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Opinion

Comprehensive Pharmacology of Azithromycin Repurposing for COVID-19

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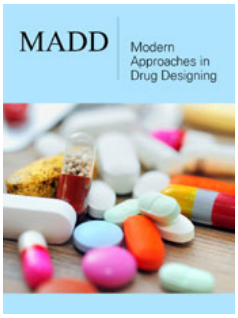

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Abstract

The theory behind the madness of azithromycin for the treatment of COVID-19 is unclear as no significant evidences are available till date. The present study aimed to discuss about the comprehensive pharmacology of azithromycin and to explore the preclinical and clinical evidences repurposing for COVID-19. Here we reviewed briefly the current knowledge about COVID-19, considering the potential explanation for the repurpose of azithromycin for this pandemic disease condition and global crisis. Azithromycin alone or in combination with Hydroxychloroquine (HCQ) modulate the anti-inflammatory processes and decreases the susceptibility to secondary bacterial pneumonia. We highlighted potential approaches to address repurpose of azithromycin for COVID-19.

Keywords: Azithromycin; Comprehensive pharmacology; Repurposing for COVID-19; Immunomodulatory activity; Combination therapy for COVID-19

Introduction

Azithromycin is a well-known broad-spectrum antibiotic amongst the macrolide group, primarily used for upper and lower respiratory tract infection [1]. Recently it is repositioned for the treatment of covid-19 pandemic [1]. However, some circumstantial scientific reports suggest that Azithromycin (AZ) in combination with hydroxychloroquine decrease the viral load in Covid patients [2]. The open level non- randomized clinical trial carried out by Gautret and co-workers stated that the patients treated with hydroxychloroquine and azithromycin had 100% recovery rate after 5-6 days, compare to 57.1% of subjects treated with hydroxychloroquine only, and 12.5% of untreated individuals [2]. There are some controversies about the use of AZ in Coronavirus disease (COVID-19) [3-4]. This article represents the research findings regarding the molecular pharmacology of AZ and how it is correlated for the treatment of COVID-19.

The immunomodulatory and antiviral properties of AZ and other macrolides was previously being established [5]. It is well known that coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered noble coronavirus [5]. Epithelial cells are the primary target of this virus and Infection is mediated by cellular expression of Angiotensin-Converting Enzyme 2 (ACE2), a carboxypeptidase that binds to the spike proteins of SARS-CoV-2; ACE2 is expressed by the epithelium of the mouth, tongue and upper airways, thus enabling endocytosis of the virus [6]. Severity and mortality of COVID- 19 are associated with host's uncontrolled inflammatory response due to the hyper production of reactive oxygen species and cytokines [7].

Macrolide antibiotics have promising activity against various respiratory viral disease reported in different studies. Azithromycin significantly reduced inflammatory cytokines such

as cytokines IL-6 and IL-8 and so far, increase the production of IFN -gamma and IFN -gamma stimulated genes expression established in Human bronchial epithelial cells in an *in vitro* condition [8]. AZ favouring tissue repair after inflammation by shifting helper T cell phenotype from type I to type II, reported by Murphy et al. [9] & [10]. Several studies have been reported about the anti-inflammatory activities of AZ. AZ significantly reduced the production of pro-inflammatory cytokines IL-12 and IL-6, increased production of the anti-inflammatory cytokine IL-10 as shown in Figure 1; [11]. Preclinical research found that AZ attenuated the accumulation of inflammatory cells in the lung tissue and significantly decreased the aggregation of macrophages, lymphocytes and neutrophils [11].

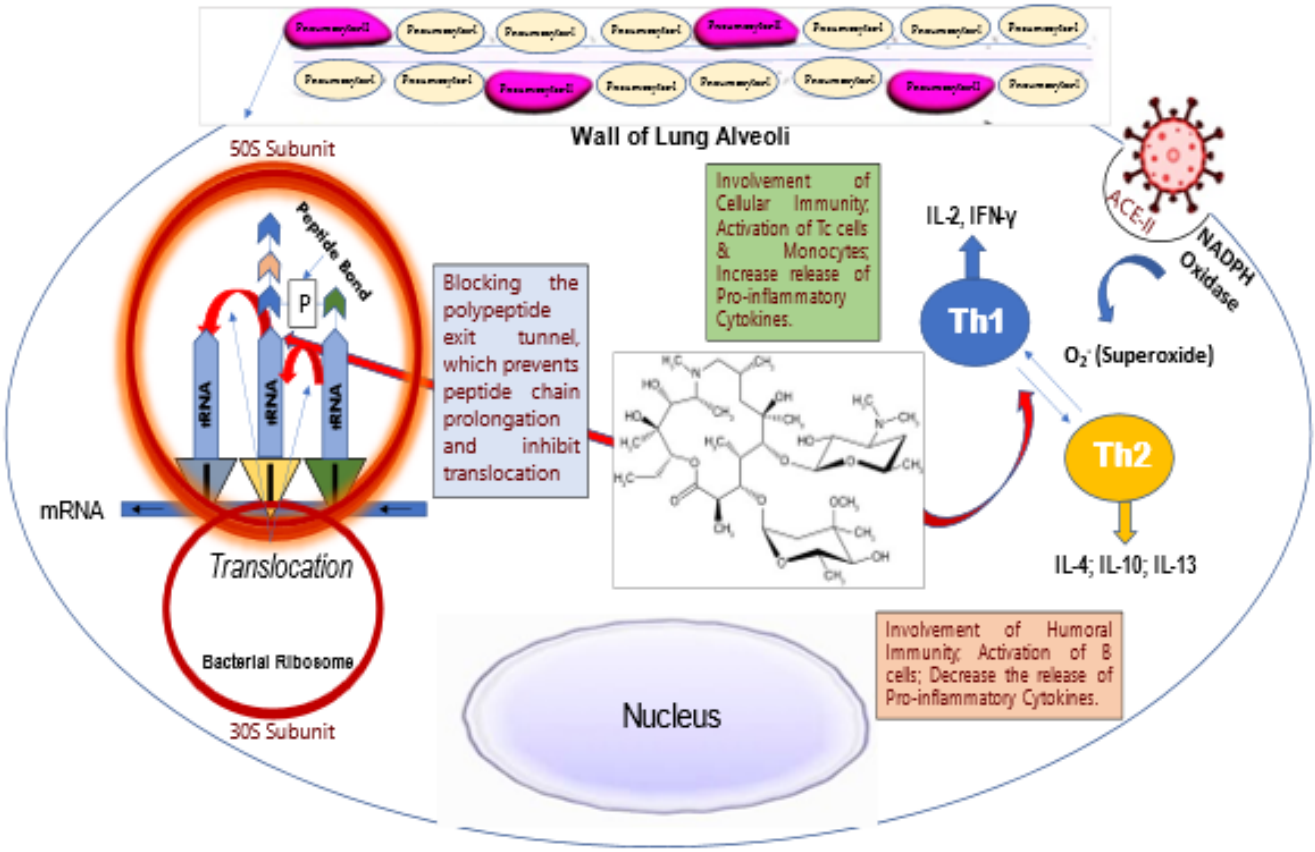

Figure 1: The schematic representation of Azithromycin mechanism of action for inhibiting the viral translation and the possible way of explaining the immunomodulating role of Azithromycin.

CD147 is a transmembrane receptor glycoprotein, present in host epithelial cell responsible for interaction with Covid-19 spike protein. Thus, it mediates the viral entry inside the host cell [12]. CD147 also present in RBC and inflammatory cells used as a receptor for parasite Plasmodium falciparum - protozoan that causes Malaria in humans and also regulates cytokine secretion and leukocytes chemotaxis. AZ interfere with the tight junction formation between spike protein and CD147 and prevents virus entry [13]. Previously it was reported that Az blocks the invasion of Plasmodium falciparum in RBC. AZ reduces the expression of CD147 reported by other studies. CD147 known as inducer of extracellular matrix metalloproteinase, and CD147 functions as an upstream stimulator of Matrix Metalloproteinases (MMP's). AZ exhibits reduced levels of MMP expression and activity, this may be associated to a reduced expression of CD147 in cells [12-14].

COVID-19 considerably shows some higher mortality rate in geriatric patients as it was reported that the highest mortality rate was observed in patients aged ≥80 years. Patients aged >80 years had 60% higher risk of dead compared to patients with age 70 to79 years [15]. It was also seen that patients aged eighty and older on ventilators, the fatality rate was 90 percent [15,16]. This arise the question is to whether there is any correlation between ageing and COVID-19 infection. Cellular "senescence" defined as a state in which cells cease dividing and undergo distinctive phenotypic alterations, including profound chromatin and secretome changes, and tumor-suppressor activation [17]. Senescence occurs throughout the lifespan including during embryogenesis and it plays very important role during development as well as wound healing [17,18]. There are certain kinds of biomarkers like CD26, ACE2 are express in senescent cell. Interestingly, these two receptors are used by COVID-19 for entering into the cell. Senescent cells produce large amounts of inflammatory cytokines, as a result of the senescence-associated secretory phenotype (SASP), including IL-6, increased protein synthesis, increased number of lysosomes. Corona virus uses the machinery of this cell which find

as ideal cell for their replication [18]. Azithromycin preferentially targets senescent cells, removing approximately 97% of them with great efficiency [19]. AZ also acts as an anti-inflammatory agent and reduces SASP mediators such as IL-1 beta and IL-6. Interestingly Az inhibits the replication of other viruses, such as Zika and Ebola [18-21]. It can be predicted that senolytic agent can be useful for the treatment of COVID-19. In clinical trial Az shows its efficacy against Covid-19, combinely with Hydroxychloroquine may be due to its senolytic activity. Although clinical trials are needed to establish this hypothesis and repurposing efforts of Az against Covid-19 [21,22].

There are some *in vitro* evidence that AZ may prevent replication of other viruses such as human influenza virus H1N1 and Zika virus. AZ and hydroxychloroquine combinedly inhibit the replication of SARS-CoVs 1 and 2 in *in vitro*, identified by Andreani et al. [23]. It was reported previously that AZ prevents the replication and release of Rhinovirus (RV1B & RV16) [24,25].

Conclusion

The review briefly explained the current knowledge about COVID-19, considering the potential explanation for the repurpose of azithromycin. Azithromycin modulates the anti-inflammatory processes by modulating the Th1 and Th2 cytokine level as mentioned schematically in Figure 1. and decreases the susceptibility to secondary bacterial pneumonia.

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