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Ivermectin Treatment for COVID-19

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that originated in late 2019 has become a serious global threat to human health. Presently, there are no drugs approved to combat the disease (coronavirus disease 2019, COVID-19). Therefore, it is important to find effective drugs against COVID-19 and to conduct clinical trials of these drugs. Drug repurposing is a well-known strategy applied to redeploy existing licensed drugs for newer indications, thereby providing the quickest possible transition from bench to bedside for meeting therapeutic needs. At present, several existing licensed drugs such as tetracycline (e.g., doxycycline), macrolide antibiotics (e.g., azithromycin), corticosteroids (e.g., prednisolone and dexamethasone), and IL-6 inhibitor (e.g., tocilizumab), have been used because of their potential efficacy in inhibiting COVID-19. Recently, the anti-SARS-CoV-2 effects of macrolide antiparasitics (e.g., ivermectin, IVM) have attracted considerable attention.

IVM is also an inhibitor of SARS-CoV-2, with a single treatment causing approximately 5,000-fold reduction in the virus at 48 hours in cell culture [1]. The mechanism by which IVM inhibits SARS-CoV-2 is thought to be via the inhibition of the nuclear import of viral and host proteins. Importin $\alpha/\beta 1$, a host protein, is a heterodimer that binds to the SARS-CoV-2 cargo protein and moves it into the nucleus, where the complex falls apart and the viral cargo can reduce the host cell's antiviral response. IVM destabilizes the importin $\alpha/\beta 1$ heterodimer, preventing it from binding to viral protein and thus from entering the nucleus. As a result, the inhibition of antiviral responses is likely to be reduced, leading to a normal, more efficient antiviral response [1]. IVM also inhibits the binding of the SARS-CoV-2 spike protein to ACE2 [2]. Besides the anti-SARS-CoV-2 effects, IVM possesses anti-inflammatory and immunomodulatory effects to reduce the production of IL-6, IL-8, and TNF-α, in a dose-dependent manner [3].

Regarding IVM treatment for mild and moderate COVID-19, Ahmed et al. [4] reported that a 5-day course of IVM (12 mg daily) for COVID-19 reduced the duration of the illness. Prasad [5] reported a case of COVID-19 with pulmonary lesion successfully treated with the early administration of IVM (6 mg twice daily for 3 days), azithromycin (500 mg daily for 5 days), doxycycline (100 mg twice daily for 5 days), and prednisolone (50 mg daily for 5 days) followed by dexamethasone (6 mg daily).

COVID-19 is characterized by early exponential viral replication, cytokine-associated organ damage, and thrombosis. Severe COVID-19 involves this cytokine-associated organ damage, including acute respiratory distress syndrome (ARDS). Elevated levels of blood IL-6, IL-8, IL-10, and TNF-α were noted in COVID-19-induced ARDS [6]. COVID-19-induced ARDS was reported to be effectively treated with cytokine suppression, using a combination of IVM (12 mg single dose) and tocilizumab (240 mg single dose) [7]. Rajter et al. [8] reported that additional IVM (200 μg/kg daily) treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. A combination of IVM (200 μg/kg daily for 2 to

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3 days) and doxycycline (100 mg twice daily for 5 to 10 days) reduced the time to recovery and the percentage of patients who progressed to a more advanced stage of the disease; in addition, this treatment reduced the mortality rate in patients with severe COVID-19 from 22.72% to 0% compared to standard care [9].

Taken together, treatment with IVM alone or in combination with other drugs may show efficacy in COVID-19 in mild to severe stages and may be beneficial throughout the course of COVID-19.

In any case, clinical trials need to be conducted to better assess the optimal doses and durations as well as the efficacy and tolerability of these treatments before they can be adopted on a wider basis.

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