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A POTENTIAL ROLE OF ISOPRINOSINE IN PROPHYLAXIS AND EARLY TREATMENT OF COVID-19

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ABSTRACT
By the end of 2019, reports of a cluster of patients infected with a novel coronavirus emerged from Wuhan, China. From then on, rapid spread of infection occurred around the world and the end of this pandemic is still beyond scope. The emerging disease, coronavirus disease 2019 (COVID-19) has variable clinical presentations ranging from asymptomatic, mild pneumonia to life threatening acute respiratory distress syndrome, septic shock, and multiple organ failure. lymphopenia is a common finding in COVID-19 and this phenomenon is more obvious in ICU patients. Isoprinosine is a synthetic compound with immunomodulatory and antiviral properties. Based on its rapidly induced lymphoproliferative responses, isoprinosine may have a potential role in prophylaxis and early treatment of COVID-19.

KEYWORDS: COVID-19, Isoprinosine, cytokine storm, lymphopenia.

Coronaviruses are a diverse family of viruses, which cause clinical illnesses that range from common cold to serious respiratory disease, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).[1] By the end of 2019, reports of a cluster of patients infected with a novel coronavirus emerged from Wuhan, China. From then on, rapid spread of infection occurred around the world. The emerging disease, coronavirus disease 2019 (COVID-19) has variable clinical presentations ranging from asymptomatic, mild pneumonia to life threatening acute respiratory distress syndrome, septic shock, and multiple organ failure.[2] As of this writing, more than 230,000,000 cases and over 4,500,000 deaths have been reported around the world and the number is still going on. The current therapeutic approaches of patients with COVID-19 are mainly supportive including, fluid therapy, oxygen therapy, respiratory support and other life support methods.[3]

One of the most crucial functions of the innate immune system is the recognition of certain conserved microorganism structure, known as pathogen-associated molecular patterns (PAMPs) via expressing certain pattern recognition receptors (PRRs).[4] Certain endosomal and cytoplasmic PRRs as Toll like Receptor (*TLR) 3, TLR7, retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein5 (MDA-5*) can recognize RNA viruses like SARS and COVID-19 and stimulate type 1 interferons (IFN) (IFN-α and IFN- β) production.[4] IFN-α and β play a basic role in the induction of antiviral responses and blocking of viral replication.[4] Corona viruses inhibit the production of type I IFN via expression of certain proteins (like M protein and papain-like protease) which facilitate rapid replication and excessive virus-induced cytopathic effects in early disease stages and delay the antiviral response by suppressing TLR3 and TLR7 signaling pathways.[5]

The suppressed and dysregulated type 1 IFN response together with increased production of cytokines and chemokines from virus infected cells as pneumocytes may eventually lead to exaggerated infiltration of lung parenchyma with neutrophils and monocyte/ macrophage.[6] The invading neutrophils and monocyte/macrophages in turn, produce high levels of pro-inflammatory cytokines (including interleukin (IL) 1β, IL-6 and tumor necrosis factor alpha (TNFα)) and chemokines, which eventually lead to hyperinflammation and cytokine storm that characterizes the most severe cases of COVID-19.[7]

Like the case for SARS and MERS infections, lymphopenia is a common finding in COVID-19 and this phenomenon is more obvious in ICU patients.[2,8] A study carried out in Wuhan, China on 389 hospitalized patients with confirmed COVID-19 from January 24 to February15, 2020 showed a significant increase in the cytokine profiles including IL-1β, IL-6, IL-8, IL-10 and TNF-α with increased severity of illness while the number of lymphocytes was significantly decreased.[9] Furthermore, the levels of IL-6, IL-8, IL-10, TNF-α were significantly decreased while there was a gradual increase in lymphocyte number to normal levels in the recovered patients. On the contrary, lymphocyte number further decreased, while cytokines significantly increased in the deteriorated patients.[9]

According to a recently published descriptive and predictive study, one possible mechanism of lymphopenia associated with COVID-19 may be apoptosis of lymphocyte that result from the dysregulated inflammatory response and the resulting cytokine storm induced by the virus.[10]

Isoprinosine is a synthetic compound with immunomodulatory and antiviral properties. The drug first introduced in 1971 and currently approved in over 70 countries around the world. Isoprinosine continues to be attractive subject of various clinical and non-clinical studies.[16] Isoprinosine is a well-tolerated drug as evidenced by the small number of adverse reactions, the limited number of subjects withdrawn from clinical trials, as well as available post-marketing surveys.[17] The antiviral and immunomodulatory effects of isoprinosine are evident both in vitro and in vivo. In an effort to elucidate the immunomodulatory and antiviral properties of Isoprinosine, several mechanisms of action have been assumed. Isoprinosine stimulates a nonspecific immune response to viral infections irrespective of the specific viral antigen, a finding, which suggests a possible direct antiviral effect through inhibition of viral transcription and translation processes.[18] Isoprinosine enhances host cell RNA synthesis, which become decreased markedly after viral infections and decreases viral RNA synthesis.[19,20] It has been suggested that isoprinosine binds to the ribosomes of the infected cells, producing a structural change of host ribosome, thus providing a benefit to host cellular RNA over viral RNA in the competition for binding to the ribosomal binding sites.[20] The result would be a non-reading or misreading of the viral genome.[21] Another hypothesis suggests a role for inosine, which is a metabolite of isoprinosine. Isoprinosine is rapidly metabolised into inosine, which in turn, inhibits the synthesis of the phosphoribosyl pyrophosphate, an intermediate of purine biosynthesis, an effect which may block viral RNA synthesis, as this process is faster than host RNA synthesis.[22] Moreover, a recent study has revealed the ability of inosine to cause ribosome hedging and circumstantial decoding during translation to either adenosine or uracil.[23] Isoprinosine induces a T helper-1 (Th-1) cells-type response in mitogen- or antigen-activated cells but not in resting lymphocytes and increases levels of pro-inflammatory cytokines, such as IL-2, IFN-β, IFN-γ and TNF-α.[24-27] The Th1 cell-type response and the increased cytokine levels develop rapidly after Isoprinosine administration.[28] Such response recruits T-lymphocyte maturation and differentiation and stimulates induced lymphoproliferative reactions.[25-27,29] Overall, the restoration of the depressed T-lymphocyte function to normal by isoprinosine may be mediated by increasing lymphokine production, or alternatively by stimulating cell ribosomal RNA and protein synthesis while instantaneously inhibiting the utilization of cell ribosomal RNA for viral replication.[16]

To date, the treatment approaches of COVID-19 are largely supportive as specific antiviral therapy is not available. The production of effective antiviral agents is in general a challenging and time-consuming process, and the rise of resistant strains due to the extended use of antiviral drugs, is an important concern in the development of novel antivirals. An alternative useful strategy would be to maximize the efficacy of the present antiviral drugs by conjoining them with the currently available vaccines and other drugs that potentiate their action.

Since lymphocytes play a pivotal role in viral eradication. cytotoxic $CD8^+$ T-cells help to clear viruses from the host by secreting substances as IFN-γ and granzymes. Helper $CD4^+$ T-cells can aid cytotoxic T-cells and increase their ability to fight against pathogens, prevention of reduced blood lymphocyte levels is expected to provide an effective strategy for prevention and treatment of COVID-19.[14] Isoprinosine may have a potential role of in prophylaxis and early treatment of COVID-19 based on its rapidly induced immunomodulatory and lymphoproliferative responses, thus initiating preliminary trials of isoprinosine therapy in COVID-19 patients as soon as possible is strongly recommended.

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Conflict of interest Authors declare that they have no conflict of interest.

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