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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Iloprost for COVID-19-related vasculopathy

Published **Online** July 10, 2020 https://doi.org/10.1016/S2665-9913(20)30232-0

COVID-19 is presenting an unparalleled challenge for clinicians. In critical cases, the combination of severe inflammation, systemic coagulopathy, and acute respiratory failure results in a multisystem illness with high morbidity and mortality. The coagulopathy associated with COVID-19 has been associated with high rates of pulmonary embolism, myocardial infarction, ischaemic stroke, digital ischaemia, and renal failure, despite prophylactic anticoagulation.[1,2] The hypercoagulable state associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to be the result of endothelial cell dysfunction secondary to endotheliitis.[3] Endotheliitis causes vasoconstriction, altered barrier permeability, and a procoagulant state. Here, we explore the potential of iloprost as a therapy to mitigate the pathological effects of COVID-19, describing three patients who benefitted from its use. Its potential ability to reduce endothelial dysfunction and systemic inflammation could make iloprost a key player in management of COVID-19 vasculopathy.

See **Online** for appendix

Iloprost is a prostacyclin receptor agonist that promotes vasodilation of circulatory beds with minimal impact on haemodynamic parameters. It is licensed for the treatment of pulmonary arterial hypertension and is widely used for the management of peripheral vascular disease and digital vasculopathy, including digital ulcers and critical digital ischaemia in systemic sclerosis.[4,5] Iloprost is antithrombotic, anti-inflammatory, and antifibrotic, exerting these effects via inhibition of platelet activation and suppression of interleukin-6 and tumour necrosis factor production.[6,7] Autopsy studies have shown that endotheliitis and microvascular thrombi in pulmonary capillaries are part of the disease pathogenesis in COVID-19.[8] By restoring healthy endothelial function, iloprost might minimise the lung damage and thrombotic complications seen in COVID-19. It is increasingly recognised that peripheral vascular insufficiency occurs in some cases, leading to acrocyanosis and chilblains.[8] Systemic iloprost, given as a low-dose continuous infusion, is often used in patients with autoimmune peripheral vasculopathy.[5,9] Given its efficacy and its favourable safety and tolerability profile, it is an attractive candidate for use in patients with COVID-19. On the basis of this rationale, we added iloprost to standard treatment in three patients with COVID-19.

Three patients were admitted to hospital with severe COVID-19, defined as acute onset of bilateral lung infiltrates, and hypoxaemia requiring more than 40% of the fraction of inspired oxygen (FiO_2) to maintain saturations above 94% (appendix p 4). All had positive RT-PCR nasopharyngeal swabs for SARS-CoV-2. Two patients presented with clinical evidence of digital ischaemia and the third developed changes during hospital admission. The patients were all male, with a median age of 46 years (range 44–62), and all were morbidly obese. Full demographic and clinical characteristics are shown in the appendix (p 2). All three patients were commenced on supportive treatment with oxygen via a Venturi mask and fluids, prophylactic anticoagulation, and intravenous co-amoxiclav. Two patients also received oral clarithromycin. The mean Sequential Organ Failure Assessment score was 6 (range 5–7), and the mean initial pre-iloprost ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) was 155 (range 152–158). The

decision to start a 5-day intravenous infusion of iloprost was based on an expert clinical diagnosis of digital ischaemia by the treating consultant and a persistent oxygen requirement that probably reflected systemic microvasculopathy.

After a continuous 5-day infusion of 0·5 mg/kg per min, we noted a sustained clinical improvement in the digital ischaemia, as well as in cardiovascular and respiratory parameters. In all patients, decreasing oxygen requirements, increasing PaO_2:FiO_2 ratio, and normalisation of heart rate were seen up to 48 h after the cessation of the iloprost infusion (appendix p 3). None of the patients required mechanical ventilation during their hospital admission and all tolerated the iloprost infusion well with no bleeding complications or serious adverse events to warrant cessation. One patient had diarrhoea during the infusion that terminated upon iloprost withdrawal. Notably, upon cessation of iloprost on day 5, a mild rebound tachycardia and transient worsening of symptoms was observed, but these issues resolved without further treatment before discharge in all patients. One patient's hospital course was complicated by a pulmonary embolus that required a longer stay, but the patient remained stable and was discharged on rivaroxaban.

This case series illustrates that iloprost might be a useful adjunctive therapy for COVID-19 vasculopathy, improving digital ischaemia as well as cardiorespiratory parameters. Inhaled iloprost has been shown to improve ventilation parameters through its vasodilatory effects, thereby improving gas exchange.[10] Furthermore, systemically infused iloprost might also improve ventilation and perfusion matching in the lung, leading to the effects observed in our patients. Although larger controlled studies are needed to confirm our observations and despite the limitations inherent to small case series, based on the pharmacological effects of iloprost in analogous pathological states and its favourable safety profile, we suggest that iloprost might be a useful adjunctive treatment in COVID-19.

We declare no competing interests. The Royal Free Hospital Ethics board committee approved this study. All patients provided written and verbal informed consent for treatment and publication.

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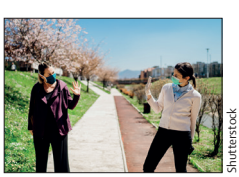
Patients with rheumatic diseases adhere to COVID-19 isolation measures more strictly than the general population

There is a continuous debate about the risks of increased incidence of COVID-19 in vulnerable patient groups, which includes patients with rheumatic diseases and especially those treated with immunosuppressive antirheumatic drugs, including biologics. So far, results on the incidence and the outcomes of COVID-19 in these groups are reassuring: to date, neither presence of a rheumatic disease nor use of immunosuppressive medication have shown associations with higher infection rates or worse disease course of COVID-19.[1–5] However, these studies do not account for preventive measures taken by patients, despite suggestions that patients are aware that their infection risk might be increased.[1,4,5] If patients subject themselves to stricter isolation measures than the general population, we might be falsely reassured. In this study, we compared the isolation measures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Published **Online**
August 27, 2020
https://doi.org/10.1016/S2665-9913(20)30286-1