Itraconazole: a potential drug during the COVID-19 pandemic: hypothesis

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continue to expand worldwide. The article focused on the broad spectrum antifungal itraconazole as antiviral prodrug with its possible role against SARS-CoV-2, via immunomodulation, anti-inflammatory actions, and direct role on the virus non-structural proteins

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continue to evolve with no approved treatment or vaccines yet. Itraconazole (ITZ) is a broad-spectrum triazole antifungal with recently indicated antiviral activity. Shim et al. reported the therapeutic and prophylactic function of ITZ against the human rhinovirus (HRV) infection , a major causative organism of human respiratory tract infection, in a murine model. In this setting, ITZ act through decreasing the level of pro-inflammatory cytokines and chemokines induced by HRV infection including IL-6, TNF-α , IL-1β , CXCL1/KC, and CCL2 ,correlating with reduced viral load. ITZ improved the histological acute lung inflammatory changes, particularly the neutrophils infiltrate , pulmonary edema, and hemorrhage (1). ITZ, by its action on CYP450 enzyme 5-lipooxigenase, interferes with the synthesis of leukotriene B4 (LTB4), the major product of arachidonic acid metabolism, which has been referred as a potent mediator of inflammatory processes and immunoregulation (2). This immunomodulatory role of ITZ could be beneficial against cytokine storm created by SARS-CoV-2 , which is characterized by high levels of pro-inflammatory cytokines and chemokines ,particularly CCL2 and TNFα ,being significantly higher in patients requiring admission to intensive care units (3). Additionally, itraconazole dramatically reduced the mortality and improved the survival from the Influenza A virus (IAV) , another common cause of respiratory tract infection , in vitro and in vivo utilizing a mouse model, via a probable mechanism of action that included priming of the interferon response and the imbalance of cellular cholesterol (4). Pulse therapy of itraconazole could significantly raise the serum level of IFN-γ secretion ,an important cytokine which is crucial in antagonizing viral infections, during and after treatment in seborrheic dermatitis patients (5).

Interestingly, itraconazole is supposed to be a potential inhibitor of non-structural protein Nsp12, an RNA-dependent RNA polymerase (RdRp), which has a vital role in coronavirus replication and transcription (6). In the research of SARS-CoV and MERS-CoV inhibitors, Nsp12-RdRp has been used as a very important drug target , due to the fact that active site of RdRp is highly conserved ,strengthening its chance as an anchor for inhibitory molecules (7) .Targeted inhibition of Nsp12-RdRp is proposed to be safe without significant toxicity and adverse effects on host cells (8).

In an experimental model of pulmonary paracoccidioidomycosis, itraconazole , alone or in combination with neutrophil depletion, achieved improvement of the inflammatory response and the pulmonary fibrotic sequelae through the down-regulation of gene expression , such as IL-6, IL-10, IL-17 genes, associated with both inflammation and fibrosis process. This could point to ITZ importance in minimizing the risk of fibrotic lung disease if used in SARS-CoV-2 treatment (9).

Notably, combination of azithromycin, the widely used drug against SARS-CoV2, with antifungal agents, including itraconazole, could result in synergistic interactions with better therapeutic outcome (10). Therefore, itraconazole could be suggested in a new COVID-19 protocol and we could encourage the enrollment of this relatively cheap, available ,well tolerated drug for clinical trials to investigate its potential for COVID-19 treatment.

Abbreviations

ITZ: Itraconazole

COVID-19: Coronavrus Disease 2019

IL-6,10,17: Interleukin 6,10,17

TNF-α: Tumor necrosis factor alpha

IL-1β: Interleukin 1β

CXCL1/KC: Chemokine (C-X-C motif) ligand 1

CCL2: Chemokine (C-C motif) ligand 2

CYP450: Cytochrome P450

LTB4: Leukotriene B4

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SARS-CoV: Severe acute respiratory syndrome coronavirus

MERS-CoV : Middle East respiratory syndrome coronavirus

RdRp: RNA-dependent RNA polymerase

Nsp12: Non-structural protein 12

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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