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) 102563

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Why judiciously timed anti-IL 6 therapy may be of benefit in severe COVID-19 infection

ARTICLE INFO

Keywords:
Interleukin-6
IL-6
Perforin
COVID-19
SARS-CoV-2
Natural killer cells
Macrophage activation syndrome
Cytokine storm

Dear Editor,

We read with interest the recent article by McGonagle et al. on the role played by interleukin-6 (IL-6) in severe COVID-19-induced pneumonia and macrophage activation syndrome (MAS)-like disease (which has clinicopathological overlap with secondary haemophagocytosis lymphohistocytosis [sHLH]) [1]. They note that preliminary trials with an anti-IL-6 receptor (IL-6R) drug have shown efficacy in some patients with COVID-19 and this severe complication (https://www.clinicaltrials.gov/ct2/show/NCT04322773).

The authors' draw a comparison with similar MAS/sHLH-like presentations in certain autoimmune diseases such as Still's disease where there is hyperproduction of cytokines, or the so-called 'cytokine storm' [1,2]. They also discuss the reasons why in different scenarios anti-IL6R may have either positive or negative effects on survival in severe viral infection. Evidence for the importance of this cytokine in recovery from viral infections has been demonstrated using IL-6-deficient mice. In such instances, IL-6 appears to be required for promotion of T cell responses together with tissue remodelling and repair [3]. However, there is also evidence (summarized by Velazquez et al. [3]) that increased expression of IL-6 during anti-viral immune responses may promote viral persistence, partly through impairment of the lytic activity of cytotoxic T lymphocytes.

We have recently noted that parallels exist between some features of COVID-19 disease (including worse outcomes in those aged over 70 but relatively mild disease in children, and higher mortality in males and the obese) and factors affecting perforin. There is evidence to suggest that reduced expression or impaired functionality of perforin is associated with increased severity of symptoms (*Cunningham* et al. *submitted for publication*). It is also of interest that patients with a predisposition to perforin dysfunction (*'perforinopathies'*) are also prone to 'cytokine storm' [1,4]. Perforin is critically required for the immune cell-mediated death of virally infected host cells and we have postulated that adequate levels of functional perforin expression may be the 'key' to a successful immune response to COVID-19 infection. Although relatively little work has been performed on the effect of IL-6 on perforin expression, Cifaldi et al. have provided compelling evidence that IL-6 can inhibit expression of perforin and granzyme B (another essential element of cellular cytotoxicity) and thereby the death of virally-infected cells [5]. Studies in mice revealed that increased levels of IL-6 were associated with reduced natural killer (NK) cell function specifically associated with reduced expression of perforin and granzyme B. Moreover, exposure of human peripheral blood NK cells to IL-6 also resulted in reduced expression of these effector molecules [5].

Patients with heart disease and hypertension may also be at greater risk from severe COVID-19 infection. One study of patients with heart failure showed that an increased level of IL-6 correlated with reduced activity of NK cells [6]. Cifaldi et al. speculate that IL-6 may inhibit the activity of the signal transducer STAT-5 - a regulator of perforin transcription [5]. This may be how elevated levels of IL-6 cause reduced perforin levels.

We agree with the suggestion by McGonagle et al. that there may be an important role for anti-IL-6R therapy in the treatment of severe COVID-19 disease, and also agree that the timing of such intervention will likely be crucial. We postulate that the detrimental effect of increased IL-6 may be largely mediated through impaired functionality of perforin that, in turn, results in more severe symptoms including cytokine storm.

Funding sources

Nil.

Declaration of Competing Interest

There are no conflicts of interest for any of the authors.

References

[1] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020;102537.
[2] Schulert GS, Yasin S, Carey B, Chalk C, Do T, Schapiro AH, et al. Systemic juvenile idiopathic arthritis-associated lung disease: characterization and risk factors. Arthritis Rheumatol (Hoboken, NJ) 2019;71(11):1943–54.

https://doi.org/10.1016/j.autrev.2020.102563
Received 14 April 2020; Accepted 14 April 2020
Available online 05 May 2020

[3] Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. Front Microbiol 2019;10:1057.
[4] Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. Nat Rev Immunol 2015;15(6):388–400.
[5] Cifaldi L, Prencipe G, Caiello I, Bracaglia C, Locatelli F, De Benedetti F, et al. Inhibition of natural killer cell cytotoxicity by interleukin-6: implications for the pathogenesis of macrophage activation syndrome. Arthritis Rheumatol (Hoboken, NJ) 2015;67(11):3037–46.
[6] Vredevoe DL, Widawski M, Fonarow GC, Hamilton M, Martinez-Maza O, Gage JR. Interleukin-6 (IL-6) expression and natural killer (NK) cell dysfunction and anergy in heart failure. Am J Cardiol 2004;93(8):1007–11.

Louise Cunningham[a,*], Ian Kimber[b], David Arthur Basketter[c], John Paul McFadden[a]
[a] *St. John's Institute of Dermatology, Guy's and St Thomas' Hospital, London, UK*
[b] *Faculty of Biology, Medicine and Health, University of Manchester, UK*
[c] *DABMEB Consultancy Ltd, Sharnbrook, Bedfordshire, UK*
E-mail address: louise.cunningham@gstt.nhs.uk (L. Cunningham).

[*] Corresponding author at: St. John's Institute of Dermatology, Guy's and St Thomas' Hospital, London, UK.