Letter

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Tetracycline plus macrolide: A potential therapeutic regimen for COVID-19?

Masashi Ohe[1,*], Ken Furuya[1], Houman Goudarzi[2]

[1] Department of Internal Medicine, JCHO Hokkaido Hospital, Sapporo, Japan;
[2] Department of Respiratory Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan.

SUMMARY The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that struck in late 2019 and early 2020 is a serious threat to human health. Since there are no approved drugs that satisfactorily treat this condition, all efforts at drug design and/or clinical trials are warranted and reasonable. Drug repurposing is a well-known strategy that seeks to deploy existing licensed drugs for newer indications and that provides the quickest possible transition from the bench to the bedside to meet therapeutic needs. At present, several existing licensed drugs such as chloroquine, hydroxychloroquine, methylprednisolone, dexamethasone, and remdesivir have been used because of their potential efficacy in inhibiting COVID-19. Recently, antibiotics such as tetracyclines and macrolides have been reported to be effective against COVID-19. A combination of tetracyclines and macrolides may be a potential treatment for COVID-19 because there are some differences in the mechanism of action of tetracyclines and macrolides.

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

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that struck in late 2019 and early 2020 is a serious threat to human health. Since there are no approved drugs that satisfactorily treat this condition, all efforts at drug design and/or clinical trials are warranted and reasonable. Drug repurposing is a well-known strategy that seeks to deploy existing licensed drugs for newer indications and provides the quickest possible transition from the bench to the bedside to meet therapeutic needs. At present, several existing licensed drugs such as chloroquine, hydroxychloroquine, methylprednisolone, dexamethasone, and remdesivir have been used because of their potential efficacy in inhibiting COVID-19. Recently, antibiotics such as tetracyclines and macrolides have been reported to be effective against COVID-19.

Tetracyclines such as doxycycline, minocycline, and tetracycline are highly lipophilic antibiotics that are known to chelate zinc compounds on matrix metalloproteinases (MMPs). Several functions of SARS-CoV-2 are associated with the host MMP complex, including replication. Therefore, the zinc-chelating properties of tetracyclines may aid in inhibiting COVID-19 in humans, limiting the ability of SARS-CoV-2 to replicate within the host (*1,2*). Tetracycline is also reported to inhibit the binding of the SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE2) (*3*). Thus, infection of cells by SARS-CoV-2 may be inhibited. Tetracyclines are effective in reducing the duration of ventilator support and intensive care unit stay from acute respiratory distress syndrome caused by COVID-19 (*3*). In addition, Yates *et al*. reported that doxycycline, at doses of 100-200 mg/day over 5-14 days, successfully treated 4 high-risk COVID-19-positive patients with pulmonary disease (*4*).

Macrolides such as erythromycin, clarithromycin, and azithromycin exhibit antibacterial activity, immunomodulatory action, and anti-inflammatory action. Lately, the antiviral action of macrolides has attracted considerable attention (*5*). Azithromycin 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 (*5*). Moreover, azithromycin blocks the interaction points between SARS-CoV-2 and the ACE2 receptor, precluding SARS-CoV-2 from entering host cells (*5*).

Gautret *et al*. conducted a study that divided patients with COVID-19 into three groups: 6 patients with COVID-19 who were treated with hydroxychloroquine

(200 mg, 3 times per d, for 10 d) in combination with azithromycin (500 mg on day 1, followed by 250 mg per d for the next 4 d); 14 patients with COVID-19 who were treated with hydroxychloroquine alone; and 16 control patients with COVID-19. In these three groups, the patients' viral loads were assessed daily with a real-time reverse transcription polymerase chain reaction (PCR)-based analysis of nasopharyngeal swabs. Thus, 100% of the patients treated with hydroxychloroquine in combination with azithromycin were virologically cured on day 6. In contrast, 57.1% of the patients treated with hydroxychloroquine alone and 12.5% of the control group were virologically cured ($p < 0.001$). Moreover, 1 patient who was treated with hydroxychloroquine alone was still PCR-positive on day 6, but the patient was virologically cured by administration of azithromycin (*6*). Huang *et al*. found that clarithromycin was effective in the management of COVID-19 pneumonia within 6-12 days (*7*). Apart from the aforementioned macrolide antibiotics, ivermectin, a macrolide antiparasitic agent, is also an inhibitor of SARS-CoV-2, with a single treatment causing a ~5,000-fold reduction in the virus at 48 h in cell culture (*8*). Moreover, Ahmed *et al*. reported that a 5-day course of ivermectin reduced the duration of COVID-19 (*9*).

As an example of tetracyclines and macrolides in the treatment of COVID-19, a combination of doxycycline and ivermectin 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 with azithromycin (*10*). A combination of tetracyclines and macrolides, such as doxycycline and azithromycin, may be used because there are some differences in the mechanism of action of tetracyclines and macrolides. Moreover, this combined therapy may prevent the emergence of drug-resistant SARS-CoV-2. Taken together, the findings above indicate that a combination of tetracyclines and macrolides may be a potential therapeutic regimen for COVID-19 and open the door for an international strategy to fight this emerging viral infection.

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**Address correspondence to:*
Masashi Ohe, Department of Internal Medicine, JCHO Hokkaido Hospital, 1-8-3-18 Nakanoshima, Toyohira-ku, Sapporo 062-8618, Japan.
E-mail: oektsp1218@sweet.ocn.ne.jp

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