Azithromycin for COVID-19: Pharmacological Mechanisms, Challenges, and Prospects

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Abstract- The coronavirus disease (COVID)-19 pandemic led to a new challenge in the field of effective treatment methods for this disease. Antiviral and immunomodulatory agents were suggested as potential therapeutic methods in this field. Since the most severe clinical symptoms associated with COVID-19 disease appear to be acute respiratory syndrome, azithromycin has been proposed as a potentially effective drug in this context. We have updated the evidence and selected all relevant items to understand the mechanism of role of azithromycin, clinical efficacy, and their side effects in coronavirus disease-19 treatment on July 20th and updated on March 20th, 2020. A literature search of electronic databases including the Web of Science, PubMed, and Google Scholar was conducted by searching keywords such as "Azithromycin", "COVID-19", and "Combination therapy". The ultimate goal of this review was identifying eligible studies about the pharmacological activities, safety, and effectiveness of azithromycin in treating COVID-19 patients. Immunomodulatory properties of azithromycin include the ability to reduce cytokine production, maintain epithelial cell integrity, or prevent lung fibrosis. The use of azithromycin in some studies was associated with a decrease in mortality and need for ventilation in patients. These properties can be useful during the period of COVID-19 infection, especially in patients with underlying diseases. However, the evidence for the use of azithromycin is still scarce and the quality of the studies is low. In some retrospective studies, azithromycin was mainly evaluated in combination with hydroxychloroquine, which showed no particular advantage. The results of this review showed that azithromycin has appropriate and well-known safety characteristics in the treatment of patients with COVID-19. However, the most appropriate dosage in different stages of the disease and the effect of its combination with other drugs are important questions that should be considered in future clinical trials.

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Introduction

The advent of the new COVID-19 disease poses a challenge to finding effective Therapeutic treatments. The selected treatment with definite and positive clinical outcome for this new disease remains unknown. Therefore, we need an urgent search for effective and safe treatments in this field. Nevertheless, so far, various treatment methods have been proposed and used to solve this problem. In respiratory epidemics such as COVID-19, the severity and mortality of viral infections are associated with an excessive host inflammatory response

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and excessive production of cytokines (1).

Since the most severe clinical manifestation during the infection of COVID-19 appears to be a sudden acute respiratory syndrome, azithromycin has been proposed as an effective treatment due to its antiviral and immunomodulatory activity with a known safe profile. However, its role in COVID-19 treatment is unclear. Also, a macrolide antibiotic such as azithromycin has been used in the clinical treatment of many gram-positive and atypical bacterial species with known safety profile. The administration of azithromycin in patients with influenza led to a decrease in the mortality rate by reducing the inflammatory cytokines faster and in combination with naproxen. Azithromycin in this treatment may lead to an increase in the pH of the host cells, which may act as a barrier to prevent the entry, multiplication and spread of the virus (2,3,4).

The results of an *in vitro* study have shown that azithromycin has a strong affinity for the cross-linking of COVID-19 spike protein and angiotensin-converting enzyme 2 (ACE2). A review of the literature indicated that preventing this interaction could potentially prevent viral infection. Azithromycin regulates the relationships of genes involved in virus recognition (melanoma differentiation protein 5 and retinoic acid-inducible gene) and plays a role in the production of type I and III interferons (especially interferon β and interferon-¥) (5,6).

In this review, we would like to present the potential usefulness of azithromycin along with the side effects of its administration in patients' treatment with COVID-19. In the following, we will provide brief information on the pharmacology, clinical efficacy, and safety of azithromycin in viral infections with special emphasis on the disease of COVID-19.

Pathogenesis of COVID-19

SARS-CoV-2 enters the cell mainly via hACE2 through glycosylation. Decreased number and function of lymphocytes and severe increase in inflammatory activity of leukocytes are the immunological complications of this disease. If the immune system's response to the virus should not be adequate, the disease can become acute. In this case, the activity of immune cells causes an increase in the amount of cytokines in the blood and induces a cytokine storm, causing systemic damage to the various organs of the body and systemic injuries will lead to the death of the patient. Lung damage also causes fibrosis of lung tissue, shortness of breath, and lowers arterial blood oxygen levels (5,7). Azithromycin is known to have immunomodulation and antiviral properties. According to some results from clinical studies, azithromycin could have a potential in the fight against this new epidemic (5,6).

Azithromycin pharmacology

Azithromycin is an antibiotic medication used for the treatment of several bacterial infections. This medicinal compound prevents the translation of bacterial mRNA by binding to the 50S subunit of the ribosome. The azithromycin administration in combination with other drugs has been applied successfully in viral and severe respiratory infection treatments (8). Researchers believe that azithromycin plays a successful role in reducing the side effects of respiratory diseases by suppressing some effective immune responses in airway inflammation (6). The proposed antiviral and immunomodulatory mechanisms of azithromycin action during COVID-19 treatment were described in Figure 1. Contrary to the anti-inflammatory and immune-modulating functions of azithromycin on the immune response and reducing the complications of respiratory infections, this medicinal compound does not have a direct antiviral effect, and controversial results have been obtained from its administration in clinical trials (6,7).

In this line, Arabi *et al*., evaluated the correlation between macrolides therapy using macrolides and MERS coronavirus RNA clearance in critically ill patients with MERS over a 90-day period. The obtained results showed that macrolide therapy is not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance (9).

Antiviral activity mechanisms

There are various theories about possible mechanism of action of azithromycin against clinical spectrum of SARS-CoV-2 Infection (5,6,7). In the first step, it must be stated that the proper growth and function of the endosome requires an acidic environment. The existence of these environmental conditions is necessary for the growth and effective penetration of viruses such as influenza, AIDS and even SARS-CoV-2 into host cells. The accumulation of azithromycin as a weak base inside the cell of endosomal vesicles and lysosomes leads to an increase in the pH level. These conditions potentially block endocytosis or genetic shedding of the virus from lysosomes. As a result, virus replication is limited (10).

Poschet and colleagues (2020) stated that primary CF human bronchial epithelial cell line treatment with azithromycin (at a concentration of 100 µM) during 60 min or 1 µM (for 48 hours) lead to an increase in the pH

level of the trans-Golgi network in a more *in vitro*-like condition (from 6.1 to 6.7). Treatment of the same cells with azithromycin to concentration of 100 µM (during 60 min) increased the pH level of the recycling endosome from 6.1 to 6.7. The Golgi network and recycling endosomes play an important role in the placement of proteins into vesicles destined for their secretion. This process is used to facilitate the replication of viruses. pH changes in the two mentioned organs may cause interference in intracellular viral activities. As the pH increases in the trans-Golgi network, the glycosylation process of the angiotensin-converting enzyme 2 (ACE 2) receptor will change. The SARS-CoV-2 virus uses this enzyme to attach to the surface of the host cell. By competitively binding to the virus, the glycosylation prevents viral binding to the host cells. Azithromycin directly affects bronchial epithelial cells in order to maintain its function. This medicinal compound reduces the secretion of mucus and ultimately leads to the facilitation of lung function (11).

Poschet *et al*., stated that incubation of IB3-1 CF cells with azithromycin in concentration of 100 µM lead to a significant reduction in the levels of an enzyme called Furin ($P<0.01$) (12). SARS-CoV-2 is equipped with a Furin-like cleavage site in the spike protein. This protein facilitates the entry of the virus into the patient's cell. Azithromycin probably prevents the virus from entering these cells by interfering with the spike protein cleavage (13).

Azithromycin reduces the production of pro-inflammatory cytokines such as IL-6 and TNF-α (5). Poschet *et al*., also stated that treatment of CF cells with 1 to 100 µM azithromycin reduced basal levels of the IL-8 secretion (13). Therefore, azithromycin may reduce the proinflammatory state induced by SARS-CoV-2 infection. Finally, the administration of azithromycin can lead to a reduction in respiratory failure characterized by slow onset of widespread inflammation in the lungs. Immunomodulatory activities during the administration of azithromycin include two stages of acute phase and elimination of chronic inflammation. The ability of azithromycin to reduce the production of pro-inflammatory cytokines (such as IL-8, IL-6, and TNF-α) and matrix metallo-proteinases has been proven in the acute phase. Administration of azithromycin in the resolution phase also increases neutrophil apoptosis and oxidative stress related to inflammation. Azithromycin also reduces the effects of lipopolysaccharide on bronchial epithelial cells of the lung allograft. Azithromycin increases the activity of arginase and anti-inflammatory macrophage receptors. As a result, the expression of inducible nitric oxide synthase and pro-inflammatory macrophage receptor (CCR7) will decrease significantly (4,6).

During azithromycin therapy, due to its similar volume and chemical properties to GM1 gangliosides, led to the imitation of these gangliosides. Since the spike protein of SARS-CoV-2 displays a ganglioside-binding site, azithromycin might inhibit coronavirus 2 infection by binding to this site. This would prevent the virus spike protein to reach gangliosides on the host plasma membrane that are involved in coronavirus 2 pathogenesis. Moreover, azithromycin may interfere in the spike protein/basigin interaction or basigin expression (5,6).

Excessive inflammatory response: cytokine storm

A syndrome of systemic hyperinflammation known as cytokine storm may occur in patients who develop symptoms associated with severe pneumonia during COVID-19 infection. Cytokine profiles of patients with severe symptoms of COVID-19 were compared to those with milder symptoms of the pandemic. A significant increase in the levels of some pro-inflammatory cytokines including interleukins-1β, 2, 6, 8, 10, and 17 has been observed. The increase in the expression of TNF-α in patients with COVID-19 was similar to the results of other diseases such as SARS and MERS. Cytokine abnormalities can lead to lung infiltration and the formation of critical symptoms including septicemia, shock, respiratory failure, acute respiratory distress syndrome, multiple dysfunction syndrome, and eventually death (6,14).

Azithromycin may exhibit a novel safety profile by inhibiting several pro-inflammatory cytokines involved in severe respiratory syndrome during COVID-19.

Efficacy of azithromycin in COVID-19 treatment

The proliferation and differentiation of T lymphocytes in the innate immune response against bacterial or viral pathogens is driven by the expression of an important cytokine called IL-2. Maintaining the production of interleukin-2 leads to the persistence of the innate immune response in patients with COVID-19. Adequate generation of memory T cells and natural killer cells along with induction of regulatory T cells is necessary to control inflammation. Azithromycin can lead to the survival of memory T cell numbers and the induction of a more effective immune response by maintaining this condition. In this regard, IL-8 plays a role in neutrophil chemotaxis, which facilitates lung infiltration and causes a syndrome similar to macrophage activation in patients

with severe symptoms of COVID-19 (6,15).

Another property of azithromycin is antibacterial effect, which may be used to prevent or treat common infections caused by bacteria and the COVID-19 virus. The results of recent studies show that the lung microbiota anaerobic bacteria may play a role in the pathogenesis of COVID-19. *Prevotella spp.* as an anaerobic bacteria is involved in the severity of pulmonary symptoms in patients with severe COVID-19. This bacterium can significantly increase the pathogenic mechanisms of respiratory viruses. They have an important role in idiopathic inflammatory lung diseases, especially by facilitating the production of IL-6 and IL-8. Azithromycin as an effective drug treatment reduces the inflammation produced by this bacterium (5,6,7).

The results of an *in vitro* study showed that the administration of azithromycin in concentrations of 1 to 6 μM can reduce the activity of respiratory viruses, except H1N1 influenza, by 50% in laboratory conditions. Evidence suggesting that *in vitro* conditions, 50% inhibition of SARS-CoV-2 virulence with a concentration of 2.12 μM of azithromycin after a 72-hour incubation period of infection was associated with a ratio of infectious virions to cultured cells (multiplicity of infection) of 0.002.

Evidence suggesting that *in vitro*/*in vivo* conditions suggest a possible synergy between azithromycin and hydroxychloroquine. Conflicting results were obtained from these two studies. In one study, azithromycin alone showed a good therapeutic response against the SARS-CoV-2. While in another study, anti-SARS-CoV-2 activity was observed only by co-administration of azithromycin with hydroxychloroquine (4,15).

In a clinical trial, positive results were obtained using azithromycin in combination with hydroxychloroquine in reducing the severity of COVID-19 symptoms. In a non-randomized study, Co-administration hydroxychloroquine and azithromycin was associated with the highest efficacy of a viral treatment after a period of 6 days (16).

Rosenberg *et al*., assesmented the outcomes of in-hospital mortality in patients with COVID-19 treated with hydroxychloroquine or azithromycin. The clinical results showed that among hospitalized patients with COVID-19, treatment with hydroxychloroquine, azithromycin, or both was not associated with significantly lower in-hospital mortality in comparison with neither treatment (17). However, the interpretation of these findings may be limited by the observational design.

Abaleke *et al*., investigated whether azithromycin improves clinical outcomes in patients admitted to hospital with COVID-19. The results of this study showed that the administration of azithromycin in hospitalized patients with COVID-19 did not lead to the improvement of predetermined clinical indicators (Improvement in survival index or other pre-specified clinical outcomes). They concluded that the administration of azithromycin in hospitalized patients with COVID-19 should be limited to patients with a clear antimicrobial indication (1).

Mehra *et al*., evaluated the effect of hydroxychloroquine or chloroquine with or without a macrolide during treatment of patients with COVID-19. In this study, 96032 patients (average age of mean 53·8 years) were hospitalized and met the inclusion criteria. The obtained showed that hydroxychloroquine or chloroquine, when used alone or with a macrolide was associated with decreasing of in-hospital survival and an increased frequency of abnormal heartbeats (12).

Drug-drug interactions

The effect of drug interaction during the treatment periods of patients with COVID-19 along with the evaluation of their side effects has been one of the main concerns of researchers. In this section, we summarize some of these drug-drug interactions in patients with COVID-19, with special emphasis on azithromycin.

Chloroquine/hydroxychloroquine and azithromycin interaction

In a study, Ammor *et al*., evaluated the effects of chloroquine (500 milligrams per day to the maximum course of 10 days)/hydroxychloroquine (200 milligrams per day to the maximum course of 10 days) plus azithromycin (500 milligrams per day to the maximum course of 7 days) in patient with COVID-19. The results did not show significant improvement of symptoms in patients. Administration of hydroxychloroquine/chloroquine and azithromycin alone resulted in QTc prolongation in one third of patients with COVID-19 (18).

Antipsychotics and chloroquine/hydroxychloroquine/azithromycin

In this pharmacotherapy protocol, the primary interaction is the risk of QT prolongation and torsades de pointes because the three drugs for COVID-19 have "Known Risk of torsades de pointes" according to CredibleMeds® (19).

Borba *et al*., did not recommend the highest dosage of chloroquine for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir (20). In

Table 1, a summary of other results in this field is presented.

According to the available evidence, the role of azithromycin in combination with other drugs in improving the symptoms of patients with COVID-19 is obvious. The benefits of azithromycin administration have been confirmed, especially in reduction in the risk of invasive mechanical ventilation or hospitalization time in some patients with COVID-19. However, clinical data are still scarce. The results in this field are contradictory. Azithromycin alone can increase the release of anti-inflammatory cytokines associated with the repair of inflamed tissues. These properties can be useful during the treatment period of COVID-19. However, the clinical results of its combination with other drugs are still limited. Before starting treatment with azithromycin, a comprehensive evaluation is required to understand drug-drug interactions and risk factors of underlying diseases. Especially when its use is recommended in the first line of treatment.

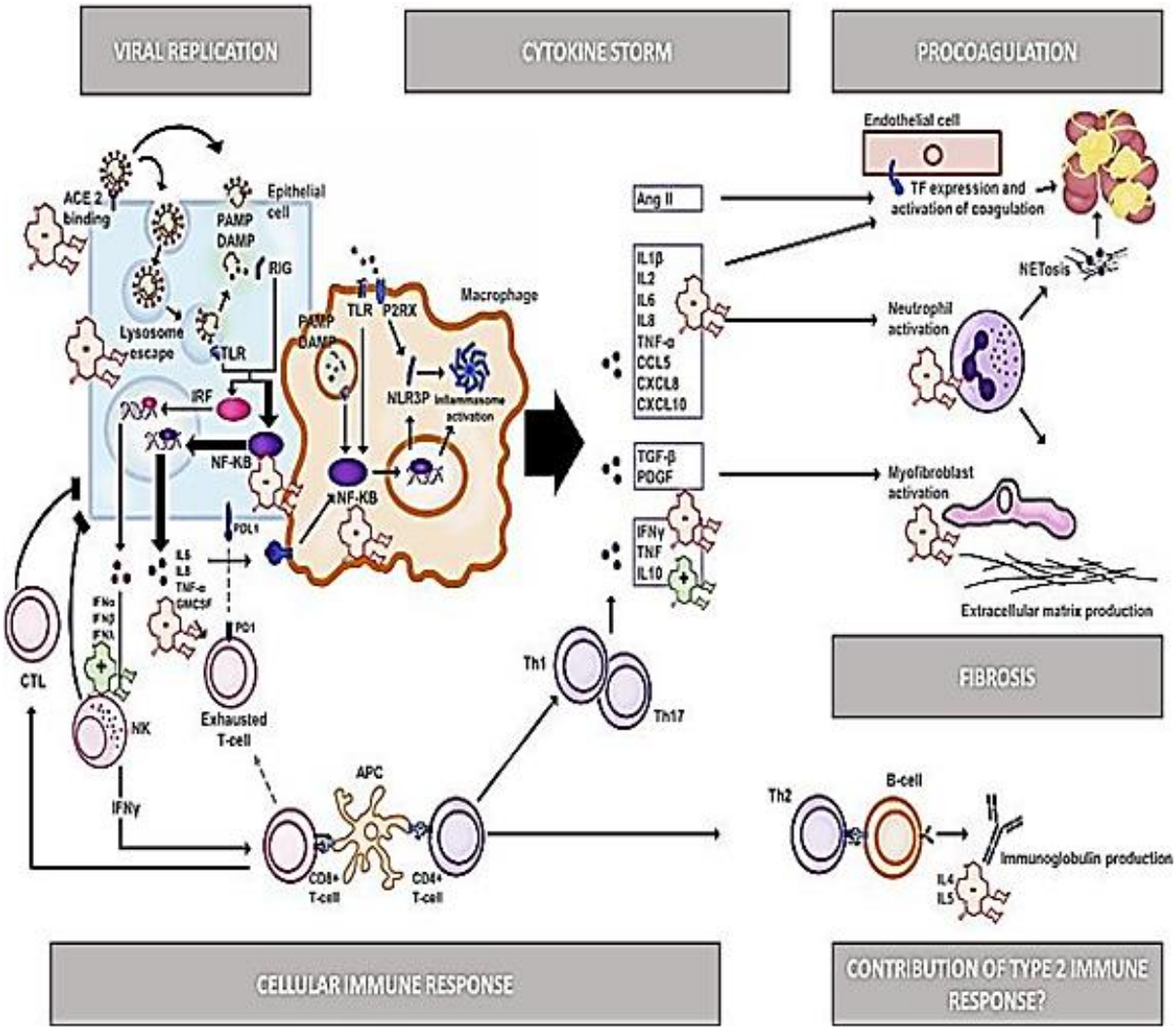

Figure 1. Azithromycin pharmaco‑ immunomodulatory therapy for patients with COVID-19. (The figure taken from reference of (8) with permission)

Table 1. Some available clinical data on the effectiveness of azithromycin alone or in combination with other drugs in patients with COVID-19

Study Population	Experiment design	Treatments	Summary of analysis results	Ref
Adult patients with severe COVID-19 (N= 81 patients)	Prospective, randomized, open labeled, controlled study. Patients will be randomized in two groups (A and B). parallel, double-masked, randomized, phase II, clinical trial	Patients were allocated to receive high-dosageof chloroquine diphosphate (ie, 600mg chloroquine diphosphate twice daily for 10 days) or low-dosage of chloroquine diphosphate (ie, 450mg twice daily on day 1 and once daily for 4 days). In addition, they received intravenous ceftriaxone (1 g twice daily for 7 days) plusazithromycin (500mg once daily for 5 days), and Oseltamivir (75mg twice daily for 5 days).	A higher dose of chloroquine should not be used in patients receiving azithromycin and seltamivir due to safety concerns regarding QTc prolongation and increased mortality	**(20)**
Hospitalized patients with COVID-19, age >12 years (N = 36 patients)	Observational, nonrandomize, external control, open-label	Non-randomized Control hydroxychloroquine (200 mg q.8h. × 10 days) hydroxychloroquine + azithromycin (500 mg for day (1) and 250 mg for day (2-5))	The symptoms of improvement in patients with COVID-19 were enhanced by the simultaneous administration of azithromycin and hydroxychloroquine. Decrease or disappearance of viral load increased in this group of patients	**(21)**
COVID-19, >18 years (N = 80 patients)	Uncontrolled, non-comparative, observational study in a cohort of 80 relatively mildly infected inpatients	Hydroxychloroquine (200 mg q.8h. × 10 days) + azithromycin (500 mg day(1) and 250 mg Day(2-5)	A rapid fall of the upper part of the pharynx viral load was noted, with 83% negative at day 7, and 93% at day 8. On the fifth day of treatment, the virus culture results were negative in 98% of the patients' respiratory samples	**(17)**
COVID-19, 53–76 years, (N = 2541 patients)	Multi-center retrospective observational study	Adminstration of hydroxychloroquine alone, Co-adminstration of hydroxychloroquine and azithromycin, azithromycin alone, or neither.	The primary outcome included in-hospital mortality of patients. During this multihospital evaluation, treatment with hydroxychloroquine alone and in combination with azithromycin led to a reduction in mortality in patients with COVID-19. Prospective trials are needed to evaluate this treatment protocol	**(22)**
COVID-19, age 20–77 years, (n = 11 patients)	Observational, single arm	Hydroxychloroquine 400mg orally b.i.d. for 10 days/azithromycin 500 mg daily for 10 days.	No evidence of potent antiviral activity was reported with co-administration of hydroxychloroquine and azithromycin	**(23)**
COVID-19, age 18–55 years (n = 60 patients)	Open-label single- group clinical trial/phase 2	Patients received hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg for day 1 and 250 mg for days 2-5)	The negative results of the RT-PCR test and the resolution of the symptoms indicated the success of the treatment	**(3)**
COVID-19, (n = 1438 patients)	In a retrospective cohort study, compared with treatment with neither drug	Quintuple therapy for 24 weeks (hydroxychloroquine, azithromycin, vitamin C, vitamin D, zinc)	Simultaneous or single administration of hydroxychloroquine and azithromycin had no significant relationship with the mortality rate of patients with COVID-19 in the hospital	**(3)**
COVID-19, >18 years (n = 415 patients)	A retrospective cohort of COVID-19 hospitalized patients treated with hydroxychloroquine /azithromycin was reviewed.	Co- or single administration of hydroxychloroquine and azithromycin.	QTc was increased in patients treated with hydroxychloroquine/azithromycin. This increase was related to several clinical factors in patients with COVID-19. There was no correlation between QTc changes and increased risk of death in these patients	**(21)**
COVID-19, ± 66.2 years old (N= 168 patients)	Patients under treatment with double (DT) and triple therapy (TT) for COVID-19 were consecutively included in this prospective	Hydroxychloroquine/azithromycin	DT and TT prolong the QTc in patients with COVID-19. Co-administration of lopinavir/ritonavir with high-dose hydroxychloroquine and azithromycin did not increase QTc compared to DT	**(25)**

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