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Novel Immunological Aspects of Sirolimus as a New Targeted Therapy for COVID-19

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Coronaviridae is a family of enveloped, single-stranded RNA viruses. Coronaviruses which were discovered in the 1960s, are a large subfamily of coronaviridae and cause a variety of illnesses such as the common cold to more severe ones, including Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19. These viruses can be transmitted to mammals and birds (1-4). Mortality percentage is observed to be higher in individuals over the age of 50, because as the individual's age increases, the activity of the Thymus gland to produce T cells is reduced considerably. Sirolimus (Rapamycin) as a macrolide molecule produced by Streptomyces Hygoscopius, weakens the immune system and paradoxically strengthens T cells activity during pathogen invasions. However, this is not the only physiological contradiction in medical sciences. For instance, while hormonal treatments for hormone-dependent cancers such as the use of testosterone to cure prostate cancer or the application of beta-blockers to treat heart failure seemed contradictory at first, they are considered significantly functional today. It has been shown that sirolimus effectively increases lifetime and reduces the aging process in numerous species such as Drosophila, C. Elegans, and mice. Sirolimus also delays age-related illnesses in humans. Consequently, it is recommended as preventive for illnesses caused by advanced age in humans (5, 6). Accordingly, it is possible that a drug, previously known as an immune system suppressant could also be an immune system stimulant in a regiment with different doses. Sirolimus is also known to have antibiotic, antitumor, and antifungal effects (6). Everolimus is a structural analog close to sirolimus. Previous clinical studies have shown the effects of everolimus on stimulating the immune system in old individuals along with a 20 percent increase in the immune responses of the elderly volunteers receiving the Influenza vaccine (5).

Another mechanism that places sirolimus as an ideal candidate for COVID-19 treatment is its inhibitory effect on the mTORC1 receptor (7). According to reports, viral protein expression and virion release have been effectively blocked by sirolimus which is an inhibitor of mammalian target of rapamycin (mTOR) (8). mTOR is a protected Serine/threonine-specific protein kinase that regulates cell growth and cell cycle progression through Phosphatidyl 3-kinase (PI3K) and kinase-B protein. There are two distinct multi-protein complexes called mTORC1, and mTORC2 (6, 7). mTORC1 is the main one with autophagy regulatory properties. Previous research has shown that the mTORC1 receptor is the main regulating factor for various viral replications in humans, such as orthohantavirus and coronavirus (8). Moreover, it has been stated that aging in mammals is regulated through the mTORC1 pathway. Animal studies have demonstrated that signaling inhibition of mTORC1 resulted in an increased lifetime and reduced illnesses related to aging. Research on old-aged individuals also showed that the inhibition of mTOR via sirolimus enhanced the individuals' immune systems (5).

To date, no effective therapies have been discovered for the coronavirus, and the existing treatments are merely a means for support. SARS-CoV-2 is a betacoronavirus which has the highest genetic similarity with SARS and MERS, particularly the former (4, 8, 9). Theoretically, the existing treatments for SARS and MERS are the most effective therapies, which probably be effective

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against SARS-CoV-2 as well. Clinical studies have shown that sirolimus reduces MERS-CoV infections by more than 60%. Additionally, several clinical studies have also confirmed the effectiveness of sirolimus in treating patients suffering from severe H1N1 pneumonia and acute respiratory failure (8).

COVID-19 involves a severe inflammatory response from neutrophils, lymphocytes, macrophages, and immune system inductors and also increases inflammatory cytokines, which are a cause of death in patients (10,11). Accordingly, mTOR plays a key role in the inherent immune system and increases inflammatory cytokines. Inflammatory responses in myeloid cells, including monocytes/macrophages and dendritic cells (DCs), are limited by mTOR through modulating classical transcription factors like NF-κB and signal transducer and activator of transcription 3 (STAT3). Additionally, type I IFN-γ production in murine DCs is fostered by the mTOR pathway, and also it plays a role in plasmacytoid DCs. Therefore, the inflammatory cytokine production through NF-κB activity and release of IL-10 by activated STAT3 in human monocytes are inhibited via mTOR inhibition (12).

Since COVID-19 engages the human immune system and given the expressed mechanisms, sirolimus can be used as an effective drug in the COVID-19 treatment protocol. Currently, several clinical trials are in process to evaluate the therapeutic effect of sirolimus in the treatment of COVID-19. One study investigates the effect of sirolimus on clinical outcomes of hospitalized patients with COVID-19. Thirty patients are randomly assigned to receive sirolimus (oral loading dose of 6 mg on day 1 followed by 2 mg daily) or placebo for a maximum treatment duration of 14 days or until hospital discharge, whichever occurs first. The primary outcome of the study is the ratio of survivors without the need for advanced respiratory support measures on day 28 (13). Another clinical trial compares the antiviral effect of sirolimus (10 mg loading dose on day 1 followed by 5 mg on days 2-7) or placebo as an adjuvant therapy to standard medical management of 40 eligible patients. Until day 7 of the study, COVID-19 viral load is measured daily and compared with the baseline value (14). The third clinical trial randomizes 58 confirmed cases of COVID-19 to hydroxychloroquine (600 mg daily)/ azithromycin (250 mg daily) or hydroxychloroquine (600 mg daily)/ sirolimus (4 mg on day 1 then 2 mg for 9 days) treatment groups for 10 days. The primary outcome of the study is the number of days spends for clinical improvement of patient symptoms (15). However, routine administration of sirolimus as a component of a standard treatment protocol for COVID-19 should be confirmed by large-scale clinical trials.

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