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Azithromycin in Coronavirus Disease-19: What We Know?

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Abstract

Azithromycin (AZM) is a broad-spectrum antibiotic with anti-inflammatory and immunomodulatory properties. It is particularly used in chronic lung diseases including chronic obstructive pulmonary disease, asthma, interstitial lung diseases, bronchiectasis, and cystic fibrosis. AZM has not approved for the treatment of viral infections, but some study supported its antiviral activity. Recently, few studies are emphasized used AZM in combination with chloroquine/hydroxychloroquine for the treatment of novel coronavirus disease-2019 (COVID-19). The present review highlighted uses, dosage, and adverse effects of AZM in COVID-19 based on available literature.

Introduction

An outbreak of coronavirus disease-2019 occurred in Wuhan, China in the month of December 2019 and rapidly spread across the world [1], [2]. On March 11, 2020, the WHO declared COVID-19 as a pandemic disease [3]. In an early stage, infection is characterized mainly by respiratory symptoms such as cough, sore throat, fever, and fatigue [4]. On later stage, high viral replication, high inflammatory activity, and exacerbated immune response lead to a "cytokine storm," which is responsible for complications, such as severe pneumonia and acute respiratory distress syndrome [5], with increased requirement of ventilatory support and intensive care unit admission [6]. About 80% of patients have mild disease and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70–79 years and 14.8% in those aged ≥80 years, but major concern is that number of asymptomatic carriers in the population, and thus, the mortality rate is probably overestimated [7]. Therefore, there is an urgent need for an effective treatment to treat symptomatic patients and decrease the duration of virus carriage to limit the transmission in the community.

Till date, there is no specific treatment which is available to treat COVID-19. However, the backbone of the treatment strategy for COVID-19 is good quality supportive care as in any viral pneumonia. There is no current evidence from randomized controlled trial to recommend any specific anti-COVID-19 treatment for patients with suspected or confirmed COVID-19 infection. The clinicians are using various drugs such as antiviral drugs that include inhibitors against protease, integrase, and polymerase enzymes based on anecdotal data and some recent publications. Moreover, antiviral effects of azithromycin (AZM) have been attracted considerable attention [8].

There are various treatments being used to control COVID-19 based on previous experiences with other viral infections. In the present review, we aim to summarize the uses of AZM in COVID-19.

Materials and Methods

Data sources

We performed thorough literature search on published studies between January 1, 2020, and April 15, 2020. PubMed and Google Scholar databases were used to find articles providing information on the efficacy and safety of AZM in patients with COVID-19. No language restrictions were imposed.

Inclusion and exclusion criteria

The studies which describe used of AZM in COVID-19 and previous epidemic viruses such Ebola, severe acute respiratory syndrome, and Middle-East respiratory syndrome were selected. Meanwhile, studies which (a) duplicate publications, (b) full articles not available, (c) literature reviews, and (d) do not provided sufficient information or support regarding their recommendation of their proposed drugs or treatment process were excluded from the study.

Results

A total of 170 articles initially identified. After removing duplicates, checking title, abstract, and full text 30 were found eligible based on the predetermined exclusion and inclusion criteria for this study. Among these three articles were relevant which showed used of AZM in COVID-19 patients as summarized in Table 1 while rest of all articles were used for basic information.

Discussion

AZM

AZM is a macrolide antibiotic with a 15-membered lactone ring. It is broad-spectrum antibiotics with long serum half-life near about 68 h and large volume of distribution [9]. AZM has excellent tissue penetration. In infected tissues, AZM concentrations are about 300-fold higher than in plasma, due to recruitment of leukocytes at the site of infection [10]. It also has anti-inflammatory activity, decreases pro-inflammatory cytokine and hastening of the macrophages phagocytosis ability [11]. Due to its antibacterial and anti-inflammatory effects, it is used for many chronic lung diseases including chronic obstructive pulmonary disease, asthma, interstitial lung diseases, bronchiectasis, and cystic fibrosis [12].

AZM as antiviral

Azithromycin effective against rhinovirus, respiratory syncytial virus, influenza virus, Zika virus and Ebola viruses [13], [14], [15], [16]. The mechanism is unknown. The multiple mechanisms have been proposed for antiviral activity observed with AZM. The antiviral activity may be mediated by amplification of the host's interferon (IFN) pathway by inducing pattern recognition receptors, IFNs, and IFN-stimulated genes that lead to a reduction of viral replication [17], by directly acting on bronchial epithelial cells which reduce mucus secretion (19). Moreover, a recent quantum mechanical modeling suggests a potential role of AZM in COVID-19 by interfering with viral entry through binding interaction between coronavirus spike protein and host receptor angiotensin-converting enzyme-2 protein; further, experimental work on this is necessary to confirm the model [18].

Clinical study

The symptoms of COVID-19 are similar to those seen in these lung infections; therefore, it is not surprising that AZM treatment was initiated early in the current pandemic of COVID-19. The use of AZM in 25 of 138 patients who were suffer from COVID-19 in Wuhan, China, reported in a recent JAMA article [19].

First French clinical study

A French confirmed COVID-19 positive; 36 patients (n = 20 in treatment group and n = 16 in control group) were enrolled in an open-label non-randomized clinical trial. In the treatment group, 600 mg HCQ daily was given to patients and their viral load in nasopharyngeal swabs was tested daily. On basis of clinical presentation of patients, six patients received AZM (500 mg on day 1 followed by 250 mg/day for the next 4 days) to prevent bacterial superinfection under daily electrocardiogram (ECG) control. Untreated patients from another center and cases refusing the protocol were included as negative controls. The presence and absence of virus at day 6 post-inclusion was considered the end point. The combination of hydroxychloroquine and AZM results in negative PCR results in nasopharyngeal samples was significantly

Table 1: Clinical study of azithromycin in COVID-19

Study population	Sample size	Study design	Treatments	Results	Reference
COVID-19	n=36 Treatment group n=20 Control group n=16	Observational open-label non-randomized clinical trial	HCQ 200 mg, TID×10 days HCQ+AZM (500 mg D1 and 250 mg D2-5)	At day 6 post-inclusion, virologically cured HCQ+AZM: 100% HCQ: 57.1% Control: 12.5% p<0.001	20
COVID-19	n=80	Uncontrolled non-comparative observational	HCQ 200 mg, TID×10 days+AZM (500 mg D1 and 250 mg D2-5)	Nasopharyngeal viral load tested by qPCR; 83% negative at day 7 and 93% at day 8 Virus cultures from patient respiratory samples were negative in 97.5% of patients at day 5	21
Suspected COVID-19; flu-like symptoms	n=636 Treatment group n=412 Control group n=224	Observational open-label non-randomized	HCQ 800 mg on D1 and 400 mg D2-D7+AZM 500 mg D1-D5	HCQ+AZM: 1.9% of patients required hospitalization Control: 5.4% of patients required hospitalization (p<0.0001) Patients treated before versus after day 7 of symptoms required less hospitalization (1.17% and 3.2%, respectively, p<0.001)	22

different between the two groups at days 3-4-5 and 6 post-inclusion. At day 6 post-inclusion, 100% of patients treated with hydroxychloroquine and AZM were virologically cured compared to 57.1% in patients treated with hydroxychloroquine only and 12.5% in the control group ($p < 0.001$). Therefore, addition of AZM to hydroxychloroquine treatment results in significantly viral load reduction/disappearance in COVID-19 patients. The limitations of study are small sample size, limited long-term outcome follow-up, and dropout of six patients from the study [20].

Second French clinical study

Gautret *et al*. conducted an uncontrolled non-comparative observational study in a cohort of 80 confirmed COVID-19 patients. All patients received 600 mg/day oral hydroxychloroquine sulfate for 10 days combined with AZM (500 mg on day 1 followed by 250 mg/day for the next 4 days). Patients with pneumonia and NEWS score ≥5, a broad-spectrum antibiotic (ceftriaxone), were added to hydroxychloroquine and AZM. Twelve-lead ECGs were performed on each patient before treatment and 2 days after treatment began. The median age of patients was 52 years (ranging from 18 to 88 years) and had at least one chronic condition such as hypertension, diabetes, and chronic respiratory disease. About 81.3% of patients had favorable outcome and were discharged from unit while only 15% required oxygen therapy during their stay. A rapid fall of nasopharyngeal viral load tested by quantitative polymerase chain reaction was noted, with 83% negative at day 7 and 93% at day 8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at day 5. Moreover, patients were able to be rapidly discharged from infectious disease unit with a mean length of stay of 5 days. Therefore, a beneficial effect of coadministration of AZM along with hydroxychloroquine observed in COVID-19 patients [21].

Brazil telemedicine clinical study

A telemedicine study was conducted in Sao Paulo, Brazil, after the pandemic was officially declared in city. Patients with persistent flu-like symptoms (suspected COVID-19 infection), persisting for a period equal to or greater than 2 days, were first evaluated by the telemedicine team or by the emergency department medical doctor. Participants who did not need immediate hospitalization and azithromycin was not contraindications were invited to participate in the study. A total of 636 symptomatic outpatients enrolled in the study. The treatment group (n = 412) received hydroxychloroquine 800 mg on the 1st day and 400 mg for another 6 days and AZM 500 mg once daily for 5 days. A total of 224 patients who refused to medications served as control group. The swab laboratory was not mandatory and chest computed tomography was performed according to medical judgment. All patients were followed daily by telemedicine consultations until the 5th day of symptoms, after that, patients were contacted twice a day until the 14th day of initial symptoms. In the treatment group, 1.9% of patients required hospitalization as compared to 5.4% of patients in the control group ($p < 0.0001$) which indicates 2.8 times greater need for hospitalization compared to those without medication. An absolute risk reduction is 3.5% and a number needed to treat (NNT) is 28 to prevent one hospitalization. The patients treated before versus after day 7 of symptoms required less hospitalization (1.17% and 3.2%, respectively, $p < 0.001$). Comparing the early treatment (< 7 days of symptoms) to those without treatment (control group), the NNT was 23. Therefore, empirical treatment of hydroxychloroquine and AZM for suspected cases of COVID-19 reduces the need for hospitalization [22]. To sum up, Table 1 shows clinical studies of AZM in COVID-19.

Adverse events

Common side effects of AZM include abdominal pain, diarrhea, constipation, nausea, dizziness, headaches, photosensitivity, or a skin rash [23]. Tinnitus and even hearing loss are associated with this medication [24], [25]. It should be avoided in patients with a history of Stevens-Johnson syndrome [26] and other serious skin reactions [27] as well as those with myasthenia gravis. Prolonged cardiac repolarization and prolongation of the QT interval can occur [28]. An ECG should be performed to assess the normal heart rhythm because the medication can cause arrhythmias. Patients with abnormal QT intervals, congenital long QT syndrome, a history of torsades de pointes, bradyarrhythmias, or heart failure may be at risk for fatal QT prolongation [29]. Elderly patients are more at risk. Abnormal liver function tests, hepatitis, hepatic necrosis, cholestatic jaundice, and hepatic failure have been reported with its use. AZM increased levels of theophylline and aminophylline, warfarin, digoxin, phenytoin, and statins. Nelfinavir increases serum concentration of AZM, so those receiving single oral doses need to have liver enzyme tests and hearing monitored [30].

Conclusion

The literature presented here provides a significant role of AZM in COVID-19 when combined with HCQ. It helps to reduce nasopharyngeal viral load, hospitalization and patients were able to be rapidly discharged from infectious disease unit. A well-designed randomized double-blind placebo control clinical trials are needed for further clarity and evidence. Results of

near future researches will assess safety data of its use to guide clinical usage during this pandemic.

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