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.

[95% CI 1·71–18·32], p=0·0044). In the subgroup of patients who did not seroconvert after the first vaccine dose, an enhanced T-cell response was seen after the second dose in those who received ChAdOx1 nCoV-19 (11 [48%] of 23 *vs* one [17%] of six with BNT162b2; p=0·17), although the difference was not significant, potentially due to small numbers of patients. Higher rates of seroconversion were observed after the second dose in those who received BNT162b2.

This study highlights the differences in T-cell and antibody responses after a single dose of vaccine between the ChAdOx1 nCoV-19 and BNT162b2 vaccines in patients with rheumatoid arthritis taking DMARDs. Due to our small sample size, the responses to subsequent doses need further evaluation. Furthermore, the use of a delayed dosing schedule in the UK for the BNT162b2 vaccine might have led to bias and limits the generalisability of our study.

Whether these differences translate to variations in SARS-CoV-2 cases and hospital admissions is unknown. However, for patients with rheumatoid arthritis with reduced antibody responses to vaccines, the potential to enhance T-cell responses with the ChAdOx1 nCoV-19 vaccine is a finding that deserves further consideration.

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Severe COVID-19 as a virus-independent immunothrombotic process

We read with interest the Viewpoint[1] by Dennis McGonagle and colleagues in which they question the strategy of universal immunosuppression in patients with moderate-to-severe COVID-19 because of a concern about ongoing alveolar viral replication in these patients. We believe that this concern is unwarranted, as the key pathology driving severe COVID-19 is not active viral replication in the pneumocytes, but rather antibody-dependent inflammation leading to immunothrombosis.

First, in COVID-19, there is evident temporal and spatial dissociation between active viral replication in the respiratory tract and the development of lung injury. Although initial viral loads are higher and duration of viral shedding is longer in patients who develop severe illness (when compared with those who do not), the viral load typically trends downwards from the time of symptom onset, irrespective of eventual illness severity. Culturable virus is typically absent by the second week after symptom onset, when patients progress to severe illness.[1] Pathologically, there is a lack of topological correlation between the location of lung pathology and presence of the virus,[2] suggesting tissue tolerance to viral multiplication and a mechanism of lung injury other than viral cytopathy. Supporting this interpretation, studies in humanised mice have shown that viral infection of alveolar cells is not necessary for severe COVID-19 to occur.

Second, as we have previously argued,[3] the peripheral ground glass changes seen in patients with COVID-19, which typically appear in the later part of the first week of illness, represent pulmonary infarcts due to small-vessel immunothrombosis rather than viral alveolitis. Inhaled thrombolytics seem to resolve these radiological changes, which would be highly uncharacteristic of viral-induced alveolar injury. Consistent with this explanation, the characteristic silent hypoxaemia of COVID-19 indicates a predominant perfusion problem rather than a ventilation problem.[3]

Third, the key determinant of severe illness appears to be antibody-dependent inflammation,[4] a phenomenon that occurs due to abnormal fucosylation of antibodies specific for viral spike protein during the seroconversion phase of COVID-19 in susceptible patients. These aberrant antibodies are pro-inflammatory;

they activate platelets and macrophages and disrupt alveolar endothelial integrity, promoting in-situ thrombosis in the lung vasculature. The temporal association of severe illness with the onset of humoral immunity is also explained by this phenomenon. Autoantibodies directed at phospholipids, possibly emerging through molecular mimicry or redox-related conformational changes of innate epitopes, could also play a prominent role in disease progression.[5]

As the initial viral load determines the strength and duration of the antibody response, it might be prudent to avoid downregulation of the innate immune response by immunosuppression during the early viral replication phase. However, if there is evidence of disease progression to the immunothrombotic phase, key treatment strategies include immunosuppression and anticoagulation to suppress the aberrant antibody response and lung-centric microthrombosis. Once immunothrombotic lung injury is fully established, with diffuse alveolar damage manifesting as clinical acute respiratory distress syndrome, neither antiviral therapy nor immunosuppression is likely to modify the disease trajectory, and the management would essentially be supportive.

RNAaemia seen at this stage might not have implications for therapy, but rather might be a marker of disease severity and immune paralysis, portending poor prognosis.

We declare no competing interests.

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Authors' reply

We thank Robin Cherian and colleagues for their interest in our Viewpoint[1] discussing the potential importance of RNAaemia in severe COVID-19 and its possible implications for refining therapy with a goal of improving survival.[1] We wish to emphasise that we acknowledge the value of immunosuppression, but we question the value of universal immunosuppression for all patients with moderate-to-severe COVID-19, and specifically in the subgroup of patients with ongoing alveolar viral replication as set out in figure 1 of our Viewpoint. We agree with Cherian and colleagues that viral shedding from the upper airways has ceased by the time patients develop severe disease, but our focus was specifically on alveolar viral territory replication in the face of strong immunosuppression.

As stated in our Viewpoint, culturable virus might be absent in the second week after symptom onset, when patients progress to severe illness, but nevertheless there is a subgroup of patients in whom upper airway viral replication persists. The impact of this on viral replication in the alveolus remains poorly defined, and alveolar viral replication is likely important for immunosuppression.[1] Cherian and colleagues point out a lack of topological correlation between the location of lung pathology and viral presence, but this is based on one small cross-sectional study,[2] so it is difficult to extrapolate from these data.

We fully agree with Cherian and colleagues that small-vessel immunothrombosis is central to the pathogenesis of COVID-19 pneumonia, but this nevertheless represents a strategy to restrict viral spread via containment of viral dissemination.[3] As set out in figure 3 of our Viewpoint,[1] we agree that immunosuppression works in several different ways, especially in patients in whom viral replication has ceased in the alveolar territory. We did not include the antibody response in our figure, and we fully agree that anti-SARS-CoV-2 antibody responses in the second week could contribute to immunopathology and could be another mechanism underlying immunosuppression, especially in patients without alveolar viral replication.[4]

Finally, we fully agree with Cherian and colleagues that very early immunosuppression might be detrimental and that once clinical acute respiratory distress syndrome has developed, medical therapy is also limited and antiviral agents to counteract RNAaemia would be of limited value.[1]

We declare no competing interests.

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