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Combining immunomodulators and antivirals for COVID-19

Authors' reply

We thank Luke Chen and Tien Quach for their interest on our Comment. We could not agree more with the title of their reply letter, combining immunomodulators and antivirals for COVID-19, which is consistent with the conclusion of our Comment: "the available evidence would support combined strategies to simultaneously control viral replication and deleterious inflammation, based on specific indicators or biomarkers of both pathophysiological processes".[1] Our conclusion already proposed using biological indicators to guide anti-inflammatory and antiviral therapies in COVID-19, which converges with the so-called threshold concept of pathological immune activation raised by Chen and Quach. Our Comment is not to diminish the role of immunopathology or that of immunomodulators in this disease. Our intention was to balance the participation of the virus and that of inflammation in the pathogenesis of severe COVID-19, stressing the direct association between those signatures of increased viral replication and those of increased inflammation, immunosuppression, endothelial dysfunction, coagulation activation, and tissue damage, which support the role of uncontrolled viral replication as a major driver of severe disease. We agree with Chen and Quach that the two phases (viral replication and inflammation) model has actually become quite obsolete. However, the effect of this model in research and social networks has been, and still is, very important—eg, one of the founding articles proposing this model has received 464 citations and 2171 tweets in less than 1 year.[2]

Our Comment highlighted the necessity of developing effective antivirals for this disease. As outlined by Chen and Quach with their example of Epstein-Barr virus and cytomegalovirus infections, the future of COVID-19 treatment is likely to involve administering effective antivirals combined with anti-inflammatory or even immune-stimulatory therapies[3] in those patients with biomarker signatures predicting successful response to each one of these approaches. We strongly advocate a personalised medicine approach for COVID-19 disease, as we have proposed for sepsis.[4] Alternative antivirals to those already tested in multidomain clinical trials (such as remdesivir or ritonavir–lopinavir) could be helpful to prevent progression from mild to severe disease or to improve outcome of patients with COVID-19 once severe disease is already evident.[5] New trials should be implemented to test this notion. Additionally, combined therapies with immunomodulators and antivirals could have much to say in preventing complications of COVID-19 in the long-term.

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