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COVID-19 cytokine storm: the interplay between inflammation and coagulation

Coronavirus disease 2019 (COVID-19) has spread rapidly throughout the globe. It is associated with significant mortality, particularly in at-risk groups with poor prognostic features at hospital admission.¹ The spectrum of disease is broad but among hospitalised patients with COVID-19, pneumonia, sepsis, respiratory failure, and acute respiratory distress syndrome (ARDS) are frequently encountered complications.¹

The pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced ARDS has similarities to that of severe community-acquired pneumonia caused by other viruses or bacteria.^{2,3} The overproduction of early response proinflammatory cytokines (tumour necrosis factor [TNF], IL-6, and IL-1 β) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are unabated over time.⁴ Therefore, therapeutic strategies under investigation are targeting the overactive cytokine response with anticytokine therapies or immunomodulators, but this must be balanced with maintaining an adequate inflammatory response for pathogen clearance.

Activation of coagulation pathways during the immune response to infection results in overproduction of proinflammatory cytokines leading to multiorgan injury. Although the main function of thrombin is to promote clot formation by activating platelets and by converting fibrinogen to fibrin,⁵ thrombin also exerts multiple cellular effects and can further augment inflammation via proteinase-activated receptors (PARs), principally PAR-1.⁵ Thrombin generation is

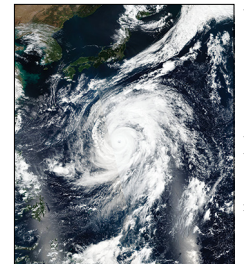
tightly controlled by negative feedback loops and physiological anticoagulants, such as antithrombin III, tissue factor pathway inhibitor, and the protein C system.⁵ During inflammation, all three of these control mechanisms can be impaired, with reduced anticoagulant concentrations due to reduced production and increasing consumption. This defective procoagulant-anticoagulant balance predisposes to the development of microthrombosis, disseminated intravascular coagulation, and multiorgan failure—evidenced in severe COVID-19 pneumonia with raised d-dimer concentrations being a poor prognostic feature and disseminated intravascular coagulation common in non-survivors.^{1,6}

The finding of increased d-dimer levels in patients with COVID-19 has prompted questions regarding coexistence of venous thromboembolism exacerbating ventilation-perfusion mismatch, and some studies have shown that pulmonary emboli are prevalent.⁷ However, due to increased risk of bleeding and despondence related to previous negative trials of endogenous anticoagulants in sepsis, clinicians might be reluctant to offer it to all. Outside of the prevention and management of venous thromboembolism, it is clear that effects of coagulation activation go beyond clotting and crosstalk between coagulation and inflammation can significantly affect disease progression and lead to poor outcome.

Prophylactic dose low molecular weight heparin (LMWH) is recommended for hospitalised patients with COVID-19 to prevent venous thromboembolism and treatment dose LMWH is contemplated for those with significantly raised d-dimer concentrations due to concerns of thrombi in the pulmonary circulation; but LMWH also has anti-inflammatory properties that might be beneficial in COVID-19. In this context, it is therefore paramount to look at the role of PAR antagonists and other

coagulation protease inhibitors. PAR-1 is the main thrombin receptor and mediates thrombin-induced platelet aggregation as well as the interplay between coagulation, inflammatory, and fibrotic responses, all of which are important aspects of the pathophysiology of fibroproliferative lung disease,⁵ such as seen in COVID-19. Although less likely to have an effect on venous thromboembolism, PAR-1 antagonists developed as antiplatelet drugs for the treatment of cardiovascular disease,⁸ might potentially attenuate the deleterious effects associated with activation of the coagulation cascade and thrombin formation. A clinically approved PAR-1 antagonist was shown to reduce levels of proinflammatory cytokines, neutrophilic lung inflammation, and alveolar leak during bacterial pneumonia and lipopolysaccharide-induced lung injury in murine models.^{9,10} Moreover, the role of PAR-1 in host immunity to viruses has been investigated: in one study, PAR-1 was protective against myocarditis from coxsackie virus and decreased influenza A viral loads in murine lungs,¹¹ while in another study, activation of PAR-1 following influenza A challenge was associated with deleterious inflammation and worsened survival,¹² suggesting the initial PAR-1 activation is required for host control of virus load but if left unabated, PAR-1-mediated inflammation results in reduced survival. The half-life of vorapaxar, might be considered too prolonged in the context of managing acute illness, especially without a known reversal agent for its antiplatelet effect and the associated bleeding risk. However, it is important to note that in clinical trials of vorapaxar, most participants received both aspirin and a thienopyridine at enrolment,⁸ and PAR-1 antagonists (eg, RWJ58259), which never progressed to clinical trials, have short half-lives and could be revisited.

Antithrombin and antifactor Xa direct oral anticoagulants are well



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For British Thoracic Society guidelines on venous thromboembolism see <https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-guidance-on-venous-thromboembolic-disease-in-patients-with-covid-19/>

established in the prevention and management of venous thromboembolism, and since thrombin is the main activator of PAR-1, and coagulation factor Xa can induce production of proinflammatory cytokines via activation of PAR-2 and PAR-1,⁵ these drugs might be promising in ameliorating disease progression and severity of COVID-19. Bleeding risk will always be a concern, but in this procoagulant state the benefits might outweigh the risk and reversal drugs for the anticoagulant effects of these inhibitors now exist.

Targeting thrombin, coagulation factor Xa or PAR-1, might therefore be an attractive approach to reduce SARS-CoV-2 microthrombosis, lung injury, and associated poor outcomes.

We declare no competing interests.

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