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Macrolide treatment for COVID-19

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), broke out in late 2019 to become a serious global threat to human health. The recent, rapid development of vaccines against COVID-19 represents a huge achievement and offers hope of ending the global pandemic. However, only a fraction of the world population can receive vaccines as of yet. As a result, large numbers of people continue to be exposed and become infected. Therefore, finding effective and low-priced drugs against COVID-19 and carrying out clinical trials of these drugs remain a worthwhile and beneficial pursuit.

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. Several existing licensed drugs such as hydroxychloroquine (HC), corticosteroids (e.g., prednisolone (PSL), and dexamethasone (DEX)), tetracycline (e.g., doxycycline (DOX)), macrolide antibiotics (MACs) (e.g., azithromycin (AZM), and clarithromycin (CAM)), a macrolide antiparasitic (e.g., ivermectin (IVM)), and IL-6 inhibitor (e.g., tocilizumab) are currently in use because of their efficacy in inhibiting COVID-19. Since the beginning of 2020, the anti-SARS-CoV-2 effects of MACs have attracted considerable attention.

AZM accumulates within the lysosomes and increases their pH, resulting in lysosomal membrane disruption. Thus, viral replication is inhibited because SARS-CoV-2 replication depends on intact lysosomes [1]. Moreover, AZM blocks the interaction points between SARS-CoV-2 and the angiotensin-converting enzyme2 receptor, precluding SARS-CoV-2 from entering host cells [2]. Besides the anti-SARS-CoV-2 effects, MACs possess anti-inflammatory and immunomodulatory effects to reduce the production of interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α, in a dose-dependent manner [3].

Regarding MACs treatment for mild and moderate COVID-19, Tsiakos et al. reported that treatment with CAM (500 mg, b.i.d., for 7 days) was associated with early clinical improvement in patients with moderate COVID-19 [4]. Gautret et al. reported that a combination of HC (200 mg, t.i.d., for 10 days) and AZM (500 mg on day 1, followed by 250 mg, daily, for the next 4 days) reduced the viral load to an undetectable level on day 6 [5]. Lima-Morales et al. showed that a combination of IVM (12 mg, single dose), AZM (500 mg, daily, for 4 days), montelukast (MK; 60 mg on day 1, followed by 10 mg, daily, for 2–21 days), and acetylsalicylic acid (ASA; 100 mg, daily, for 30 days) prevented hospitalization and death among ambulatory COVID-19 cases [6].

They prescribed MK because it seemed to reduce the risk of COVID-19 infection in asthma patients. Similarly, they prescribed ASA in consideration of its anti-inflammatory and antithrombotic effects [6]. Prasad reported a patient with COVID-19 accompanied by pulmonary lesions who recovered after receiving early treatment with AZM (500 mg, daily, for 5 days), IVM (6 mg, b.i.d., for 3 days), DOX (100 mg, b.i.d., for 5 days), and PSL (50 mg, daily, for 5 days) followed by DEX (6 mg, daily) [7].

COVID-19 is characterized by early exponential viral replication, cytokine-associated organ damage and dysfunction, including acute respiratory distress syndrome (ARDS), and thrombosis. Severe COVID-19 indicates cytokine-associated pulmonary lesions with severe hypoxemia, including ARDS. Moreover, elevated levels of blood IL-6, IL-8, IL-10, and TNF-α were noted in COVID-19-induced ARDS [8].

Lauriola et al. enrolled patients with COVID-19 accompanied by pulmonary lesion and divided them into three groups: 297 patients treated with HC (200 mg, t.i.d., for 10 days) combined with AZM (500 mg on day 1, followed by 250 mg, daily, for the next 4 days), 17 patients treated with HC as a single drug, and 63 control patients [9]. They recorded 146 death: 102 in HC combined with AZM treatment group, 7 in HC treatment group, and 35 in control group. Consequently, HC combined with AZM treatment proved significantly effective for reduction of the mortality rate [9]. According to their study, about twenty percent of the enrolled patients received continuous positive airway pressure or mechanical ventilation; therefore, some of them were probably suffering from severe COVID-19. The reason AZM reduced the mortality rate was thought to be via the reduction of cytokine, such as IL-6, IL-8, and TNF-α. Additionally, treatment with MACs has been also associated with reduced mortality in non-COVID-19-induced ARDS [10].

Taken together, treatment with MACs 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.

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