

## Hydroxychloroquine and Azithromycin as Treatments for COVID-19

### COVID-19 Tedavisi için Hidroksiklorokin ve Azitromisin

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#### ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that originated in late 2019 and continues to spread as of 2020 is taking a severe toll on human health and has been acknowledged as a worldwide pandemic. There have been no readily available vaccines or drugs that have been approved to combat the disease (COVID-19) as of yet. Chloroquine (CQ), a drug well-known for its effectiveness in treating malarial and autoimmune disease such as rheumatoid arthritis and lupus erythematosus, has exhibited a promising inhibitory effect for SARS-CoV-2. Hydroxychloroquine (HCQ), a more tolerable derivative of CQ, has also been shown to display potent activity against SARS-CoV-2. Macrolides (MACs) such as erythromycin, clarithromycin, and azithromycin (AZM) not only have the potential for anti-bacterial activity but also have immunomodulatory effects. Lately, the anti-viral effects of MACs have attracted considerable attention. Very recently, HCQ in combination with AZM treatment was reported to be effective for mild form of COVID-19. Because mild form of COVID-19 may take a turn for the worse, resulting in acute respiratory distress syndrome, or mild COVID-19 patients may infect surrounding people with COVID-19, patients should be treated with HCQ in combination with AZM.

**Key Words:** COVID-19, SARS-CoV-2, Hydroxychloroquine, Macrolide, Azithromycin

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#### ÖZET

2019'un sonlarında ortaya çıkan ve 2020'den itibaren yayılmaya devam eden şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) salgını insan sağlığı üzerinde ciddi bir zarar görüyor ve dünya çapında bir salgın olarak kabul ediliyor. Hastalıkla savaşmak için onaylanmış olan hazır aşılardan veya ilaçlar (COVID-19) henüz mevcut değildir. Romatoid artrit ve lupus eritematozus gibi sıtma ve otoimmün hastalıkların tedavisinde etkinliği ile iyi bilinen bir ilaç olan klorokin (CQ), SARS-CoV-2 için umut verici bir inhibitör etki göstermiştir. Daha tolere edilebilir bir CQ türevidir olan hidroksiklorokin (HCQ) 'nun ayrıca SARS-CoV-2'ye karşı güçlü aktivite sergilediği gösterilmiştir. Eritromisin, klaritromisin ve azitromisin (AZM) gibi makrolidler (MAC'ler) sadece anti-bakteriyel aktivite potansiyeline sahip olmakla kalmaz, aynı zamanda immünomodülatör etkilere de sahiptir. Son zamanlarda, MAC'lerin anti-viral etkileri büyük ilgi gördü. Son zamanlarda, AZM tedavisi ile kombinasyon halinde HCQ'nun hafif COVID-19 formu için etkili olduğu bildirilmiştir. Hafif COVID-19 formu daha kötüye gidebilir, bu da akut solunum sıkıntısı sendromuna neden olabilir veya hafif COVID-19 hastaları COVID-19 olan çevreleyen kişilere bulaşabilir, hastalar AZM ile kombinasyon halinde HCQ ile tedavi edilmelidir.

**Anahtar Sözcükler:** COVID-19, SARS-CoV-2, Hidroksiklorokin, Makrolid, Azitromisin

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that originated in late 2019 and continues to spread as of 2020 is taking a severe toll on human health and has been acknowledged as a worldwide pandemic. As there have been no readily available vaccines or drugs that have been approved to combat the disease (COVID-19) as of yet, all efforts at developing drugs and/or carrying out clinical trials of already approved drugs based on their mechanism of action are a worthy and credible cause. At present, several approved drugs such as chloroquine (CQ), hydroxychloroquine (HCQ), and remdesivir, have been tested for efficacy in inhibiting SARS-CoV-2 infection in vitro or in clinical studies.

CQ, a drug well-known for its effectiveness in treating malarial and autoimmune disease such as rheumatoid arthritis and lupus erythematosus, has exhibited a promising inhibitory effect for SARS-CoV-2. Previous studies have revealed that it has the potential to carry out broad-spectrum anti-viral activities by increasing the pH of endosomes and lysosomes, through which the fusion process of the virus with host cells and subsequent replication are prevented (1). CQ is the first drug reported to have efficacy against COVID-19 in clinical studies in China (2). Feedback from an international meeting that took place to share experiences on the prevention and control of COVID-19 highlighted that CQ demonstrated significant efficacy in reducing the time until virus-negative conversion and in restabilizing body temperature (3, 4). HCQ, a more tolerable derivative of CQ, has also been shown to display potent activity against SARS-CoV-2 in vitro (5). Clinical studies in China have indicated that HCQ can help to reduce the time until body temperature returns to normal, decrease the duration of cough, and improve lung imaging findings (6).

Macrolides (MACs) such as erythromycin (EM), clarithromycin (CAM), and azithromycin (AZM) not only have the potential for anti-bacterial activity but also have immunomodulatory effects, including anti-inflammatory effects (7). Lately, the anti-viral effects of MACs have attracted considerable attention. EM is the first MAC proved to have efficacy against rhinovirus (RV) and influenza virus (INFLU) (8). Thereafter, CAM and AZM were also proved to be effective for combating RV, respiratory syncytial virus, and IFNV (8, 9). Apart from the above-mentioned respiratory viruses, Zika and Ebola viruses have also been reported to be inhibited by AZM (10, 11). Recently, Caly et al. reported that ivermectin, a macrolide, previously shown to have broad-spectrum anti-viral activity in vitro, is an inhibitor of SARS-CoV-2, with a single treatment bringing ~5,000-fold reduction in the virus at 48h in cell culture (12).

In the case of HCQ and MAC treatments for COVID-19, Gautret et al. enrolled patients with COVID-19 in his study and divided them into three groups: six patients with COVID-19 treated with HCQ (200 mg, 3 times per day, for 10 days) in combination with AZM (500 mg on day 1, followed by 250 mg per day for the next 4 days); 14 patients with COVID-19 treated with HCQ 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-based analysis of nasopharyngeal swabs. As a result, on day six, 100% of the patients treated with HCQ in combination with AZM exhibited virologic cures. In contrast, 57.1% of the patients treated with HCQ as a single drug and 12.5% of the patients in the control group exhibited virologic cures ( $P < 0.001$ ) (13). In this study, most of the enrolled patients only had mild symptoms of COVID-19. Therefore, HCQ in combination with AZM treatment may be an efficient anti-viral therapy for mild cases of COVID-19. On the other hand, Molina et al. demonstrated that there was no evidence of rapid anti-viral clearance or clinical benefits with the combination of HCQ and AZM in patients with severe COVID-19 infection (14). Therefore, HCQ in combination with AZM treatment may not be appropriate for severe COVID-19 patients.

Because mild form of COVID-19 may take a turn for the worse, resulting in acute respiratory distress syndrome, or mild COVID-19 patients may infect surrounding people with COVID-19, patients should be treated with HCQ in combination with AZM as soon as possible. However, the potential risk of severe QT prolongation induced by the combination of these two drugs should be considered. If severe QT prolongation is likely to occur, patients had better carefully receive AZM monotherapy (15).

To conclude, HCQ in combination with AZM treatment may be a promising form of treatment for mild COVID-19 patients and open the possibility of an international cooperation to fight this emerging viral infection.

#### Conflict of interest

No conflict of interest was declared by the authors.

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