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Thromboses and COVID-19: reducing inflammation in addition to thromboprophylaxis

The COVID-19 pandemic is an unprecedented global health-care emergency, with high mortality in patients who develop COVID-19 pneumonia. These patients have a prothrombotic state with both venous and arterial thrombi occurring despite thromboprophylaxis. Prothrombotic mechanisms are multifactorial, with immune activation leading to an acute phase response, resulting in elevated plasma coagulation factors (particularly fibrinogen). Other features include platelet hyperreactivity, the effects of hypoxia, formation of neutrophil extracellular traps, and complement activation. Although very high circulating D-dimer concentrations are observed in patients with COVID-19, there is little evidence of disseminated intravascular coagulation, as thrombocytopenia and hypofibrinogenaemia are not present and screening clotting times are not prolonged. Many mechanisms driving thromboses in patients with COVID-19 have been suggested, including inflammatory activation of endothelial cells. We believe that the pathogenesis of thrombosis in patients with COVID-19 pneumonia shares similarities with that in patients with Behçet's syndrome.

Behçet's syndrome is a multisystem vasculitis, most commonly characterised by recurrent orogenital ulcers and uveitis. Vascular involvement affects 10–30% of people with Behçet's syndrome, causing mainly superficial or deep venous thrombosis. Vascular wall inflammation, rather than a hypercoagulable state, is the main cause of thromboses in patients with Behçet's syndrome. Hence, treatment guidelines endorse immunosuppression (including steroids and tumour necrosis factor blockade) and discourage the use of anticoagulation, mainly due to the perceived risk of bleeding from covert pulmonary arterial aneurysms, which is not present in patients with COVID-19.[1] Although pulmonary emboli are described in patients with Behçet's syndrome and patients with COVID-19, this term could be misleading, as segmental and subsegmental changes seen on CT pulmonary angiograms might not be caused by emboli but by immunothrombosis or in-situ thrombosis due to local inflammation. There are histological similarities in the two conditions. In patients with Behçet's syndrome, thrombi are tightly adherent to the vessel wall, and some thrombus casts in patients with COVID-19 have been shown to conform to the pulmonary artery vasculature (suggesting in-situ anatomical origin) and to occur without an overt distal embolic source, such as deep venous thrombosis.[2] Therefore, pulmonary inflammation is likely to drive thrombosis in both patients with Behçet's syndrome and patients with COVID-19.

Thromboprophylaxis reduces the risk of venous thromboembolism for unwell, immobile, hospitalised patients by approximately 50%. Pharmacological thromboprophylaxis improves survival and has become standard of care in patients with COVID-19 pneumonia, but thrombotic complications still occur at high rates. We hypothesise that an anti-inflammatory strategy, in addition to thromboprophylaxis, might be beneficial in patients with COVID-19 pneumonia to reduce the burden of immunothrombosis.

The therapeutic potential of targeting inflammation to reduce thromboses was shown by the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS),[3] a placebo-controlled trial that was published before the COVID-19 pandemic. This trial showed that targeting interleukin-1β significantly reduced the frequency of recurrent thrombotic events (eg, myocardial infarction, stroke, and cardiovascular death), particularly in patients with greater reductions in high-sensitivity C-reactive protein.[3] Although the CANTOS patient population had arterial thromboses only (and are therefore not directly comparable to patients with COVID-19), the results might signal a therapeutic opportunity for patients with COVID-19. A meta-analysis of clinical trials in critically ill patients with COVID-19 showed that systemic corticosteroids were associated with a decreased 28-day all-cause mortality,[4] although the effect of corticosteroids on haemostasis has not yet been reported. A systematic review of glucocorticoid use in patients with inflammatory conditions showed a reduction in the concentration of procoagulant factors (von Willebrand factor and fibrinogen), whereas the plasminogen activator inhibitor-1 (an antifibrinolytic protein) concentration increased .[5] We therefore eagerly await data on the effect of immunomodulatory approaches on thrombotic outcomes in patients with COVID-19.

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Hydroxychloroquine treatment does not reduce COVID-19 mortality; underdosing to the wrong patients?

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An observational study published in *The Lancet Rheumatology* by Christopher T Rentsch and colleagues[1] showed no association between pre-exposure use of hydroxychloroquine and reduced mortality in patients with COVID-19 who also have systemic lupus erythematosus or rheumatoid arthritis. 138 440 (71·1%) participants were women, and the study population was relatively young, with 50% of the participants younger than 66 years. In a previous study,[2] the death rate in patients younger than 70 years was low, and it was lower for women than men; therefore, the differences in mortality might be very difficult to appreciate in the study by Rentsch and colleagues,[1] in which half of the participants are under 70 years old and more than two thirds are women. Rentsch and colleagues[1] did not reference any of the several large peer reviewed studies showing an association between hydroxychloroquine and lower mortality in patients with COVID-19, or the systematic reviews that have critically appraised and summarised these studies.[3,4] These studies were all disregarded as methodologically weak, and an opportunity to build upon the interesting aspects of previous research was missed. Rentsch and colleagues[1] mentioned that the dose at which hydroxychloroquine is given for systemic lupus erythematosus (SLE) and rheumatoid arthritis is similar to the one used in an ongoing clinical trial (NCT04303507) for prevention of COVID-19 (200–400 mg per day). However, even when hydroxychloroquine is used at maximum dose, patients with SLE or rheumatoid arthritis do not receive doses as high as those used in patients with COVID-19 in studies that showed an association between hydroxychloroquine and reduced mortality (800 mg on day 1 followed by 400 mg a day for four days).[3,4] The large number of studies on hydroxychloroquine that show contradictory results on different outcomes of COVID-19 might reflect the methodological limitations of each study on both sides of the debate. It could mean that hydroxychloroquine might only be beneficial at a certain dose, in specific phase of the disease, or in patients with a particular sociodemographic or clinical profile. Like Rentsch and colleagues,[1] we think that additional studies are required on the potential benefit of hydroxychloroquine, which is economical, has not proven to be harmful at the dose used for COVID-19, and could be prescribed to ambulatory patients right after the diagnosis before they develop respiratory distress.

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Authors' reply

We thank Luis Ayerbe and colleagues for the opportunity to further discuss our Article.[1] The choice of our study population—individuals with rheumatoid arthritis or systemic lupus erythematosus—was made to minimise the potential for confounding by indication when estimating the effectiveness of hydroxychloroquine use rather than investigating how to prevent severe COVID-19 in this population. The key question is whether our study had sufficient statistical power to detect a real difference in mortality, if one existed? As stated in the Article, the CIs around our key estimate (hazard ratio 1·03 [95% CI 0·80–1·33]) suggested that we could exclude substantial benefit, although a modest benefit or harm on a relative scale could not be ruled out; therefore, trials were warranted. Ayerbe and colleagues suggest that hydroxychloroquine might be differently effective or ineffective in specific demographics: we note that 25% of those in our study were aged over 75 years and, as reported, we found no evidence of effect modification by age.