The use of Azithromycin and Hydroxychloroquine in the Treatment of Covid-19

Yue Ma1a,*, Jiawei Lu2b,*, Si Qin3c,*

1Handan No.1 High School, Handan, 056006, China
2Chemical and Pharmaceutical Engineering, Shandong First Medical University, Qingdao, 271016, China
3coral Academy of Science Las Vegas Sandy Ridge, Las Vegas, 89052, American

*These authors contributed equally to this work and should be considered co-first authors.

Abstract. This paper mainly studies the therapeutic effect of azithromycin and hydroxychloroquine on COVID-19. Severe acute respiratory syndrome is one of the key clinical manifestations of COVID-19, and azithromycin is considered to be a feasible treatment. The purpose of this study is to investigate how to use azithromycin to treat COVID-19 better. This article describes the therapeutic effect of azithromycin alone on COVID-19, and the effect of azithromycin and hydroxychloroquine when used in combination with COVID-19. Several studies have shown that although azithromycin has antiviral activity, azithromycin alone has no significant effect on the treatment of COVID-19. In contrast, multiple data show that the combination of azithromycin and hydroxychloroquine has some efficacy in the treatment of COVID-19, and the efficacy is related to the number of days the patient has been ill. The discovery impacts the treatment by providing a different perspective on the world's treatment of COVID-19.

1 Introduction

The 2019 coronavirus disease (COVID-19) was a virus infection of the global pandemic impact from late 2019, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of October 5, 2022, there have been nearly 633 million cases worldwide and about 6.59 million deaths [1]. During this crucial time, scientists searched for medication to treat the disease. Antiviral therapy targets specific parts of the virus to inhibit its replication in the body, to prevent severe illness and death, like Paxlovid. Monoclonal antibodies help the immune system recognize and respond to viruses more effectively, like Bebtelovimab [2]. In addition, researchers are still looking for the treatment of antibiotics. Azithromycin, as an antibiotic, has been demonstrated to treat the Zika virus, an orally active synthetic macrolide antibiotic with many antibacterial, anti-inflammatory, and antiviral properties [3]. The severity of a patient's inflammatory response is associated with mortality from respiratory diseases, including COVID-19. It produces a lot of cytokines. Clinical trials have shown that macrolides can reduce the degree of the inflammatory response, reduce the amount of anti-inflammatory cytokines, and increase the amount of immunoglobulins [4]. These effects reduce the complications of respiratory viral infections. Because of these properties, macrolides have the potential to treat respiratory viral infections [5]. According to some sources with clinical evidence, the drug only has a few effects on COVID-19 patients.

On the contrary, azithromycin works better in treating patients with Covid-19 when combined with other drugs. Studies have shown that hydroxychloroquine has attracted attention and heated discussion as a possible treatment for COVID-19 due to its universally available properties, low cost, antiviral and safety in other diseases such as malaria [6]. In an in vitro experiment, hydroxychloroquine reduced the entry of SARS-CoV-2 into cells and restricted late viral replication [7]. In addition, hydroxychloroquine reduced the production of several proinflammatory cytokines. These cytokines may be related to acute respiratory distress syndrome. In one study, the combination of hydroxychloroquine and azithromycin reduced the number of SARS-CoV-2 viruses [8]. Based on these clinical evidences and the mechanism of the drug, hydroxychloroquine may be used as a treatment for COVID-19, which is still under intense discussion.

2 The Use of Azithromycin

Since studies have demonstrated that azithromycin possesses antiviral and immunomodulatory actions, it has been suggested as a possible medication for the management of SARS-CoV-2 pneumonia. It may prevent the replication of other viruses, like the Zika virus and the human influenza virus H1N1 [9]. Nevertheless, there is no study showing the mechanisms of azithromycin to treat SARS-CoV-2 at present. Poschet et al found that in an in vitro study, azithromycin raises the host cell’s pH levels, which may prevent viral entrance, reproduction and spread [10].
They also found that azithromycin may prevent viral entrance by lowering the quantity of the enzyme furin in host cells. In addition, it has been suggested that macrolide antibiotics lower levels of pro-inflammatory cytokines are produced, which may lessen the pro-inflammatory condition brought on by SARS-CoV-2 infection [11-13].

2.1 The advantages of Azithromycin in the Treatment of COVID-19

Antiviral Effects. Azithromycin is thought to have antiviral characteristics and it may work in conjunction with antiviral medications. This macrolide antibiotic has been shown in preclinical trials to have antiviral properties against the viruses Zika, rhinovirus (RV), and Ebola [14-16].

Azithromycin was able to lower the infection rate of U87 cells (a human glioblastoma astrocytoma cell line) in infections brought on by Zika, to restore cell viability, and to lessen viral production, according to in vitro studies by Retallack et al [17]. Azithromycin increased the amounts of mRNA for the pattern recognition receptor, IFN, and IFN-stimulated genes in infections brought on by RV. Azithromycin promoted antiviral responses but did not stop virus-driven pro-inflammatory reactions [18].

However, antiviral efficacy in patients with COVID-19 has not been demonstrated. Middle-East Respiratory Syndrome (MERS) is caused by a coronavirus similar to SARS-CoV-2. Experiment shows that, of 136 severe MERS patients received macrolide adenosine, 97 were treated with azithromycin, 28 were treated with clarithromycin, and 22 were treated with erythromycin, 11 patients received two macrolides at different times during the study [19]. Neither the 90-day mortality rate nor the clearance of MERS-CoV RNA was independently linked to the use of macrolides. There is no significant effect of treatment by macrolides on SARS-CoV-2.

Immunomodulating Effect. In COVID-19, cytokine release syndrome (CRS) appears to be a significant cause of mortality. The use of medications with immunomodulating activity as potential therapeutics for COVID-19 patients has been suggested [20].

Macrolides can modulate immune response and inflammation in eukaryotes without affecting homeostatic immunity thanks to their wide range of biological activities. Their long-term use in the treatment of neutrophil-dominated inflammation in diffuse pan bronchiolitis, bronchiectasis, rhinosinusitis, and cystic fibrosis is a result of these properties. There is evidence suggests that many of these effects are due to the inhibition of extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and nuclear factor kappa B (NF-κB) activation [21]. Macrolides affect intracellular MAPK, especially ERK1/2, and the NF-κB pathway downstream of ERK. These pathways are participated in many cellular functions, including inflammatory cytokine production, cell proliferation, and mucin secretion, effects on ERK1/2 and NF-κB can explain most of the reported immunomodulatory effects of the macrolides [22-23]. According to the study, azithromycin treatment significantly reduces airway-specific inflammation in vivo, which is partly due to the inhibition of neutrophil recruitment to the lung through the reduction of proinflammatory cytokine expression and the inhibition of neutrophil migration via the extracellular ERK1/2 transduction pathway [23].

In addition, macrolide acts on a variety of inflammatory cells, including monocytes, macrophages, and fibroblasts in vitro, to reduce the hypersecretion of pro-inflammatory cytokines and chemokines [24].

3 The Clinical Studies of Azithromycin in the Treatment of COVID-19

3.1 The Clinical Data Indicate that Azithromycin is Ineffective in Treating COVID-19

With sample error, the PCR NP test's moderate sensitivity can detect daily variations in positive. Standard indicators of treatment efficacy, such as quantitative viral load utilizing cycle thresholds, reproducing viruses, such as viral culture, or clinical endpoints, such as length of hospital stay or morbidity and mortality, were not assessed. It has been widely documented for COVID-19 participants that many experiences moderate or severe symptoms within the first week of symptoms, and the trial was stopped after day 6 of illness [25]. Early research termination wasted a chance for more thorough validation. However, millions of practitioners throughout the world use this regimen to treat COVID-19 patients despite the subpar methodology and paucity of evidence to demonstrate clinical benefit from the combo regimen.

3.2 The Use of Azithromycin to Treat COVID-19 Patients is not Effective

According to the results published in JAMA Network, the trial was completed by 76% of the 263 randomly assigned individuals (median age, 43 years; 174 [66%] women; 57% non-Hispanic White; and 29% Latinx/Hispanic). After the interim analysis, the data and safety monitoring committee halted the trial due to its futility. At day 14, the percentage of symptom-free patients did not differ significantly between the two groups (Azithromycin: 50%; placebo: 50%; prevalence difference, 0%; 95% CI, 14% to 15%; P > .99). 18 of the 23 secondary clinical outcomes that had been predetermined showed no meaningful difference. By day 21, 5 people in the azithromycin group and 0 in the placebo group had been admitted to the hospital (prevalence difference, 4%; 95% CI, 1% to 9%; P = .16) [26].

Treatment with a single dose of Azithromycin versus a
placebo among outpatients with SARS-CoV-2 infection did not increase the odds of being symptom-free on day 14.

The most recently published randomized trial (ATOMIC2) for outpatients included 295 adult U.K. participants. Patients with solid suspicions of or records of COVID-19 are outpatients (mean age, 46). Patients either got conventional care (500 mg/day for 14 days) or azithromycin. Hospitalization or death at 28 days was the major outcome, and it was similar in both groups (10.3% vs. 11.6%, P=0.8). There was a fatality in each group. The primary outcome occurred equally frequently in the azithromycin and standard-care groups (14.7%) in the subset of patients who had positive polymerase chain reaction (PCR) testing for SARS-CoV-2 (approximately half the study population) [27].

4 The Combination of Hydroxychloroquine and Azithromycin

In addition to being effective against SARS-CoV-2, chloroquine and hydroxychloroquine have also been shown to be effective in patients with COVID-19, according to an article in the International Journal of Antimicrobial Drugs. According to clinical trials, adding azithromycin and hydroxychloroquine to the treatment of patients has a better effect on eliminating the virus.[28]

4.1 Mechanism of Action of Hydroxychloroquine

Hydroxychloroquine is an immunomodulator and antimalarial drug, as well as a safe chloroquine analogue. Current studies have shown that hydroxychloroquine has antiviral activity against SARS-CoV-2 [29]. According to the researchers, its mechanism of action is to increase intracellular pH, leading to phage-lysosome fusion and reduction. Therefore, the glycosylation of the viral receptor is destroyed and the antiviral activity is exerted. Moreover, it can inhibit Toll-like receptor signaling, reduce the production of cytokines (IL-1 and IL-6), and has an immunomodulatory effect [30]. Recently, antiviral effects in vitro have been demonstrated on SARS-CoV-2. A recent study showed that a concentration of 0.36mg/L chloroquine reduced the amount of virus by half in a cell model [31]. In experiments with hydroxychloroquine alone in COVID-19 patients, researchers found that its use led to shorter clinical recovery times and enhanced absorption of pneumonia.[32]

4.2 The Clinical Studies of the Combination of Azithromycin and Hydroxychloroquine in the Treatments of COVID-19

There is both evidence that the treatment works and does not. The results were influenced by how long patients had been sick at the time of treatment, the dose of the treatment, and also the size of the experience.

The Combination of Azithromycin and Hydroxychloroquine Had no Significant Effect. Some scientists studied 120 COVID-19 patients, 60 of whom received a combination drug treatment and 60 of whom received a placebo. The combination treatment was given by 500mg/d azithromycin for three consecutive days, then 250mg/d azithromycin for 12 consecutive days, and 200mg/d hydroxychloroquine twice a day for 15 consecutive days. Placebo was chosen for the control group. The number of days alive and the number of people discharged within 14 days was the main criteria. The results of DAOH over 14 days were broadly similar between the experimental and control groups. Median 9.0DAOH14(IQR, 3-11) in the experimental group compared with 9.0DAOH14(IQR, 7-10) in the control group, P=0.91 [33].

The Combination of Azithromycin and Hydroxychloroquine Is Superior. Philippe Gautret et al conducted a study on 36 COVID-19 patients, which include 20 patients received treatment, and 16 patients were chosen as controls from a different hospital. Among the 20 patients, 6 of them were treated with a combination of hydroxychloroquine and azithromycin on Day 6. The results showed that hydroxychloroquine treatment was significantly associated with a reduction in viral load in patients with COVID-19, and azithromycin enhanced its effect [28]. Small patient populations are used to infer differences between treatment groups, hence statistical analysis to assess the possibility of mistakes in assuming these groups were distinct was not done.

However, hydroxychloroquine alone is not effective in the treatment of covid-19, and there is no significant reduction in mortality [34]. In a preliminary clinical trial, researchers showed that hydroxychloroquine and azithromycin have synergistic effects against SARS-CoV-2 in vitro [35], when controlling for COVID-19 risk factors, combination therapy with azithromycin was associated with reduced COVID-19-related mortality [36]. One experiment reported that all patients were cured after 6 days of hydroxychloroquine and azithromycin treatment [37]. In a retrospective analysis of patients in Marseille, France, hydroxychloroquine and azithromycin contributed greatly to the early treatment of patients with COCID-19. Of the 1061 cases, 973 patients were successfully cured within 10 days (91.7%). 46 patients (4.3%) had poor clinical outcomes and 8 died (0.75%) [38].

One study showed that mortality in COVID-19 patients treated with a combination of hydroxychloroquine and azithromycin was associated with the number of days the patient was sick. Of the 1,265 patients, there were no
deaths in those treated for less than 72 hours. The patient's death occurred on the fourth day of treatment. Death rates increase as patients stay sick longer [39].

4.3 Limitations of the Combination of Hydroxychloroquine and Azithromycin

When azithromycin is used with hydroxychloroquine, there has been speculation about safety issues. One study showed that High clinical concentrations of hydroxychloroquine and azithromycin can prolong the duration of action potentials and increase the spatial dispersion of action potential repolarization in the heart. As a result, long QT intervals appear and arrhythmias occur. Arrhythmias may be produced by hydroxychloroquine and azithromycin due to their alternating amplitude growth in certain cycles. And it migrates the origin of alternans to relatively high cycle lengths, which include CLs generated by normal sinus nodes [40].

5 Conclusion

As COVID-19 is a highly contagious disease, effective treatment is especially important. This review discusses the effect of using Azithromycin and the combination of using Azithromycin and hydroxychloroquine to treat COVID-19.

In conclusion. Although Azithromycin has antiviral effects on other viruses, the clinical data shows that this antibiotic has no significant effect on treating COVID-19 patients.

However, the combined effects of Azithromycin and Hydroxychloroquine are also discussed in this paper. At present, the exact mechanism of treatment is not clear. There is more evidence for the use of Azithromycin in addition to the use of Hydroxychloroquine has beneficial effects. The results were affected by how long patients had been sick at the time of treatment, and the dose of the treatment. The larger size of the experience and the control of the variable accurately can make the results more valid.

The use of Azithromycin in combination with other antibiotics to treat COVID-19 should also be discussed in the future.

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