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## Brief communication

# Calcineurin inhibitors revisited: A new paradigm for COVID-19?



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### ABSTRACT

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can cause mild, moderate or severe disease (COVID-19). In severe disease, there is hyperinflammation causing severe symptoms. Severe COVID-19 is an immunological phenomenon, rather than a direct viral damage disease. Therapies for COVID-19 are all investigational therapies. In case of severe disease, treatment with a calcineurin inhibitor could be promising. In this article we explain the mechanisms of calcineurin inhibitor treatment for COVID-19, based on experiences seen in solid organ transplant recipients who suffered from COVID-19.

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For the infection with the novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which causes the Coronavirus Disease 2019 (COVID-19) there is currently no effective evidence-based therapy. Recently, a preliminary Canadian guideline for the treatment of immunocompetent patients was proposed.<sup>1</sup> At the moment various investigational therapies are being studied at different levels mainly compounds that have been previously developed for other conditions (Table 1). Pathogenicity of the coronaviruses can be either low (such as in the coronavirus subspecies named 229E, OC43, NL63 and HKU1) or high (such as in the Middle East Respiratory Syndrome Coronavirus, MERS-CoV, the Severe Acute Respiratory Syndrome Coronavirus, SARS-CoV, and the novel coronavirus SARS-CoV-2). In the first group, treatment generally is not necessary because the virus causes mild respiratory or gastrointestinal symptoms. In the latter

group, the virus infection potentially causes severe disease associated with a relatively high mortality. In the alarming increase in cases of COVID-19 worldwide, the fastest therapeutic option is to use existing medications against SARS-CoV-2 infection that have been either effective *in vitro* or *in vivo* against other highly pathogenic coronaviruses, such as in SARS and MERS, or even SARS-CoV-2.

In COVID-19, three stages of severity have been proposed.<sup>2</sup> Stage I (early infection) includes patients with mild constitutional symptoms, and are generally treated in the ambulatory setting including home quarantine. Stage II (pulmonary phase) patients have pneumonia with cough and/or fever. This can be subdivided in Stage IIa (no hypoxia) and IIb (hypoxia, defined as PaO<sub>2</sub>/FiO<sub>2</sub> < 300 mmHg). These patients generally will be hospitalized. In Stage III (systemic hyperinflammation) there is severe COVID-pneumonia with ARDS, SIRS/shock, and/or cardiac failure. These patients are often treated with mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

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**Table 1 – Investigational therapies considered for treatment of COVID-19.**

Therapy	Mechanism of action / Rationale
(Hydroxy)chloroquine*	Blocks viral entry in endosome * negative study results so far, further results pending
Remdesivir	Blocks RNA dependent polymerase
Lopinavir/ritonavir	Protease Inhibitor, first study with disappointing results.
Tocilizumab	Anti-IL-6 (anti-inflammatory)
Corticosteroids	T-cell inhibition (anti-inflammatory)
Tacrolimus	T-cell inhibition / suppresses cytokines (i.e. IL-2, IL-4, TNF- $\alpha$ and IFN- $\gamma$ )
Umifenovir	Prevents viral host cell entry by inhibition of membrane fusion of viral envelope and host cell cytoplasmic membrane via inhibition of clathrin-mediated endocytosis
Favipiravir	Selectively inhibits viral RNA-dependent RNA polymerase (RdRp)
Ribavirin	Guanosine analog that interferes with the viral replication
Anticoagulation (Heparine)	Hypercoagulability, thromboembolic events
Vaccination	Half-life of antibodies appears to be short
Plasmapheresis	Binds key components of viral replication or the virus itself

RNA = ribosomic nucleic acid; IL = interleukin; TNF = tumor necrosis factor; IFN = interferon.

In COVID-19 Stage III, it is not only the viral damage (cytopathic effect) causing disease, but also mainly the hyperinflammation (cytokine storm). In this stage, there is an overshooting reaction of both innate and adaptive immune system, leading to further systemic multiorgan damage.<sup>3</sup> The virus enters the endothelial cells in the lungs via the angiotensinogen converting enzyme receptor-2 (ACE2) and can provoke a cytokine storm.

Interestingly, SARS-CoV-2 is a virus probably originating from bats. In bats there could be a natural protection against this virus as they have high levels of melatonin inactivating the ACE2, and therefore blocking SARS-CoV-2 from entering the immune cells of the bats. By this mechanism the bats are probably not strongly affected by the presence of the virus.

In humans, the ACE2 normally inactivates the ligand of the bradykinin receptor. However, when SARS-CoV-2 occupies ACE2, bradykinin cannot be inhibited, and the bradykinin concentration increases.<sup>4</sup> Bradykinin leads to increased vessel permeability, vasodilatation with angioedema, and increased natriuresis, thus leading to hypotension. The local plasma leakage triggers extensive fibrin production and clotting leading to extensive thrombosis of the small vessels, which then also progresses to the larger blood vessels.<sup>5</sup>

Moreover, in this phase there is also an overreacting innate and adaptive immune system. The innate immunity comprises environmental barriers (skin, mucosa), cells (macrophages, monocytes, neutrophils), and mediators of the

immune response (cytokines, chemokines, complement). The adaptive immunity comprises the antiviral B-cell (antibody-mediated) and T-cell immune response.

The B-cell response is involved in antibody-mediated viral binding, but in the acute setting the T-cell response has a dominant role in recognizing and destroying the infected cells. Normally, the secretion of cytokines such as interleukin (IL)-1 $\beta$ , IL-6, TNF- $\alpha$ , and IFN- $\gamma$  is a transient event. However, in hyperinflammation, aggravated by the high bradykinin concentration, this response is exaggerated and causes a massive destruction of host tissue by a cytokine storm. This cytokine storm can worsen the bradykinin-related vascular collapse, associated with disseminated intravascular coagulation and septic shock, as can be observed in patients with severe COVID-19.

The thrombo-angiopathy results in extensive and prolonged plasma leakage and (further) clotting, ultimately developing a pulmonary fibrosis.<sup>6</sup> In the near future, COVID-19 related fibrosis could be an important new entity and, in severe cases, this population may even be considered for lung transplantation.<sup>7</sup> Attenuating this severe inflammatory response could therefore be an important treatment strategy. One strategy may include the use of corticosteroids. However, as is known for other viral diseases, high doses of corticosteroids may be associated with prolonged viral shedding of the virus, as has been observed with SARS, and additionally worsened ARDS may occur. In animal experiments with SARS, dexamethasone promoted viral replication after prolonged administration.

An alternative anti-inflammatory treatment could be the immunosuppressant tacrolimus, known from patients needing immunosuppression after a solid organ transplantation (SOT). Surprisingly, despite over 4.000.000 patients worldwide infected with SARS-CoV-2, only a few case reports describing COVID-19 in SOT patients have been published.<sup>3</sup> These SOT patients generally are under chronic dual or triple immunosuppressive therapy, which in general increases the risk of severe infections. However, as part of the immunosuppressive therapy, tacrolimus has shown a potential benefit in other highly pathogenic coronaviruses, and might be an interesting compound in the treatment of severe COVID-19 (Ref 4,5). Tacrolimus is immunosuppressive by inhibiting calcineurin, and suppressing the early phase of T-cell activation, and the expression of many cytokines (IL-2, IL-4, TNF- $\alpha$  and IFN- $\gamma$ ) that are needed in the activation of the cellular immune response, possibly preventing a cytokine storm as observed in severe COVID-19. It has been suggested to be effective in MERS-CoV, based on case reports in the literature.<sup>8</sup> In animal experiments, it showed effective inhibition of viral replication of SARS-CoV.<sup>9</sup> This could explain the relatively low number of SOT patients with (symptomatic) COVID-19. Also, the severe COVID-19 stage III has hardly been reported in patients with COVID-19 under tacrolimus therapy so far. Although firm conclusions are not possible yet, tacrolimus may be an interesting compound for COVID-19 to reduce, prevent or even treat the hyperinflammation caused by the SARS-CoV-2 infection. Tacrolimus should be considered as a component in the treatment as part of the proactive management in hospitalized immunocompetent patients with moderately severe or even severe COVID-19.

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## Conflicts of interest

The authors declare no conflicts of interest.

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