensive Care Unit, Paris Saint Joseph Hospital Group, Paris, France

[3] Endotoxins, Structures and Host Response, Department of Microbiology, Institute for Integrative Biology of the Cell, UMR 9891 CNRS-CEA-Paris Saclay University, 98190 Gif-sur-Yvette, France

patients to drugs of debatable safety in a weak and very frail rationale.

Declarations

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