Communication

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Multidrug treatment for COVID-19

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SUMMARY An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which began in Wuhan, China in December 2019, has rapidly spread all over the world. The World Health Organization characterized the disease caused by SARS-CoV-2 (COVID-19) as a pandemic in March 2020. In the absence of specific treatments for the virus, treatment options are being examined. Drug repurposing is a process of identifying new therapeutic uses for approved drugs. It is an effective strategy to discover drug molecules with new therapeutic indications. This strategy is time-saving, low-cost, and has a minimal risk of failure. Several existing approved drugs such as chloroquine, hydroxychloroquine, doxycycline, azithromycin, and ivermectin are currently in use because of their efficacy in inhibiting COVID-19. Multidrug therapy, such as a combination of hydroxychloroquine and azithromycin, a combination of doxycycline and ivermectin, or a combination of ivermectin, doxycycline, and azithromycin, has been successfully administered. Multidrug therapy is efficacious because the mechanisms of action of these drugs differ. Moreover, multidrug therapy may prevent the emergence of drug-resistant SARS-CoV-2.

Keywords hydroxychloroquine, doxycycline, azithromycin, ivermectin, COVID-19

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which began in Wuhan, China in December 2019, has rapidly spread all over the world. The World Health Organization characterized the disease caused by SARS-CoV-2 (COVID-19) as a pandemic in March 2020. In the absence of specific treatments for the virus, treatment options are being examined. Drug repurposing is a process of identifying new therapeutic uses for approved drugs. It is an effective strategy to discover drug molecules with new therapeutic indications. This strategy is time-saving, low-cost, and has a minimal risk of failure. Several existing approved drugs such as chloroquine, hydroxychloroquine, doxycycline, azithromycin, and ivermectin, are currently in use because of their efficacy in inhibiting COVID-19.

Chloroquine, a drug known for its efficacy in treating malarial and autoimmune diseases such as rheumatoid arthritis and lupus erythematosus, offers promise in inhibiting SARS-CoV-2. Previous studies have revealed that it potentially has broad-spectrum anti-viral activity by increasing the pH of endosomes and lysosomes, thus preventing the process by which the virus fuses with host cells and subsequently replicates (*1*). Chloroquine 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 related to the prevention and control of COVID-19 highlighted the fact that chloroquine demonstrated significant efficacy in reducing the time to virus-negative conversion and in restabilizing body temperature (*3,4*). Hydroxychloroquine, a more tolerable derivative of chloroquine, has also been found to display potent activity against SARS-CoV-2 *in vitro* (*5*). Clinical studies in China have indicated that hydroxychloroquine can help to reduce the time until body temperature returns to normal, decrease the duration of coughing, and improve lung imaging findings (*6*).

Tetracyclines such as doxycycline, minocycline, and tetracycline are well-known antibiotics in clinical use. Tetracyclines are known to inhibit matrix metalloproteinases (MMPs) through their ability to chelate zinc compounds on MMPs. Several functions of the coronavirus, including replication, are associated with the host MMPs complex. Therefore, the zinc-chelating properties of tetracyclines may be efficacious against COVID-19 in humans (*7,8*). Tetracycline was also reported to inhibit the binding of the SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE2) (*9*). Doxycycline inhibits the entry and replication of SARS-CoV-2 *in vitro* (*10*). Yates *et al*. reported that four high-risk patients with COVID-19

and comorbid pulmonary disease were successfully treated with doxycycline, the doses and durations of which were 100-200 mg/day and 5-14 days, respectively (*11*). Meyboy *et al*. reported that treatment of COVID-19 with doxycycline (100 mg, *b.i.d*., for 7 days) alleviated shortness of breath, coughing, a fever, and O_2 saturation (*12*).

Macrolides such as erythromycin, clarithromycin, and azithromycin exhibit antibacterial activity, immunomodulatory action, and anti-inflammatory action. Recently, the antiviral action of macrolides has attracted considerable attention (*13*). Azithromycin accumulates within lysosomes, increases their pH, and hampers lysosomal functions allowing viral replication (*13*). In addition, azithromycin blocks the interaction points between SARS-CoV-2 and the ACE2 receptor, preventing SARS-CoV-2 from invading host cells (*13*). Tsiakos *et al*. reported that treatment with clarithromycin (500 mg, *b.i.d*., for 7 days) was associated with early clinical improvement in patients with moderate COVID-19 (*14*). Moreover, Ghiasvand *et al*. reported that three patients diagnosed with COVID-19 who did not respond to initial treatment improved after additional treatment with azithromycin (*15*).

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 (*16*). The mechanism by which ivermectin inhibits SARS-CoV-2 is thought to be *via* the inhibition of the nuclear import of viral and host proteins. In specific terms, importin (IMP) α/β1, 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. Ivermectin destabilizes the IMPα/β1 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 (*16*). Ivermectin also inhibits the binding of the SARS-CoV-2 spike protein to ACE2, much like macrolide antibiotics (*17*). Ahmed *et al*. reported that a 5-day course of ivermectin (12 mg, daily) for COVID-19 reduced the duration of the illness (*18*).

Examining multidrug therapy for COVID-19, Gautret *et al*. reported that a combination of hydroxychloroquine (200 mg, *t.i.d*., for 10 days) and azithromycin (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. Moreover, this combined therapy proved to be superior to hydroxychloroquine monotherapy (*19*). Alam *et al*. reported that a combination of ivermectin (0.2 mg/kg, single dose) and doxycycline (100 mg, daily, for 10 days) was efficacious in viral clearance in patients with mild or moderate COVID-19 (*20*). Procter *et al*. treated outpatients with COVID-19 with at least two agents with antiviral activity against SARS-CoV-2 (zinc, hydroxychloroquine, and ivermectin) and one antibiotic (azithromycin, doxycycline, and ceftriaxone) along with inhaled budesonide and/or intramuscular dexamethasone. Consequently, multidrug therapy of early ambulatory patients (not hospitalized and treated at home) was found to be safe, feasible, and associated with low rates of hospitalization and mortality (*21*). Prasad reported a patient with COVID-19 and pulmonary lesions who recovered after receiving early treatment with ivermectin (6 mg, *b.i.d.*, for 3 days), azithromycin (500 mg, daily, for 5 days), doxycycline (100 mg, *b.i.d.*, for 5 days), and prednisolone (50 mg, daily, for 5 days) followed by dexamethasone (6 mg, daily) (*22*). Apart from the aforementioned multidrug therapy, a combination of ivermectin and azithromycin (*23*), a combination of doxycycline and azithromycin (*24*), and a combination of hydroxychloroquine, ivermectin, and azithromycin (*25*) are proposed treatments to be studied in clinical trials.

Multidrug therapy is more efficacious than single-drug therapy because there are differences in the mechanisms of action of the drugs described. Moreover, multidrug therapy may prevent the emergence of drug-resistant SARS-CoV-2. Clinical trials need to be conducted to better assess the efficacy and tolerability of the aforementioned multidrug therapy before it can be adopted on a wider basis.

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