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.

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it has been described in other autoimmune diseases such as lupus, and is seen more frequently among children and adolescents than in adults. Bleeding, however, occurs more frequently in MAS than thrombosis does.[3,4]

Antiphospholipid antibodies have been reported in some patients with COVID-19, and one study found a high concentration of lupus anticoagulant antibody in 50 (88%) of 57 tested individuals.[5] When reviewing the diagnostic criteria, causes, and clinical forms of catastrophic antiphospholipid antibody syndrome, and the autopsy findings from patients with COVID-19, this syndrome is very likely to be the cause of exaggerated inflammatory response and thrombosis in most patients with severe COVID-19, even in children with severe multisystemic inflammatory response who have had an initial negative test for SARS-CoV-2. The medical community must address this diagnostic possibility since it could radically change the treatment and prognosis of critically ill patients with COVID-19.

I declare no competing interests.

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Authors' reply

We thank Gianfranco Ferraccioli and colleagues, Brandon Reines and colleagues, and Hisyovi Cárdenas Suri for their comments on our Viewpoint[1] discussing the diffuse, alveolar-centred inflammation that triggers immunothrombosis in the lung microvasculature of patients with COVID-19 pneumonia.

Ferraccioli and colleagues posit the role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of angiotensin-converting enzyme 2 (ACE2)-expressing endothelial cells in driving this immunothrombosis and other systemic COVID-19 manifestations, including cardiac, neurological, and occasional cutaneous features. It is worth noting that other respiratory viral infections, including severe acute respiratory syndrome, resulted in a similarly high degree of pulmonary intravascular coagulopathy.[2] Since there is no compelling evidence of cardiac endothelial damage, we favour the pulmonary intravascular coagulopathy model, particularly as thrombosis is predominantly observed within the lungs. Nevertheless, ACE2 expression on endothelial cells, detection of SARS-CoV-2 in the endothelium by electron microscopy, juxtaposition of infected alveoli, and reported circulatory viral RNAaemia support the importance of endothelium in pulmonary intravascular coagulopathy. Ferraccioli and colleagues further highlight the pivotal role of endothelium in experimental murine influenza, and that use of a sphingosine-1-phosphate agonist improved survival. However, we can point to other influenza murine models in which similar therapies worsened survival.[3]

We also note the comments on neutrophil extracellular trap formation, or NETosis, and pulmonary vasculature megakaryocytes as potential contributors to pulmonary thrombosis. These factors might indeed be important but they do not detract from our central concept of pulmonary intravascular coagulopathy driven by initial infection of ACE2-expressing pneumocytes in SARS-CoV-2 infection.

Reines and colleagues argue for a new conceptual framework to understand COVID-19 disease and believe that use of the term diffuse is incorrect. We used this term to reflect the extensive and widespread lung involvement typically seen in patients with severe COVID-19. Given the large surface area of the lungs, together with the close juxtaposition of endothelium to pneumocytes, a vast territory for triggering immunothrombosis exists. We acknowledge that other pathological factors, including those relating to type 2 pneumocyte and surfactant biology, might contribute to the disease pathophysiology but these considerations are beyond the remit of our Viewpoint, which is to highlight how a pulmonary intravascular coagulopathy with secondary pulmonary hypertension accounts for mortality in some groups. As indicated in our Viewpoint and previous publications,[4] it seems highly probable that multiple mechanisms contribute to the pulmonary intravascular coagulopathy, which clearly diverges from the classic macrophage activation syndrome pattern typically observed in rheumatology practice.

Hisyovi Cárdenas Suri points out that critically ill patients with COVID-19 might actually be developing a catastrophic antiphospholipid antibody syndrome and that antiphospholipid antibodies should be checked in an effort to improve the management of these patients. In a cohort of 56 patients, 25 (45%) were reported to be positive for lupus anticoagulant.[5] Crucially, however, whether these antiphospholipid antibodies are transient or persistent in nature, or whether they play any pathological role in the development of thrombi within the lung microvasculature, is not known at this stage. Pending the results of further studies to address these key questions, we consider it premature to implicate catastrophic antiphospholipid

antibody syndrome in the aetiology underpinning pulmonary intravascular coagulopathy in severe COVID-19.

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Anifrolumab in lupus: the promise and the caution

We credit Richard Furie and colleagues[1] for their unbiased presentation of the results of the much awaited TULIP-1 study on the safety and efficacy of anifrolumab versus placebo in patients with active systemic lupus erythematosus (SLE). However, we wish to emphasise some points that merit consideration.

Given that the kinetics of the time to response showed good divergence of the two groups at around 12–16 weeks, and the proportion of patients in the anifrolumab group who had an SLE responder index-4 (SRI-4) response at 24 weeks was the same as at 52 weeks (41% [74 of 180] *vs* 36% [65 of 180]), the protocol for corticosteroid tapering could have been stricter to reduce the cumulative steroid dose, as this cumulative dose could have contributed to the high rates of placebo response. At 1 year, 64% (161 of 253) of trial participants with baseline corticosteroid dose of 10 mg/day or higher had not achieved the target dose of less than 7·5 mg/day, despite exclusion of patients with internal organ involvement and the use of steroid-sparing therapies. Also, only 73% (334 of 457) of patients in the trial were receiving antimalarials despite this being the standard of care.

Response amplification was not seen in patients with high type I interferon gene signatures. Studies have emphasised the heterogeneity of interferon signatures, with robust and tunable components and different transcriptional modules, each with different functions and correlations with disease activity.[2,3] The four genes used to define an interferon signature in the TULIP-1 study belong predominantly to one transcriptional module and are not representative of this complexity. Response rates could also be influenced by differences in interferon signatures in the peripheral blood and tissues.

We also noted that post-hoc removal of the restrictions on the use of non-steroidal anti-inflammatory drugs led to a disproportionate increase in the proportion of responders in the anifrolumab group compared with the placebo group, despite the two groups being similar at baseline. This amended re-analysis resulted in a greater percentage of improvement observed in the anifrolumab group.

The discrepancies in the proportion of patients achieving British Isles Lupus Assessment Group-based composite lupus assessment (BICLA) and SRI-4 responses in TULIP-1 are partly unexplained. A substantial improvement in arthritis and serological biomarkers of disease activity with anifrolumab in TULIP-1 did not translate into a commensurate improvement in SRI-4 response, despite this score having a greater weight for arthritis and serology. These results contrast with the MUSE[4] and TULIP-2 trials,[5] which reported significant results regarding SRI-4 and BICLA responses with anifrolumab. Finally, the data showing an effect of anifrolumab on quality of life indices and fatigue, as noted by the authors, would be interesting, as these indices might not mechanistically correlate with inflammation.

With the putative role of type II interferon in the pathogenesis of SLE[3] and the complexities of the type I interferon signature, therapies with distal modes of action (eg, JAK inhibitors) or dual blockade for interferon type I and type II hold great promise. Combinatorial therapies targeting non-interferon biological pathways that are implicated in this disease are warranted. It would be interesting to see how anifrolumab fares in a pragmatic setting in patients with autoantibody-negative SLE and major internal organ involvement, especially in patients with CNS and renal involvement, in whom type I interferon has been strongly implicated in pathogenesis. Results of the ongoing long-term extension study (NCT02794285) and TULIP-LN (NCT02547922) are likely to address our current qualms.

We declare no competing interests.

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