Immunosuppression for hyperinflammation in COVID-19: a double-edged sword?

Mehta and colleagues[1] postulate that hyperinflammation in coronavirus disease 2019 (COVID-19) could be a driver of severity that is amenable to therapeutic targeting since retrospective data have shown that systemic inflammation is associated with adverse outcome. However, correlation does not equal causation, and it is equally plausible that increased virus burden (secondary to failure of the immune response to control infection) drives inflammation and consequent severity (as shown for other viruses[2]) rather than augmented inflammation being an inappropriate host response that requires correction.

The authors hypothesise that approaches such as corticosteroids or Janus kinase (JAK) inhibitors could be considered if hyperinflammation is present.[1] Broad immunosuppression in patients with overwhelming viral illness might be inadvisable. Beneficial anti-inflammatory effects should be weighed up against the potentially detrimental effects of inhibiting anti-viral immunity, thereby delaying virus clearance and perpetuating illness. Accordingly, findings from multiple studies in humans and animals indicate that corticosteroid immunosuppression (both inhaled and systemic) impairs induction of anti-viral type-I interferon responses to a range of respiratory viruses,[3,4] effects that are likely to also occur in the context of COVID-19. Selective therapies with JAK inhibitors could be expected to have similar effects. JAK-STAT signalling is a major component of the type-I interferon pathway.[3] Tofacitinib has been shown to inhibit interferon-α production in vitro.[5] Suppression of interferon or other mediators (eg, interleukin 6) could also promote secondary bacterial infection and further complicate the disease course.[3]

The decision to pharmacologically immunosuppress a critically unwell patient with COVID-19 remains a difficult one. Possible beneficial effects of reducing inflammation should be carefully weighed up against the potential for deleterious impairment of anti-microbial immunity.

AS reports personal fees for consultancy from AstraZeneca and funds from grants from the Wellcome Trust, the British Lung Foundation, and others, all unrelated to this Correspondence. AIR declares no competing interests.

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1 Mehta PM, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; published online March 16. https://doi.org/10.1016/S0140-6736(20)30628-0.

2 Lee N, Chan MC, Lui GC, et al. High viral load and respiratory failure in adults hospitalized for respiratory syncytial virus infections. *J Infect Dis* 2015; **212:** 1237–40.

3 Singanayagam A, Glanville N, Girkin JL, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nat Commun* 2018; **9:** 2229.

4 Thomas BJ, Porritt RA, Hertzog PJ, Bardin PG, Tate MD. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. *Sci Rep* 2014; **4**: 7176.

5 Boor PPC, de Ruiter PE, Asmawidjaja PS, Lubberts E, van der Laan LJW, Kwekkeboom J. JAK-inhibitor tofacitinib suppresses interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and antiviral effects of interferon alfa. *Transl Res* 2017; **188:** 67–79.

Published **Online**
March 23, 2020
https://doi.org/10.1016/S0140-6736(20)30691-7