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Inhibiting inflammasome; the possible mechanisms of action of azithromycin against COVID-19?

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Abstract

Cytokine storm and destructive inflammation in the severe form of COVID-19 lead to acute respiratory distress syndrome (ARDS)/acute lung injury (ALI), and dysfunction of several different body organs in patients. SARS-CoV-2 contains all inflammasome-activating proteins belonging to SARS-CoV and MERS-CoV viruses. Macrolides are known to possess immunomodulatory properties. Given the desirable results of azithromycin treatment for patients with a severe case of COVID-19, based on studies, it could be concluded that the immunomodulatory properties of azithromycin to inhibit inflammasome can help the treatment of patients with this disease.

Key point

Recent studies imply the immunomodulatory properties of azithromycin to inhibit inflammasome which may help the treatment of COVID-19.

Inflammasome dysregulation has been observed in a wide range of inflammatory, autoimmune, and respiratory diseases. Besides, an increase in IL-1α, IL-1β, and IL-18 cytokines as downstream cytokines of inflammasome has been specifically shown in patients with chronic obstructive pulmonary disease (COPD) (1). Beta-coronaviruses of SARS-CoV and MERS-CoV viruses activate the inflammasome through various direct or indirect ways. According to protein modeling studies, SARS-CoV-2 contains all inflammasome-activating proteins belonging to the mentioned viruses. Cytokine storms and destructive inflammation in the severe form of COVID-19 lead to acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and dysfunction of several different body organs in patients (2). Therefore, clinical trials primarily aim to inhibit this type of inflammation using immunomodulators and immunosuppressants, such as tocilizumab, corticosteroids, and dozens of other drug combinations. In addition to their antibiotic activity, macrolides (a group of antibiotics) have a wide range of immunomodulatory properties. In this regard, researchers have confirmed the positive effects of different macrolides on the prevention of intensification of COPD and non-cystic fibrosis bronchiectasis and improvement of lung function in cystic fibrosis patients and the course of the disease in asthma patients (3). Macrolides are known to possess immunomodulatory properties. These drugs' effects on cytokine secretion from human monocytes have been assessed to understand their immunomodulatory properties better (4). Contrasting clarithromycin or roxithromycin, azithromycin effectively inhibits IL-1α and IL-1β secretion following lipopolysaccharide (LPS) stimulation. Intracellular accumulation of azithromycin applies its modulatory effects on cytokine secretion by interfering with Ca++ efflux. Azithromycin specifically affects IL-1β levels in the rat sepsis endotoxin model. This is the first report of the specific effect of azithromycin on the inflammasome/IL-1β axis. This property of azithromycin might affect inflammatory diseases such as COPD

or asthma (5). In a study, researchers evaluated the effects of azithromycin on NLRP3, NACHT, and PYD proteins as key components of the NLRP3 complex in human monocytes (THP-1). Besides, NALP3 and IL-1β protein levels were measured after treatment with azithromycin. The results confirmed the immunomodulatory effects of azithromycin applied through the destabilization of mRNA of key components of inflammasome complex (e.g., NLRP3) and decreased cytokine IL-1β secretion (6). To date, studies have shown the key role of macrophages originating from inflammatory monocytes in the pathogenesis of the severe form of COVID-19 (7). However, the respiratory tract's myeloid cells' composition is different in the severe form of COVID19 than the mild form. Healthy individuals and macrophages derived from inflammatory monocytes replace alveolar macrophages with immunomodulatory properties (8). The inhibitory effects of azithromycin on inflammasome (specifically on monocytes) can be a possible mechanism of azithromycin in treating patients with COVID-19. Mice with chronic lung infection of *Pseudomonas aeruginosa* were treated with azithromycin and placebo, and the severity of lung injury, cleansing of bacteria, and proteins associated with inflammasome were measured. Furthermore, activation of adenosine triphosphate (ATP) or flagellin-induced inflammasome in LPS-primed macrophages with or without macrolide treatment was assessed in vitro. Azithromycin treatment eliminated bacteria in rats with chronic *P. aeruginosa* lung infection, thereby decreasing pulmonary injury by reducing IL-1β and IL-18. In vitro, azithromycin and erythromycin inhibited the activation of NLRC4 and NLRP3 inflammasome. According to the results, azithromycin and erythromycin applied their immunomodulatory and anti-inflammatory effects by reducing inflammasome activation (9). Different body organ injuries occur due to infant inflammation caused by Toll-like receptor (TLR) signaling and activation of inflammasomes. A study assessed the impact of a combination of azithromycin, dexamethasone, and pentoxifylline drugs on the decrease of this inflammation. The results demonstrated the drugs' age-dependent inhibitory effects on TLR signaling and inflammasome in the blood from infants and adults in vitro (10). Severe and destructive inflammation is the leading cause of death in patients with SARS-CoV-2, a disease that has infected millions of people and has led to the death of thousands of people. Inflammasome dysregulation is a key factor for inflammation and several inflammatory diseases, including respiratory inflammatory diseases. Given the desirable results of azithromycin treatment for patients with a severe case of COVID-19, it could be concluded that the immunomodulatory properties of azithromycin or its ability to inhibit inflammasome and inflammation can help the treatment of patients with this disease.

Authors' contribution

ASB, MB and MMS were the principal investigators of the study. BK, and AKH were included in preparing the concept and design. MMS, MB and MAE revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. Authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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