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.1 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 (mTORC1) and 2 (mTORC2). The mTORC1 mediates T-Helper 1 (TH1) and T-Helper 17 (TH17) differentiation at the time of viral antigenic presentation by dendritic cells (DCs); mTORC2 mediates T-Helper 2 (TH2) differentiation, while both complexes restrict differentiation of the regulatory T-cell (Treg).4

Optimal mTOR activity is required for proper T cell differentiation and function. Over-activation of mTORC1 destabilizes Treg and impairs their suppressive function with an increase in TH17 response. Data reported in the literature suggest that in patients with severe COVID-19, TH17 cells were increased,5 while Treg count was below normal value.6 SARS-CoV-2 infection can cause an imbalance in TH1/TH17 cells by dysregulation of the mTOR pathway. TH17 cells, by secretion of pro-inflammatory IL-17A, are involved in neutrophil-mediated inflammation and combat against the microbes attacking epithelial layers. TH17 cells also play significant roles in the pathophysiology of chronic inflammation observed in rheumatoid arthritis, psoriasis, multiple sclerosis, or inflammatory bowel disease at the time of viral antigenic presentation.

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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Conflict of interest
The authors declare no conflict of interest.

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Not applicable.

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AR and SM contributed equally to the study.

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