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.

Combining immunomodulators and antivirals for COVID-19

We read with interest the Comment by Jesus Bermejo-Martin and colleagues[1] on impaired viral control in severe COVID-19. They highlight the importance of ongoing research on plasma viral load monitoring and antiviral therapies, and we agree with these points. However, three concepts in their Comment regarding host inflammatory responses and immunomodulatory therapy require clarification or rebuttal.

First, the simple biphasic model of viral invasion followed by uncontrolled inflammation, which Bermejo-Martin and colleagues oppose, is already obsolete. SARS-CoV-2 elicits highly heterogeneous host responses ranging from mild illness in most people, to severe disease and critical illness in 2–10% of those infected.[2] Much of this heterogaeneity is due to differences in immune responses to the virus. Severe disease is characterised by a defective type I or III interferon response followed by persistent, maladaptive hypercytokinemia, termed COVID-19 cytokine storm syndrome.[3,4] The cytokine system most implicated in prognosis and treatment is the interleukin (IL)-6-soluble IL-6 receptor axis.[2]

Second, the authors rightly caution against overly reductive models of COVID-19; unfortunately, this advice is immediately followed by the rather reductive statement that COVID-19 is "a viral disease, not an autoimmune one".[1] 10% of patients with severe disease have autoantibodies against type I interferons;[5] even so, no clinicians seriously consider COVID-19 an autoimmune disease in the same vein as, say, rheumatoid arthritis. A more useful parallel is viral haemophagocytic lymphohistiocytosis, which is characterised by an excessive, deleterious host immune response to various viral infections. Epstein-Barr virus haemophagocytic lymphohistiocytosis has a much worse prognosis than cytomegalovirus haemophagocytic lymphohistiocytosis. One factor that explains this difference is the existence of effective antiviral therapies against cytomegalovirus, which are used in addition to immunosuppressive therapy, whereas there are no such antiviral therapies for Epstein-Barr virus haemophagocytic lymphohistiocytosis. A combined immunomodulatory and antiviral approach would likewise be ideal in COVID-19.

Finally, investigating the pathological immune activation of COVID-19 does not detract from antiviral research. The main domains of trials have included antivirals (eg, lopinavir or remdesivir), immunomodulation (eg, corticosteroids or tocilizumab), and immunoglobulins (eg, convalescent plasma). Only the immunomodulation domain has currently improved mortality (appendix). We have noted that pathological immune activation can be a troublesome, transformative, threshold concept.[4] This threshold concept has practical, real world benefits. Any debate pitting immunomodulation against antiviral therapy is counterproductive. Corticosteroids and IL-6 inhibitors save lives; finding effective antivirals to complement them would be a welcome development.

We declare no competing interests.

Luke Y C Chen, Tien T T Quach
lchen2@bccancer.bc.ca

Division of Hematology (LYCC) and Centre for Health Education Scholarship (LYCC, TTTQ) University of British Columbia, Vancouver, BC V5Z 1M9, Canada

1 Bermejo-Martin JF, Almansa R, Tedim AP, et al. Mounting evidence of impaired viral control in severe COVID-19. *Lancet Microbe* 2021; published online April 15. https://doi.org/10.1016/ S2666-5247(21)00084-7.

2 Chen LY, Biggs CM, Jamal S, et al. Soluble interleukin-6 receptor in COVID cytokine storm syndrome. *Cell Rep Med* 2021; published online April 19. https://doi.org/10.1016/j.xcrm.2021.100269

3 Galani I-E, Rovina N, Lampropoulou V, et al. Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison. *Nature Immunol* 2021; **22:** 32–40.

4 Chen LYC, Quach TTT. COVID-19 cytokine storm syndrome: a threshold concept. *Lancet Microbe* 2021; **2:** e49–50.

5 Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; **370:** eabd4585.

See **Comment** page e228

See **Online** for appendix