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Letter to Editor

Sirolimus to treat SARS-CoV-2 infection: an old drug for a new disease

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Dear Editor,

The development and study of new drugs to treat the pandemic coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), is a challenge for the global scientific community. Although scientific research for new targeted therapeutic strategies is the primary issue, in emergency conditions, the use of already known and studied old drugs represents a fascinating and possible therapeutic option.

Evidence suggests that excessive activation of the immune system is responsible for the severe clinical complications of COVID-19. Consequently, using drugs to reduce the exaggerated inflammatory response is an attractive therapeutic choice.[1]

Appelberg et al demonstrated that SARS-CoV-2 causes excessive activation of the mammalian target of rapamycin (mTOR) signaling pathway in an in vitro model.[2] Using the network-based drug repurposing model and based on data from other human coronavirus infections, the in silico studies reported mTOR as a highly effective molecule in COVID-19 progression.[3] Dysregulation of the mTOR pathway seems to enhance SARS-CoV-2 pathogenicity, which may result in severe COVID-19.

The mTOR exerts a vital role in regulating inflammation within the immune system, and controls multiple effector T cell fates. The mTOR exists in two distinct complexes, defined as mTOR complex 1 ($mTORC_1$) and 2 ($mTORC_2$). The $mTORC_1$ mediates T-Helper 1 (TH_1) and T-Helper 17 (TH_{17}) differentiation at the time of viral antigenic presentation by dendritic cells (DCs); $mTORC_2$ mediates T-Helper 2 (TH_2) differentiation, while both complexes restrict differentiation of the regulatory T-cell (T_{reg}).[4]

Optimal mTOR activity is required for proper T cell differentiation and function. Over-activation of $mTORC_1$ destabilizes T_{reg} and impairs their suppressive function with an increase in TH_{17} response. Data reported in the literature suggest that in patients with severe COVID-19, TH_{17} cells were increased,[5] while T_{reg} count was below normal value.[6] SARS-CoV-2 infection can cause an imbalance in TH_{17}/T_{reg} cells by dysregulation of the mTOR pathway. TH_{17} cells, by secretion of pro-inflammatory IL-17A, are involved in neutrophil-mediated inflammation and combat against the microbes attacking epithelial layers. TH_{17} cells also play significant roles in the pathophysiology of chronic inflammation observed in rheumatoid arthritis, psoriasis, multiple sclerosis, or inflammatory bowel disease secrete. In contrast, T_{reg} cells are responsible for maintaining the immune homeostasis by suppressing the activation, proliferation, and pro-inflammatory function of most T and B lymphocytes, and natural killer cells.[7]

Based on these observations, mTOR inhibitor (mTORi) drugs, as sirolimus (SRL) and its analogs (everolimus and temsirolimus), drew attention as a possible therapy to treat the COVID-19 and reduce the clinical manifestations. SRL, also known as rapamycin, inhibits effector T-cell proliferation and promotes T_{reg} accumulation.[4] The effects of SRL on the immune response make it an ideal therapeutic choice, because it may reduce immune-mediated damage during SARS-CoV-2 infection, but at the same time, does not alter the immune system's defensive ability to respond to another possible infection.

To date, several clinical trials are registered on clinicaltrial.gov to investigate the role of SRL as a treatment for COVID-19. Table 1 reports the main characteristics of the studies.

In conclusion, the relationship between SARS-CoV-2 and mTOR pathway represents an interesting hypothesis, able to justify the development of exaggerated immunopathological responses related to the worst clinical outcomes. Consequently, we suppose that the early administration of mTORi can exert a protective role and prevent clinical worsening. Although clinical data about the therapeutic effects of SRL against COVID-19 are absent, and several clinical trials are still ongoing, immunomodulation can present a fascinating strategy for the treatment of COVID-19.

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Table 1. The main characteristics of ongoing studies registered on clinicaltrial.gov on sirolimus as a treatment for SARS-CoV-2 infection

Trial Registration Number	Title	Status	Outcomes	Completion Date
NCT04461340	Efficacy and safety of sirolimus in COVID-19 infection	Not yet recruiting	Time to clinical recovery, viral clearance, radiological lung extension, adverse drug events, 28-day mortality, intensive care unit admission rate, duration of hospital stay	October 30th, 2020
NCT04341675	Sirolimus treatment in hospitalized patients with COVID-19 pneumonia	Recruiting	Proportion of patients who are alive and free from advanced respiratory support measures at day 28, proportion of patients who require escalation in care, change over time in study-specific biomarkers (LDH, ferritin, D-dimer, lymphocyte count), proportion of patients surviving to hospital discharge, drug safety profile, duration of advanced respiratory support, duration of hospital stay, time from treatment initiation to death, time to resolution of fever, the proportion of patients who require initiation of off-label therapies	September 2020
NCT04371640	Sirolimus in COVID-19 phase 1	Recruiting	Change in SARS-CoV-2 viral burden from baseline to day 7 of treatment, change in SARS-CoV-2 viral burden at days 1 to 6, rate of treatment-emergent adverse events	August 2020
NCT04482712	Effects of mTOR inhibition with sirolimus (RAPA) in patients with COVID-19 to moderate the progression of ARDS	Not yet recruiting	The survival rate, change in clinical status assessed by the World Health Organization (WHO) scale and National Institute of Allergy and Infectious Disease (NIAID) scale	October 2022
NCT04374903	Hydroxychloroquine in combination with azithromycin or sirolimus for treating COVID-19 Patients	Not yet recruiting	Time to Clinical improvement, clinical failure defined as death or need for intubation and mechanical ventilation, adverse effects, QT interval prolongation, failure to continue assigned therapy, time to viral clearance	September 1st, 2020

Conflict of interest
The authors declare no conflict of interest.

Ethical Approval
Not applicable.

Authors' Contributions
AR and SM contributed equally to the study.

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