COVID-19 treatment: Possible role of itraconazole as new therapeutic option

Coronaviruses are enveloped, positive-sense, RNA nucleic acid viruses characterized by a distinctive replication strategy; they are round and are of sometimes pleomorphic shapes. COVID-19 is regarding the new genera of coronaviridae that appear for the first time in Wuhan, China, in early December 2019.[1] At present, the number of cases due to the novel (COVID-19) coronavirus presents a serious public health problem worldwide, so effective treatment methods and more effective management strategies should be developed as soon as possible to prevent or treat this new virus.[2] Until this moment, no specific drug or other therapeutics have been approved by the FDA; organ support in seriously ill individuals and symptomatic treatment are major steps in clinical management. To develop specific antivirals for treating novel COVID-19, it may take a long time for evaluation and approval.[3]

Experts are working across the world to locate a pharmacological cure for COVID-19. There was so much uncertainty here.[4] Pharmaceutical repurposing, representing from licensed drugs as an successful drug development technique, could shorten the time and minimize costs relative to *de novo* drug exploration. The medications being studied range from repurposed flu medicines, Ebola medications, to the medicines for malaria, which were first formulated decades earlier.[5]

Studies demonstrated the clinical and virologic benefits of chloroquine and hydroxychloroquine in patients with COVID-19 compared to controls.[6,7] Both drugs have known safety profiles; the main side effect is cardiotoxicity (prolonged QT syndrome) after prolonged use in patients with hepatic or renal impairment and those who are immunosuppressed; side effects are suspected in some antimicrobial agents.[8,9] Azithromycin (Zitromax®), an antibacterial (not antiviral) antibiotic, is used to counter bacterial super-infection in serious viral illness and has been given to some COVID-19 patients in combination with hydroxychloroquine.[4]

Two common antiviral drugs called remdesivir (remdesivir was originally developed as an Ebola treatment) and favipiravir were tested *in vitro* against COVID-19, which showed that they inhibit COVID-19 infection.[10] Kaletra® is a mixture of two antiviral drugs, ritonavir and lopinavir, usually used for the diagnosis of human immunodeficiency virus, where laboratory tests report that they could be useful in the diagnosis of COVID-19.[11] The antiviral medication, favipiravir, or Avigan, developed in Japan by Fujifilm Toyama Chemical, has been used to treat influenza; the medication has been approved as an experimental therapy for at least mild-to-moderate COVID-19 cases. Antiviral EIDD-2801 is the drug which blocks the COVID-19 virus more effectively than remdesivir. Although remdesivir stops the COVID-19 from fully replicating, EIDD-2801 incorporates genetic mutations into the RNA of the virus. Therefore, when the RNA makes its copies, enough harmful mutations occur so that the COVID-19 can no longer kill cells.[5]

The new drug, APN01, mimics the human enzyme ACE2 that is used by the COVID 19. The virus attaches to soluble ACE2/APN01, instead of ACE2 on the surface of the cell, which means that the virus is incapable of infecting the human cells. Additionally, APN01 diminishes the harmful inflammatory reactions in the pulmonary system and defends against acute lung injury.[12] Losartan is a blood-pressure drug; some scientists are hoping that it could treat patients with COVID-19.[5]

Doctors in China have diagnosed several seriously ill patients with COVID-19 with the revived patients' blood plasma. The reasoning is that the blood will produce antibodies to help prevent the infection.[11] Other doctors are now seeking an immunosuppressive medicine known as Actemra®, or tocilizumab. The drug is approved for treating rheumatoid arthritis and rheumatoid arthritis in juveniles. It inhibits the binding of a cell receptor to interleukin (IL)-6. IL-6 is a cytokine produced by the immune system, which can trigger hazardous inflammatory cascades.[5] Another scientist has been given fast-track clearance to the UK biotech company Synairgen to study a lung disease treatment in novel coronavirus sufferers. The hope is that interferon (IFN)-β administration will improve the body's ability to fight the virus, particularly in those that have compromised immune systems.[11]

In the present study, we suggest the use of the antifungal therapeutics itraconazole (ICZ) in the therapy of COVID-19. It showed antiviral effects against enterovirus 71, suggesting that it has broad-spectrum antiviral

efficacy against Picornaviridae.[13] As well as, it showed antiviral activity against some enveloped viral infections such as influenza A virus.[14]

Changes in cellular cholesterol are linked with the immune system both as a cause and as a consequence, as a disrupted cholesterol biosynthesis triggers the activation of the IFN-mediated innate immune response.[15] ICZ interferes with the ergosterol synthesis pathway of the host cell and inhibits cytochrome P450 enzymes, particularly the lanosterol 14α-demethylase, which impairs cholesterol homeostasis and *de novo* synthesis in mammalian cells.[16] Disturbed ergosterol metabolism shifts the tightly balanced type I IFN expression levels toward the induction of a preactivated state, thereby accelerating the virus-induced host cell response.[17]

IFNs can serve as the first line of immune defense against viral infections.[17] IFNs are very powerful cytokines, which play a key role in combatting pathogenic infections by controlling inflammation and immune response by directly inducing antipathogen molecular countermeasures.[18] There are three classes of IFNs: type I, type II, and type III.

Type I IFNs were first discovered in 1957 as factors that "interfere" with viral replication.[18] Type III IFNs (IFN-λs) are, therefore, arising as frontline guardians of immune defenses in the respiratory tract, fine-tuning inflammation, and as potential novel therapeutics for the treatment of diverse respiratory diseases, including influenza virus infection and asthma.[19] IFN-λs are key antiviral cytokines, directly performing an antiviral immune response at epithelial surfaces in the early stages of viral infection, and that these cytokines also skew the balance of Th1 and Th2 cells to Th1 phenotype. Besides, genetic polymorphisms in IFN-λ genes can impair antiviral immune responses in clinical treatment.[16]

In conclusion, this study speculated that ICZ may be a candidate as antiviral agents against COVID 19 infection depending on its mechanism of action and other unique features that affect on IFN expression levels, so it may be a new therapeutic option and promising branch in COVID 19 treatment. This finding may require more clinical evaluation and further studies in laboratories and clinical trials. ICZ has many advantages: it is ready for use, is available, is cheap, and has very few adverse effects, hence can be used safely in patients with pulmonary disorders.

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Conflicts of interest
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