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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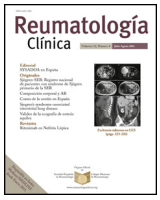

Letter to the Editor

Calcineurin Inhibitors and COVID-19

Inhibidores de la calcineurina y COVID-19

Dear Editor,

Currently, a disease caused by the Severe Acute Respiratory Coronavirus-2 (SARS CoV-2), named COVID-19, is causing an alarming rate of novel infections, in which Mexico and the South American countries now belong to the most affected countries in the world. SARS CoV-2 is one of the three highly pathogenic coronaviruses being associated with severe, life-threatening disease. Similar to the other dangerous coronaviral infections, namely the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and the Severe Acute Respiratory Coronavirus (SARS-CoV), there are no clear therapy guidelines.

The authors[1] describe an interesting therapeutic option with cyclosporin A (CsA) as first-line therapy in COVID-19 pneumonia. A definitive treatment for COVID-19 is still not available, and novel therapies (i.e. biologicals) are urgently being investigated.[2] Unfortunately evaluating these new therapies takes a lot of time and is very expensive. CsA has been around for decades and could be of special interest due to the large knowledge base.

We certainly agree with the authors that calcineurin inhibitors (CNIs) should be considered in the treatment of COVID-19.[3] Both CsA and tacrolimus are commonly prescribed CNIs and widely used for transplant recipients. There are several arguments that suggest a favourable response of CNIs in coronaviral disease.

First of all there are the recent lessons learnt in transplant medicine during the current pandemic of SARS CoV-2: The solid organ transplant recipients showed less severe COVID-19 and thus a better outcome in comparison to the general immunocompetent population.[4] Renal-, liver-, heart- and lung transplant recipients are all on long-term immunosuppressive therapy, which generally includes a CNI.[4] This kind of immunosuppressive therapy should therefore be considered beneficial rather than labelling it as a risk factor. The lower number of COVID-19 patients among transplant recipients may partially be related to the awareness of their susceptibility to infections since transplantation.[4]

Secondly, the inhibiting effect of CNIs on viral replication of other coronaviruses has been demonstrated in some studies. In vitro studies showed effectiveness of CsA in some coronaviruses.[5,6] Tacrolimus has been suggested to be effective for disease caused by the MERS-CoV.[7] Tacrolimus was also beneficial in animal experiments, showing effective inhibition of viral replication of SARS-CoV.[8] For coronaviruses of low pathogenicity tacrolimus showed effective inhibition of viral replication.[8,9]

The mechanism of coronaviral inhibition could be the protein-protein interactions between SARS-CoV-2 and the human host proteins. These proteins such as the cyclophilin family members and FK506 (tacrolimus)-binding proteins, lead to protection against irreversible cell damage of pneumocytes and T-lymphocytes by SARS CoV-2-induced mitochondrial failure.[1]

This might prevent the immunological reaction leading to severe hyperinflammation (cytokine storm), which is a feared complication in COVID-19. This systemic overreacting inflammation is characterized by Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS) and/or cardiac failure.[4]

Preventing post-COVID-19 lung fibrosis probably cannot be achieved by corticosteroids alone. On the contrary, corticosteroids could lead to prolonged viral shedding and disease progression. In order to inhibit the cytokine storm, CNIs have been suggested to be superior to corticosteroids. The role of other immunosuppressants, such as the antiproliferative agents mycophenolate mofetil (MMF) or azathioprine remains to be determined. However, antiproliferative agents probably are not beneficial in COVID-19, as they diminish the clonal expansion of alloreactive T-cells, and showed high viral loads with more severe or even fatal disease in animal experiments.

Currently, the number of transplant recipients with COVID-19 is limited and therefore only preliminary conclusions concerning CNIs can be made. Even less can be said about CNI treatment for immunocompetent patients with COVID-19.

Therefore we look forward to the results of the Spanish TACROVID trial, in which the role of tacrolimus in the immunocompetent population will be investigated.[10]

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