Letter

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Macrolide treatment for COVID-19: Will this be the way forward?

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SUMMARY The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that has developed in late 2019 and 2020 is a serious threat to human health. With no vaccines or drugs approved for prevention and treatment until now, all efforts at drug design and/or clinical trials of already approved drugs are worthy and creditable. Using structure-based drug selection for identification of SARS-CoV-2 protease inhibitors, old drugs such as macrolides (MAC) were predicted to be effective for COVID-19. Lately, the anti-viral effects of macrolides have attracted considerable attention. Very recently, hydroxychloroquine in combination with azithromycin treatment was reported to be effective for COVID-19. We believe that treatments with macrolides alone or in combination with other drugs are promising and open the possibility of an international strategy to fight this emerging viral infection.

Keywords COVID-19, SARS-CoV-2, macrolide

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in late 2019 and 2020 is taking a severe toll on human health, and has been acknowledged as a pandemic. Since no vaccines or drugs to combat the disease (COVID-19) have been approved for use until now, all efforts at developing drugs and/or carrying out clinical trials of already approved drugs based on their mechanism of action are worthy and creditable. Anti-viral drugs include inhibitors against protease, integrase, and polymerase enzymes. Among these, the protease inhibitors appear to be effective in terms of blocking virus replication and may prove to be a promising treatment for COVID-19 (*1*). Dayer found several candidates for COVID-19 treatment using structure-based drug selection for the identification of SARS-CoV-2 protease inhibitors. The candidates with binding capacity and inhibitory potency are as follows: tipranavir > indinavir> atazanavir > darunavir > ritonavir > amprenavir used as human immunodeficiency virus-1 protease inhibitors, and cefditoren > cefixime > erythromycin (EM) > clarithromycin (CAM) used as anti-bronchitis medicines (*1*). Macrolides (MAC) such as erythromycin, clarithromycin, and azithromycin (AZM) not only have anti-bacterial activity but also have immunomodulatory effects, including anti-inflammatory effects. Lately, the anti-viral effects of macrolides have attracted considerable attention. Erythromycin is the first macrolide proved to have efficacy in the treatment of rhinovirus (RV) and influenza virus (INFV) (*2*). Thereafter, clarithromycin and azithromycin were also proved to be effective for rhinovirus, respiratory syncytial virus, and influenza virus (*2,3*). Apart from the above-mentioned respiratory viruses, Zika and Ebola viruses have been reported to be inhibited by azithromycin (*4,5*). Tran *et al*. indicated that influenza progeny virus replication was remarkably inhibited by treating influenza virus with azithromycin before infection. During the early phase of influenza virus infection, azithromycin blocked influenza virus internalization into host cells. Furthermore, azithromycin targeted newly budded progeny virus from the host cells and inactivated their endocytic activity. These findings indicate the potential of azithromycin treatment before and after influenza virus infection (*3*).

Regarding macrolides treatment for COVID-19, Gautret *et al*. enrolled patients with COVID-19 and divided them into three groups: six patients with COVID-19 treated with hydroxychloroquine (HC) (200 mg, 3 times per day, for 10 days) in combination with azithromycin (500 mg on day 1, followed by 250 mg per day for the next 4 days), 14 patients with COVID-19 treated with hydroxychloroquine as a single drug, and 16 control patients with COVID-19. In these three groups, patient viral load was assessed daily by real-

time reverse transcription polymerase chain reaction (PCR)-based analysis of nasopharyngeal swabs. As a result, on day 6, 100% of patients treated with hydroxychloroquine in combination with azithromycin exhibited virological cure. In comparison, only 57.1% of the patients treated with hydroxychloroquine as a single drug and 12.5% in the control group exhibited virological cure ($P < 0.001$). Furthermore, one patient, who was treated with hydroxychloroquine as a single drug and still PCR-positive at day 6, received azithromycin, resulting in virological cure. The authors propose that hydroxychloroquine in combination with azithromycin treatment might be an efficient anti-viral therapy for COVID-19 (*6*). Based on the findings for the above-mentioned candidates for COVID-19 treatment, macrolides, especially erythromycin, may generally be effective for COVID-19. Although the mechanism of azithromycin against SARS-CoV-2 is unclear at present unlike the clearly established mechanism of macrolides against influenza virus, we may be able to prescribe the low-priced erythromycin not only as a drug for treatment but also as a preventive drug. We believe that treatments with macrolides alone or in combination with other drugs are promising and open the possibility of an international strategy to fight this emerging viral infection.

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