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REPURPOSING OF AZITHROMYCIN AS AN ANTI-VIRAL DRUG

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ABSTRACT

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and it is primarily used for the treatment of respiratory, enteric, and genitourinary bacterial infections. It is not approved for the treatment of viral infections, and there is no well-controlled, prospective, randomized clinical evidence to support azithromycin therapy in coronavirus disease 2019 (COVID-19). This work assesses published and clinical evidence for azithromycin as an agent with antiviral properties.

KEYWORDS: Azithromycin, macrolides, coronavirus.

INTRODUCTION

As the novel coronavirus continues to spread its fang across the globe, the medical experts, researchers and scientist across the world have joined hands to find a remedy for the highly infectious COVID 19 disease. Development of potential drugs and vaccine is underway to combat the highly infectious virus. From hydroxychloroquin to remdisiver, there is a host of potential COVID-19 treatments which are being tested for their efficacy and safety. Viruses constitute a large group of pathogens which causes severe infectious diseases. The chronic viral infectious diseases, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV); the re-emergence of many new infections, like coronaviruses; and, also resistance developed to the available antiviral drugs are the main reasons for increased demand for new antiviral agents. The need for drugs in treatment of emerging more efficient new viruses acts as motivation for research to find new targets and mechanisms for the development of new antivirals.[1]

Macrolides as Antiviral Drugs

Till recently, only 12 new antiviral drugs have been approved by the Food and Drug Administration, eight of them are meant for the treatment of hepatitis C virus and two are combinations of anti-human immunodeficiency virus drugs. But the fact is, the world still faces the global threat of many emerging and re-emerging viruses, which are responsible for alarming out breaks in recent years. These infectious diseases, such as Zika virus, Ebola virus and Middle East respiratory syndrome corona virus and many other emerging viruses lack specific treatment.[2]

The process of finding new uses other than the original medical indication for existing drugs is also known as redirecting, repurposing, repositioning and re-profiling. Drug developers have been compelled to find new uses and new targets of the already existing drugs owing to the problem in productivity and worldwide pressure on increasing prices and the evergrowing number of regulatory hurdles.[3] Though there are few disadvantages associated with drug repurposing approach like difficulty in identifying the drug target since the drug may show poly-pharmacology, the effective concentration being higher than the levels that can be achieved and obstacles of intellectual property rights, the drug repurposing is still a better approach due to its potential in reducing time and cost of research, skipping preclinical trials and the formulation units are already setup for large scale production.

One of the examples of repurposing is the use of a macrolide, azithromycin in the current COVID-19 pandemic, owing to its proposed anti-viral effects. Several macrolide antibiotics have been shown to have anti-inflammatory effects, demonstrated by inhibition of the production of pro-inflammatory cytokines *in vitro*.[4-10] This effect occurs *via* suppression of NF-κB activation in HBECs.[4,5,10] Reduction of cytokines, such as IL-6 and IL-8 can be an advantageous mechanism that leads to attenuation of airway inflammation. A possible mechanism of anti-RV activity of macrolides has been demonstrated as reduction of ICAM-1, the receptor of major group RVs. A range of studies have suggested that macrolides inhibit replication of both major and minor groups of RV.[5,7,8]

Previous evidence suggests that macrolide antibiotics have anti-inflammatory and antiviral effects. On investigation, it was found that the anti-viral potential of macrolides is through the induction of antiviral gene mRNA and protein Furthermore, azithromycin significantly reduced virus replication and release. The results demonstrated that azithromycin has anti-viral activity in bronchial epithelial cells and increases the production of interferon-stimulated genes.[11]

Studies of patients with idiopathic pulmonary fibrosis (IPF), a chronic fatal lung disease causing dyspnea and cough, found azithromycin to be beneficial.[12,13] Azithromycin has also been shown to improve lung function in patients of cystic fibrosis with pseudomonas infection, but the mechanism is not fully understood. Azithromycin might be acting through reduced bacteria's production of substances which are damaging to lungs of patients with cystic fibrosis.[14] In one of the studies, azithromycin therapy resolved *Haemophilus influenza* and *S. pneumonia* while low levels of *Pseudomonas aeruginosa* were still detected.[15] A dosage of 500 mg per day reversed small airway lesions, improved small airway stenosis, and decreased airway resistance.[16] Because these symptoms are quite similar to those noted with SARS-COV-2 infections, it is not surprising that azithromycin treatment was initiated early in the current pandemic of COVID-19.

Among several drugs investigated for anti-Ebola virus activity in vitro and in vivo, Azithromycin was found to be potent in vitro inhibitor of the Ebola virus. Small animal studies generated mixed results. In a particular studyl, treatment with 100 mg/kg azithromycin twice daily was initially associated with a 60% survival rate, compared with 20% for the control group. Repeat testing under identical conditions did not produce statistically significant results. In addition, a different treatment regimen with 210 mg/kg oral azithromycin was associated with a 0% survival rate. An efficacy screening using different doses of azithromycin on guinea pigs similarly did not yield positive outcomes.[17 Azithromycin has also been used against Zika virus infection.[18,19] Its use has been reported in a recent *JAMA* article, "Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China."[20]

Likewise, It has been previously used to treat Middle East Respiratory syndrome, although it was later found not to be significantly beneficial.[21] A popularly referenced study in France found that Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination and drug effect was significantly higher in symptomatic patients as compared to asymptomatic patients. But the conclusions must be guarded as this was a small study.[22] However, in another study, there were no significant differences in in-hospital mortality between patients who received hydroxychloroquine with or without azithromycin and patients who received neither drug.[23]

CONCLUSION

With the ever-increasing hurdles in the pharma industry, drug repurposing is the best solution to reduce the risks involved in new drug discovery. Lack of specific therapies with antiviral agent or vaccines is becoming a major medical threat. Repurposing or repositioning the existing FDA approved drugs will serve the need. The drug repurposing has already given very positive outcomes with the drugs which are repurposed successfully and also this approach can open new pathways to overcome the challenges with emerging viral threats and antiviral resistance. The whole world wants a cure or a vaccine for the raging pandemic which has not only killed more than 3.23 lakh people worldwide but also devastated the global economy. So, there have been efforts to speed up vaccine development. The process of creating a new vaccine is a slow and deliberative one, involving a lot of peer-reviewed and evidence-based research including years of clinical trials which take at least 10 years. So the thought, that we will have a vaccine in a year is by itself very positive and would require an unprecedented global effort.

While treatment of lung disease using azithromycin appears promising, it is important to check for a few things before prescribing this drug. 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.[24] Elderly patients are more at risk.

At present, there is insufficient evidence to recommend treatment with azithromycin alone or combined with hydroxychloroquin for novel coronavirus outside of research. Both can increase QT interval; combining these drugs may result in cardiovascular risks. Clinicians may wish to use azithromycin to treat bacterial superinfection in complicated COVID-19,in line with local /national treatment protocols.

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