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.

Autoimmunity Reviews 19 (2020) 102560

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Re: Patiently waiting for the results of anti-IL 6 therapy in severe COVID-19 infection

Dear Editor,

We thank Cunningham et al. [1] and Ruscitti et al. [2] for their commentary on our article [3] on the Macrophage activation syndrome (MAS)-like lung pathology in COVID-19 pneumonia. In order to clarify the classification of MAS, we proposed two types of MAS that fit along the immunological disease continuum of inflammation against self; modified for loss or gain of function [4]. It may turn out that some of the hyper inflammation related features of COVID-19 are due to overzealous killing of virally infected cells by CD8+ cytotoxic T-cells and COVID-19 related antigen driven expansion of CD4+ helper T-cells with increased pro-inflammatory cytokine production. Such a scenario would be analogous to the gain of function that occurs in adaptive immunity with chimeric antigen receptor (CAR)-T cells where the induced MAS can be treated with anti-IL-6R [3]. This pattern of inflammation occurs in immunocompetent subjects and is also known as secondary haemophagocytic lymphohistiocytosis (sHLH). To what degree this exists for COVID-19 infection awaits elucidation.

The scenario that Cunningham et al. [1] describe relates more to loss of function in the immune system or what is termed "perforinopathies". In Fig. 3A of our article [3] we included the monogenic perforinopathies where there may be complete absence of perforin pathway machinery and where failure to clear virus leads to T-cell expansion that drives macrophage activation in what is termed primary HLH. Cunningham et al. [1] point out a scenario where high levels of IL-6 is associated with diminished T-cell perforin expression in experimental settings. Therefore, it is suggested that anti-IL6R blockade may help augment cytotoxicity of CD8+ T-cells and NK-cells consequent to IL-6 reduction. However, in other experimental studies IL-6 deficiency was associated with the different scenario of impaired viral clearance [5]. Given that the COVID-19 infection disables early type 1 interferon expression [6] then inhibition of the "second wave" of cytokines including IL-6 may be disadvantageous. As summarized in our article, it is conceivable that the pleiotrophic actions of IL-6 in the context of pleiotrophic viral interactions with the immune system may actually favour viral persistence in some models where IL-6 level elevation could be beneficial [7]. Registry data from over 16,000 tocilizumab treated rheumatoid arthritis cases showed an increased risk of bacterial infection but no evidence for an increased risk of viral infection in humans, suggesting that IL-6 reduction is not linked to the emergence of previously known common viral infections.

Ruscitti et al. [2] also comment on the potential adverse role of IL-6 on lymphocyte mediated performin killing as summarized by Cunningham et al. [1]. Ruscitti et al. [2] prefer the "cytokine storm syndrome" over macrophage activation syndrome (MAS) and indeed we used the "cytokine storm syndrome" terminology within our article but went with "MAS-like" terminology overall As summarized above, we introduced a new concept for MAS classification as gain or loss in immune function that is very relevant for COVID-19 infection. We also introduced the concept of a pulmonary intravascular coagulopathy secondary to the pulmonary MAS-like changes. This is distinct from the disseminated intravascular coagulation seen in MAS. The abundant monocytes and macrophages in the coronavirus family members like COVID-19 pneumonia certainly do not detract from the use of the terminology "MAS-like" [8].

.To conclude, we do not think that the lessons on the benefit of IL-6R antagonisms in CAR-T cell therapy or Stills disease, both in the setting of full immunocompetence, can be extrapolated to the severe COVID-19 pneumonia, in the setting of relative immunodeficiency, where vigorous cytokine response may be required to help control infection. The entire community awaits with baited breath in the hope that anti-cytokine therapy will be efficacious. We hope that we have highlighted the recognition of a MAS-like lung pathology with secondary pulmonary intravascular coagulopathy and it is far from clear whether extrapolation from Rheumatology, Haematology or Immunology to the benefits of Anti-IL6R for COVID-19 exists.

Declaration of Competing Interest

Dennis McGonagle has received speaker fees and honoraria from Roche, Sobi and Novartis and research grants from Novartis.

References

[1] Cunninghama .K.I. L, Basketterc D, McFaddena JP. Why judiciously timed anti-IL 6 therapy may be of benefit in severe COVID-19 infection. Autoimmun Rev 2020.

https://doi.org/10.1016/j.autrev.2020.102560
Received 16 April 2020; Accepted 17 April 2020
Available online 01 May 2020

[2] Ruscitti .B.O. P, Iagnocco A, Giacomelli R. Cytokine storm syndrome in severe COVID-19. Autoimmun Rev 2020.
[3] McGonagle D, et al. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev 2020:102537.
[4] McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3(8):e297.
[5] Yang M-L, et al. IL-6 ameliorates acute lung injury in influenza virus infection. 2017;7(1):1–11.
[6] Kopecky-Bromberg SA, et al. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol 2007;81(2):548–57.
[7] Velazquez-Salinas L, et al. The role of interleukin 6 during viral infections. 2019;10(1057).
[8] McGonagle D, et al. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatology 2020. In press.

Dennis McGonagle[a,b,*], Kassem Sharif[a,c], Anthony O'Regan[d], Charlie Bridgewood[a]
[a] *Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, UK*
[b] *National Institute for Health Research (NIHR) Leeds Biomedical Research Centre (BRC), Leeds Teaching Hospitals, Leeds, UK*
[c] *Sheba Medical Center, Tel Aviv, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[d] *Honorary Professor of Medicine, National University of Ireland, Galway, Saolta University Healthcare Group, Galway, Ireland*
E-mail address: d.g.mcgonagle@leeds.ac.uk (D. McGonagle).

* Corresponding author at: Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.