

## Letter to Editor

## A Potential Role for Cyclosporine in the Treatment of Severe Cases of COVID-19

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At a moment when the 2019 Novel Coronavirus (COVID-19) pandemic is ravaging the world, it is paramount for clinicians taking care of COVID-19 patients to share their experiences and thoughts with the medical community. According to Johns Hopkins University Coronavirus Resource Center, there have been more than four million COVID-19 cases confirmed globally with an average mortality rate of approximately 7 % [1]. A search of PubMed using the key word COVID-19 results in more than 20,000 publications [2]. The devastating nature of the pandemic has clearly led to worldwide efforts to find a treatment and a vaccination for the virus. We are prompted to write this letter based on our unpublished clinical experience with kidney transplant patients at Harper University Hospital in Detroit, Michigan. While it was first assumed that immunosuppressed patients with a history of organ failure who are infected with SARS-CoV-2 are at a much higher risk for poor outcomes, our experience is surprisingly different.

Our kidney transplant patients that developed COVID-19 don't fare worse than patients with intact immune systems. There is scarce and mixed literature about the results of COVID-19 in kidney transplant patients, some of which demonstrated worse outcomes in this population [3, 4]. We think that immunosuppression therapy may help mitigate the cytokine storm that is theorized to be responsible for Acute Respiratory Distress Syndrome (ARDS) in COVID-19 patients. In fact, the use of immunosuppressive agents to counteract the hyperinflammation that may accompany severe ARDS has been contemplated in the literature [6,7]. In this letter we would like to suggest the potential benefits of cyclosporine in the treatment of severe COVID-19 disease. Cyclosporine is a medication that has been used for decades to prevent rejection in organ transplantation.

Although our current immunosuppression regimen of tacrolimus, mycophenolate mofetil, and prednisone does not include Cyclosporine, the drug revolutionized immunosuppression

and transplant medicine and deserves to be investigated as an agent for potential treatment of COVID-19. Cyclosporine was first used in a kidney transplant patient in Cambridge, England, in 1978 [8]. The use of other immunosuppressive and anti-inflammatory medications for potential treatment of COVID-19 has been discussed in the literature, but further research is needed [9]. Cyclosporine, also referred to as cyclosporine A, has antiviral activity including anti-influenza activity [10,11]. Although a mouse study has shown innate antiviral immunity is suppressed by cyclosporine, other studies have demonstrated anti-hepatitis C viral activity after liver transplantation in humans [12-14]. Cyclosporine suppression of hepatitis C virus has been shown in vitro as well [15].

Cyclosporine has also been shown to suppress flavivirus and feline coronavirus in vitro [16-18]. Furthermore, cyclosporine has been demonstrated to inhibit SARS-CoV replication in cell culture [19]. In vitro inhibition of cyclophilins and cytosolic proteins by cyclosporine A has been shown to block the replication of coronaviruses of all genera including SARS-CoV [20]. In vitro cytopathology induced by MERS-coronavirus replication was inhibited by cyclosporine A treatment [21]. An important aspect of the COVID-19 pathology is the association of proinflammatory cytokines with the severity of COVID-19 disease [6,22,23]. Cyclosporine A has been shown to decrease interleukin-6, a pro inflammatory cytokine that has been implicated in the severity of COVID-19 disease [22,24-27]. Cyclosporine A can also inhibit the production of some inflammatory cytokines that are produced by human alveolar macrophages of patients with interstitial lung disease [28].

In addition to administration by enteral or intravenous route, cyclosporine can also be given in a nebulized form; a route that seems to be attractive because it may decrease the systemic side effects of cyclosporine [29-31]. Cyclosporine was advocated as a potential treatment for the coronavirus-associated Severe Acute

Respiratory Syndrome (SARS) epidemic [32]. Other literature supporting the use of cyclosporine in COVID-19 has questioned whether the antiviral activity of cyclosporine may impair the development of immunity to coronaviruses [33]. The use of alisporivir, a non-immunosuppressive analogue of cyclosporine with potent cyclophilin inhibition properties, has been advocated for the treatment for COVID-19 [34]. The antiviral properties of alisporivir may prove to be beneficial for treatment of COVID-19, but the lack of anti-inflammatory aspects could make it less than ideal. There are few case reports and case series that discuss the course of COVID-19 in solid organ transplant patients taking cyclosporine [35-42]. However, there have not been enough well-structured studies reported in literature investigating its potential use in treatment of COVID-19. Therefore, we believe further research is warranted to study the antiviral and anti-inflammatory effects of cyclosporine in patients with COVID-19.

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Shakir Hussein, Paige Aiello and David Edelman declare that they have no conflict of interest.

## Compliance with Ethics Guidelines

This commentary article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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