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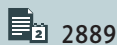
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Effect of Calcineurin Inhibitors and Mammalian Target of Rapamycin Inhibitors on the Course of COVID-19 in Kidney Transplant Recipients

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Coronavirus disease 19 (COVID-19) has been an ongoing pandemic since December 2019. Unfortunately, kidney transplant recipients are a high-risk group during the disease course, and scientific data are still limited in this patient group. Beyond the dosage of immunosuppressive drugs, pharmacological immunosuppression may also alter the infection response in the COVID-19 course. The effects of immunosuppressive agents on the development and process of infection should not be decided only by determining how potent they are and how much they suppress the immune system; it is also thought that the direct effect of the virus, increased oxidative stress, and cytokine storm play a role in the pathogenesis of COVID-19 disease. There are data about immunosuppressive drugs like calcineurin inhibitors (CNI) or mammalian target of rapamycin inhibitors (mTORi) therapy related to their beneficial effects during any infection course. Limited data suggest that the use of CNI or mTORi may have beneficial effects on the process. In this hypothetical review, the probable impacts of CNI and mTORi on the pathogenesis of the COVID-19 were investigated.

Keywords: Calcineurin • COVID-19 • Kidney Transplantation • TOR Serine-Threonine Kinases**Full-text PDF:** <https://www.annalsoftransplantation.com/abstract/index/idArt/929279>

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Background

The world has been in a great struggle with COVID-19 for about 1 year. Immunosuppression is a significant risk factor related to the disease, and kidney transplant recipients are one of the high-risk patient groups. There are case reports about COVID-19 infection seen in kidney transplant patients in the literature. These reports have been viewed in a compilation by Imam et al. In that review, the data of 129 cases from 24 articles were analyzed; 92% of the patients were receiving tacrolimus-based treatment. Acute kidney damage developed in 31% of the patients. Among all patients, 18.8% had died, in contrast to the reported general population COVID-19 mortality of 3.4% [1].

In these patients, different factors might predispose to COVID-19. Factors affecting the disease course in kidney recipients are summarized in Figure 1.

Immunosuppressive drug modification would be helpful at the beginning of the disease course, but the optimal drug modification remains uncertain at present. Poulsen et al stated that continuing the therapy, unless otherwise proven, might have a positive result during COVID-19. This recommendation is not due to a clinical study but is based on the knowledge that calcineurin inhibitors (CNI) may inhibit T cell activation by blocking transcription of cytokines and also cyclosporin analogues such as alisporivir inhibits replication of severe adult respiratory syndrome coronavirus-2 (SARS-CoV-2) in vitro [2]. In a systematic review including 50 studies and 337 patients, Moosavi et al analyzed the drug modification strategies. Generally, anti-metabolite and CNI were reduced or discontinued, and steroid doses were increased, in patients with solid-organ transplantation and COVID-19 [3], but patient outcomes could not be assessed if they were associated with decreased

immunosuppression or increased steroid dose. There are different strategies determined according to the patient's clinical condition and the approach of the transplantation centers. The most common arrangements are to decrease or withhold antiproliferative therapy, decrease CNI to a minimum dose and stop it if there is any infection progression, and to continue steroids at the usual dose or increase it if other immunosuppressive drugs were stopped [4]. In this review, we discuss 2 important drug groups – CNI and mammalian target of rapamycin inhibitors (mTORi) – in kidney transplant patients during the COVID-19 pandemic.

Pharmacological Action of CNIs and mTORi Related to COVID-19

Beyond the dosage of immunosuppressive drugs, pharmacological methods of immunosuppression may also alter the infection response in the course of COVID-19 disease. The effects of immunosuppressive agents on the development and process of infection should not be decided only by determining at how potent they are and how much they suppress the immune system because these drugs also have features other than immunosuppression, such as effects on oxidant stress, complement activation, and drug interactions. CNI and mTORi therapy are 2 groups of drugs that have been compared for many years in many studies in terms of rejection rates, costs, and adverse effects [5-7]. It could be important to know whether CNI and mTORi have different effects on the development and course of COVID-19 infection, but there are no comparative data on the possible effects on COVID-19. A recently published article argued that the use of calcineurin inhibitors would be beneficial in the pandemic course [8]. Studies have shown that the cytopathic effect of the virus, oxidant system activation, and cytokine

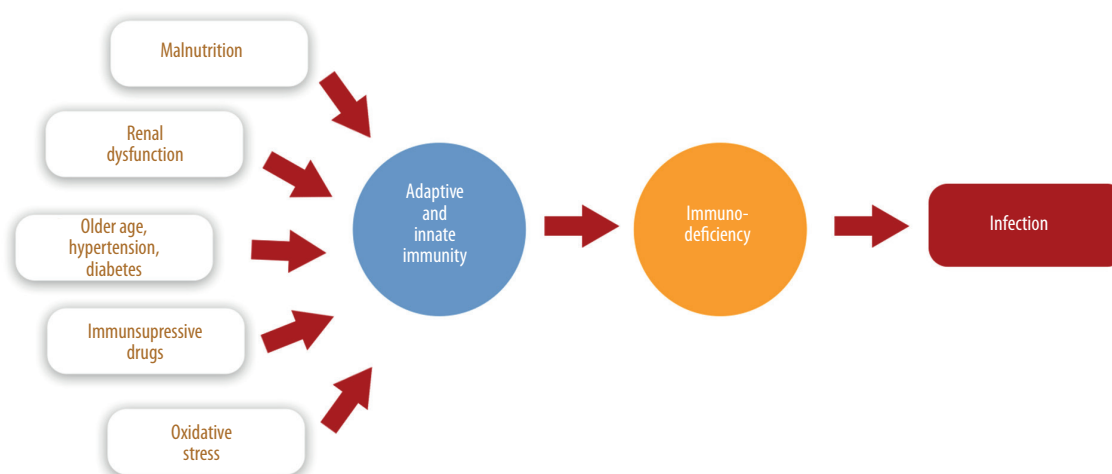


Figure 1. Factors affecting the disease course in kidney recipients.

storm are cornerstones in the pathogenesis of COVID-19 [2,3]. In the early stages of the COVID-19 pandemic, it was speculated that immunosuppressive therapy would facilitate the cytopathic effects of the virus. With a better understanding of the pathogenesis, we might prognosticate that immunosuppressive therapy would lessen the cytokine storm effect. Here, we aimed to consider, in the light of current literature, whether CNI and mTORi have different effects on antiviral activity, oxidant-antioxidant balance, and cytokine storm, which are important mechanisms known in the pathogenesis of COVID-19.

Effects of CNI and mTORi on Viral Infections

CNI and mTORi are the most critical parts of kidney transplant maintenance therapy, but they make kidney recipients more susceptible to infections. In the literature evaluating the possible relationship of CNI and mTORi with viral infections, tacrolimus has been associated with more BK viremia than cyclosporine [9]. mTORi, which are also used in post-transplant lymphoproliferative diseases related to Epstein-Barr Virus viremia, are not mainly related to increased viral infections [10]. In a meta-analysis evaluating the combination of CNI and mycophenolate mofetil (MMF) versus the combination of CNI and mTORi, fewer cytomegalovirus (CMV) infections were detected in patients treated with mTORi [11]. In another multicenter study with kidney transplant recipients, patients taking everolimus had fewer CMV and BK virus infections than patients treated with CNI and MMF [12]. In immunologically low-risk patients, the use of de novo mTORi with low-dose CNI has been reported to decrease viral infection rates [13,14].

Although studies have focused on the increased infection risk of CNI and mTORi due to immunosuppression in renal transplantation, many studies have questioned the antiviral effectiveness according to their mechanism of action [8,15]. Cyclosporin A (CsA) and tacrolimus inhibit gene transcription of interleukin (IL) 2 and produce some cytokines in T cells. Thus, they suppress T cell and T cell-dependent B cell activation [16]. Most viruses use active immunophilin pathways during their life cycle. Both the cyclophilin family and tacrolimus-binding proteins interact with viruses. This interaction allows CNI to control the inflammatory response in viral infections. For example, cyclosporine inhibits the replication of the hepatitis C virus in vitro [17]. CNI (in the therapeutic range) might be useful to control the destructive effects of cytokines in the hyperinflammatory phase of viral infection with reduction of virus-related cytokine storm. This idea was supported by a study evaluating CsA in the treatment of hemophagocytic lymphohistiocytosis, which is related to excessive proinflammatory cytokine release. Activated T cell-mediated IL-2 gene transcription can be inhibited with cyclosporin, and both cell proliferation and cytokine production decreased [18].

The Mechanism of mTORi-Induced Suppression of Cytokines

The mammalian target of rapamycin (mTOR) pathway is a protein kinase inhibited by rapamycin and plays a role in regulating cell proliferation. Protein kinases and inhibitors are divided into 2 groups according to their substrates: protein tyrosine kinases and protein serine/threonine kinases. mTOR, a serine/threonine kinase, has different biological activities and consists of 2 different multiple protein complexes. Rapamycin acts on both mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 plays a role in mitogen (eg, insulin-like growth factor) and cytokine synthesis. The function of mTORC2 is unclear. By inhibiting IL2-mediated signal transmission, mTORi causes cell cycle arrest in the G1-S phase, resulting in disruption of cellular functions such as cell division, T cell activation, and growth factor production. Thus, mTORi inhibits B and T cell proliferation and blocks the proliferative effects of IL 1, 2, 3, 4, 6, insulin-like growth factor, platelet-derived growth factor, and colony-stimulating factors. It is reasonable to conclude that the antiviral activity of mTORi may be associated with mTORC1, which is involved in cytokine synthesis. CMV infections were less prevalent with the use of mTORi and low-dose CNI, and the frequency of polyomavirus infection decreased with mTORi de novo use [19]. The antiviral efficacy of mTORi has been supported in animal studies, too. Rapamycin had protective impacts against influenza type H3N2 in animal studies [20], and the effects of influenza on alveolar type 2 cells were abolished by rapamycin [21]. Influenza studies in humans have produced conflicting results. Although severe H1N1 influenza-induced pneumonia improved with rapamycin and steroids, it was concluded that viral replication is prolonged, resulting in increased mortality [21].

The evidence shows that CNI and mTORi inhibit many pathways used by viruses and can control cytokine synthesis. They might have potential antiviral and immunomodulatory effects.

Antibody-Dependent Enhancement and Cytokine Storm

Based on previous experience with coronavirus (CoV) outbreaks such as Middle-East respiratory syndrome and severe acute respiratory syndrome (SARS) and SARS animal model studies, lung inflammation increases to reach the peak no later than 14 days after viral clearance. This period is the effector phase, which we define as the lymphocyte activation and antigen elimination of the immune system. Tissue damage occurs with uncontrolled and inappropriate antiviral response rather than viral proliferation [22]. Antibody-dependent enhancement (ADE) and cytokine storm need to be further studied to better understand the pathogenesis in this context.

High-affinity antibodies can recognize specific viral epitopes and cause neutralization. Neutralizing antibodies can be identified *in vitro* with their ability to inhibit virus entry, fusion, or exit. These neutralizing antibodies can interact with the complement system, phagocytes, and natural killer (NK) cells [22]. However, these pathogen-specific protective antibodies can promote pathology in rare cases, resulting in a phenomenon known as ADE [23]. The ADE phenomenon occurs with the participation of Fc receptors (FcR) expressed on different immune cells, including monocytes, macrophages, and B cells. Thus, preexisting specific antibodies can facilitate viral entry into cells expressing FcR. This process is independent of angiotensin-converting enzyme-2 (ACE2) expression, endosomal pH, or proteases, and results in both viral replication in immune cells and immune complex-mediated inflammatory response. Studies have shown that new CoVs increase tumor necrosis factor (TNF) and IL-6 production in macrophages through ADE [24]. In SARS-CoV-infected mice, the ADE phenomenon has been associated with decreased levels of IL-10 and transforming growth factor- β (TGF- β). Increased proinflammatory circulating chemokine ligand (CCL) 2 and CCL3 chemokine levels, which have anti-inflammatory and immunosuppressive properties, are also prominent [25]. Thus, although not fully proven in SARS-CoV-2, the ADE phenomenon can lead to severe disease.

Cytokine storm, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis are not specific to COVID-19. They are leading causes of acute respiratory distress syndrome (ARDS) and can also occur in sepsis, other viral infections, and as the adverse effects of some drugs [26]. Inflammatory damage can be weakened by anti-cytokine or anti-cytokine receptor treatments, as well as small-molecule complement inhibitors at an early stage of infection. Clinical studies on tocilizumab, anakinra, and Janus kinase (JAK) inhibitors are ongoing. The above evidence suggests that maintenance immunosuppression agents can affect COVID-19, since kidney transplant patients who use continuous immunosuppressive drugs overcome the disease, with a possible milder clinical picture.

Surmising Risks and Benefits of CNI and mTORi for Kidney Transplant Recipients

In studies discussing the effects of COVID-19 in kidney transplant patients, immunosuppressive agents were discontinued, or the dose was reduced [27,28], but we do not know if there is a difference in the course of the disease among those using mTORi or CNI. Willcombe et al stated that CNI could be continued to be used in kidney transplant patients for 2 different reasons. The first is the ability of these agents to reduce viral replication, as demonstrated by experimental studies on SARS-CoV. The second is the assumption that they may have the ability to reduce a similar cytokine storm during the

course of COVID-19, based on the effectiveness of CNI in hemophagocytic lymphohistiocytosis and capillary leak syndrome [8].

Bourboulis et al evaluated immune responses of COVID-19 patients (n=54) with macrophage activation syndrome and found that CD4+ T lymphocytes, CD19+ B lymphocytes, and NK cells, and their human leucocyte antigen (HLA)-DR expression were significantly decreased [29]. In another study, everolimus reduced the amount of interferon gamma (IFN-gamma)-induced HLA-DR in endothelial cells [30]. In contrast, tacrolimus affects basal or IFN-gamma-induced HLA-DR in monocytic cell lines [31]. It has been reported that mTORi reduces cytotoxic T cells and effector memory T cells in Belatacept-resistant kidney transplant rejections [32]. This benefit may help to prevent the tissue damage caused by viral replication in COVID-19 disease or protect against recurrent infections by under-controlling the immune memory.

The effects of sirolimus and tacrolimus on B cells may differ from each other. Sirolimus has been shown to reduce CD19+ CD27+ memory B cells and their conversion to plasma cells. Sirolimus reduces the total number of B cells more than tacrolimus but makes them stronger by increasing HLA-DR expression [33,34]. In this way, sirolimus may control neutralizing antibody production in COVID-19 patients. In kidney transplant recipients using mTORi (everolimus or sirolimus), there were also higher proportions of regulatory T cells (Treg) [35]. Tregs suppress effector T cell induction and proliferation, which prevents cytokine storm. In contrast, in a cell culture study by Eleftheriadis et al, tacrolimus was more effective in suppressing cellular immunity compared to everolimus and both have similar impacts on humoral immunity [36]. Tacrolimus might be the other option to prevent the production of T cell-induced cytokines in COVID-19 cases.

Effects of CNI and mTORi on Transplantation-Related Oxidative Stress

Oxidative stress results from a disturbance between oxidant and antioxidant balance, producing a large number of reactive oxygen species (ROS, an atom or group of atoms that have 1 or more unpaired electrons) in the cells. ROS are normally generated in a constant amount and are essential to life, but increased numbers of ROS damage proteins, lipids, and deoxyribonucleic acid (DNA) [37]. Antioxidant capacity is related to enzymes catalyzing oxygen radicals (eg, oxidases, glutathione peroxidase, superoxide dismutase (SOD)) and antioxidants (eg, tocopherols, glutathione, ascorbic acid) in the organisms [37]. Triggers of oxidative stress are mainly xenobiotics, microorganisms, inflammation, and radiation. In enhanced inflammatory conditions like chronic kidney disease (CKD) and kidney transplantation, oxidative stress promotes

inflammation by activating the proinflammatory transcription factors, and chronic inflammation reciprocally amplifies the oxidative stress [38]. In the early phase of kidney transplantation, end-stage kidney disease (ESKD)-related radicals such as hydrogen peroxide (H_2O_2) or hypochlorous acid (HOCl), and free radicals such as superoxide (O_2^-), hydroxyl radical, and nitric oxide, ischemia-reperfusion injury, and immunosuppressive drugs are responsible for oxidative stress. Endothelial injury, atherosclerosis, and increased creatinine participate in oxidative stress in the late phases [39]. Immunosuppressant drugs like CNI and mTORi are candidate drugs that change the balance in the direction of antioxidation.

CNI, especially tacrolimus, has some nonimmunological effects unrelated to transplantation, such as improvement in ischemia-reperfusion injury (IRI). Control of ischemia thought to be related to nitric oxide synthase (NOS) inhibition, resulting in decreased oxidative stress [40]. In an experimental model of IRI, tacrolimus decreased ROS, lipid peroxidation products, and TNF- α expression of cells [41]. CsA-related antioxidant activity is thought to be weaker than that of tacrolimus. In kidney and heart transplantation, it is reported that CsA was related to increased production of ROS, but in another study, CsA and tacrolimus were compared to advanced oxidation protein products in the sixth month of transplantation, and no difference was found [42]. Cvetkovic et al analyzed nitrosative stress parameters (asymmetric and symmetric dimethylarginine), and antioxidative parameters (total SH groups and catalase activity) after 1 year of transplantation. There was no significant difference in parameters concerning the immunosuppressive protocol [43].

The effects of mTORi (including rapamycin and everolimus) on oxidative stress are controversial. Some groups demonstrated that mTOR signaling is crucial to prevent ischemia preconditioning and IRI, but other evidence suggests that mTORi inhibits IRI [44]. In an experimental model of Friedreich's ataxia, the authors found that rapamycin protects cells against oxidative stress, with increased transcription of antioxidant genes. Lower doses of rapamycin may be beneficially combined with other drugs such as antioxidants and iron chelators [45]. Rapamycin, together with metformin, were also found to reverse age-dependent biomarkers of oxidative stress, suggesting a synergistic response in rats [46].

In the course of COVID-19 disease, it is likely that the antioxidant response is also explicitly changed since there is a clinical spectrum from asymptomatic to systemic inflammatory response syndrome. Recent data shows that lethal outcomes are related to age and underlying clinical conditions like diabetes and hypertension, which are prone to altered oxidant-antioxidant balance. SARS-CoV-2 itself also potentiates this already pathological antioxidant system. The virus uses the encoded protein of ACE2 as a functional receptor to enter cells. ACE2 catalyzes the cleavage of angiotensin II to vasodilator angiotensin 1-7. Angiotensin 1-7 mainly works as a blocker for SOD and decreases ROS, while angiotensin II promotes radical formation. Theoretically, SARS-CoV-2 blocks ACE2 and causes an increased ROS production with the help of increased angiotensin 2 levels [47]. Beyond this specific effect, SARS-CoV-2, as any infection, triggers a nonspecific inflammatory response from macrophages through activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, resulting in increased superoxide levels [48]. Increased ROS also damages host endothelial cells via inactivation of nitric oxide, resulting in thrombosis, which is also commonly in COVID-19.

As a result, in the treatment of COVID-19, controlling the inflammatory response may be as important as targeting the virus. Although there is no proven treatment for oxidative stress yet, routinely used immunosuppressive drugs like tacrolimus, CsA, and mTORi in kidney recipients may control the overreacted system. Further studies of oxidative stress management and to identify biomarkers would help us to triage patients with COVID-19 and underlying diseases like kidney transplantation.

There are several limitations of this review. The review has been built on mechanisms that are well understood in the pathogenesis of COVID-19. However, there may be many mechanisms that we still do not know about regarding the pathogenesis of COVID-19 and that may emerge later. Clinical studies on the effect of CNI and mTORi on the course of COVID-19 are lacking in the literature. Therefore, the present review is theoretical.

Conclusions

During the COVID-19 process, both CNI and mTORi may hypothetically have beneficial effects on kidney transplant patients. Immunosuppressants are not necessarily turned down for kidney transplant recipients in the pandemic of COVID-19. It is recommended to consider the pharmacological action of each immunosuppressive drug. Drug-comparative studies are needed on this subject.

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