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CORRESPONDENCE

Cyclosporine therapy in cytokine storm due to coronavirus disease 2019 (COVID-19)

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Dear Editor,

There is no absolutely proven treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The infection continues to spread rapidly worldwide and causes many people deaths. Patients with rheumatic disease can become easily and severely infected with SARS-CoV-2 because their immune system is suppressed [1]. Patients with rheumatic diseases use many immunosuppressants such as disease-modifying antirheumatic drugs. It has been shown in many studies that hydroxychloroquine is effective for SARS-CoV-2 infection [2]. Tocilizumab is used for patients with severe SARS-CoV-2 infection [2]. Steroids use is not recommended during SARS-CoV-2 infection since the drugs may increase the tendency to pneumonia [1].

Cyclosporine is a potent immunosuppressive agent and often uses for immunosuppression after organ transplantation. It is widely used in the treatment of vasculitis by rheumatologists [3]. Cyclosporine can be used in the treatments of Behçet's disease, psoriatic arthritis, and lupus nephritis [3]. Nowadays, it is not used for the treatment of rheumatoid arthritis [3]. Serious side effects of cyclosporine have limited its use. Administration of immunosuppressive agents inhibits the activation of T cells and render patients with rheumatic diseases susceptible to infections [1]. Therefore, it should be clarified whether cyclosporine can be used in SARS-CoV-2 infection. Cyclosporine is a calcineurin inhibitor that inhibits calcium-dependent interleukin (IL)-2 production. It blocks the calcineurin activity by complexing with cyclophilin in the cell and suppresses gene transcription of IL-2. Cyclosporine has been shown to inhibit SARS-COV viral replication at very low and non-toxic doses [4–6]. Similarly, it inhibits the replication of other coronaviruses and *human immune deficiency* virus [5, 6]. Cyclosporine can inhibit cyclophilin functions of the SARS-COV virus by inhibiting the peptidyl-prolyl isomerase activity or may act by directly inhibiting the nsp12 RNA-dependent RNA polymerase activity of the virus [6]. There is a resemblance between SARS-CoV-2 and SARS-CoV based on the full-length genome phylogenetic. Therefore, cyclosporine can be successful in SARS-CoV-2 treatment.

It is known that the virus binds to the angiotensin-converting enzyme 2 (ACE2) and enters the cell. The virus binds to ACE2 at low cytosolic pH [7]. The upregulation of ACE2 is thought to increase the viral load and exacerbate the disease [7]. Three important structures maintain cell pH. These ion regulators are lactate/H^+ ion symporter (also called monocarboxylate transporters), Na^+/H^+ exchanger (NHE), and Cl^-/HCO_3^- exchangers. Hydroxychloroquine does not affect any of these channels. It increases intracellular pH through hemi-gap junctional channels [8]. The SARS-CoV-2 infection creates a hypoxic environment by increase lactate. In anaerobic conditions, lactate formation increases by lactate dehydrogenase. MCT pumps lactate and H^+ ion simultaneously from the extracellular area to the cytosol to lower the elevated lactate level. NHE becomes active as a reflex due to the increase of H^+ ion in the cell [7]. After the activation of NHE, Na^+ and Ca^{+2} are introduced into the cell, while H^+ ion is pumped out of the cell. As this reaction continues, the cell continues to swell and lose its functions and eventually dies [7]. It seems that both MCT and NHE are active at the maximum level in SARS-CoV-2 infection.

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To break this vicious circle, it is necessary to decrease lactate production and to improve the anaerobic environment. Cyclosporine has been shown to lower the lactate/pyruvate ratio in ischemia–reperfusion injury [9]. The most common NHE isoform in the body is NHE-1. Cyclosporine does not activate NHE-1; it only activates NHE-3 [10]. Therefore, it has no known direct effect on cytosolic pH. Cyclosporine can, thus, prevent cell damage and cell death. Cyclosporin can reduce the viral load by keeping the cytosolic pH at normal values.

Cytokine storm can occur for several reasons. Secondary hemophagocytic lymphohistiocytosis (SHL) is the cause of the cytokine storm in SARS-CoV-2 [11]. Cyclosporine is an appropriate option in the treatment of SHL [12]. Cyclosporine and other calcineurin inhibitors function by blocking key signal pathways downstream of the T-cell antigen receptor. Cyclosporine prevents the production of IL-2, a cytokine necessary for the survival and proliferation of T cells. Influenza through nourin stimulates leukocyte chemotaxis, stimulates acute and chronic inflammation, and releases several cytokine storm mediators from monocytes, neutrophils, and endothelial cells [13]. Cyclosporin prevents cytokine storm in H1N1 influenza patients [13].

On the other hand, cyclosporine has undesirable effects. ADAM17 is the metallopeptidase responsible for cleavage of the transmembrane protein tumor necrosis factor-alpha. ADAM17 causes ACE2 cleave [14]. Increasing ACE2 shedding may increment SARS-CoV-2 infection by increasing the ACE2 upregulation [14]. Cyclosporine increases the ADAM17 activity up to threefold [15]. Cyclosporine causes ACE2 upregulation by increasing the ACE2 shedding. Thus, cyclosporine can increase the viral load of SARS-CoV-2.

Cyclosporine has serious side effects such as blood pressure increase, nephrotoxicity, and immune suppression. Its nephrotoxic effect is dose and duration dependent [16]. Cyclosporine can cause hyperlipidemia, gingival hyperplasia, nausea, vomiting, abdominal pain, headache, susceptibility to infections, and triggering of cancer development [16]. Cyclosporine is not administered together with protease inhibitors such as lopinavir/ritonavir. Patients receiving azithromycin are recommended to reduce the cyclosporine dose [17]. It is not clear whether cyclosporine will alleviate or aggravate the SARS-CoV-2 infection. We think that low-dose cyclosporine can only be used in SARS-CoV-2-induced cytokine storm. However, we do not recommend it in SARS-CoV-2 infection since cyclosporine does not have enough preclinical trials yet. Preclinical studies are needed to show that the use of cyclosporine in SARS-CoV-2 infection is beneficial or harmful. We do not ethically approve the use of a drug with serious side effects, such as cyclosporin, in SARS-CoV-2 without detailed preclinical studies.

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Compliance with ethical standards

Conflict of interest All authors reported that they have no conflict of interest to declare.

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