Role of long-term azithromycin therapy for severe bronchial asthma

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Macrolides, including erythromycin, clarithromycin, and azithromycin, are one of the most widely used antibiotics.[1] They are commonly prescribed for acute respiratory infections.[2] The efficacy of the long-term use of macrolides has been documented for other chronic respiratory infections, i.e., chronic obstructive pulmonary disease and bronchiectasis.[3,4] In view of the well-known antibacterial, immunomodulatory, and potential antiviral properties of macrolides, they are likely to have a beneficial effect on chronic asthma and asthma exacerbations.[5]

Epidemiology studies have shown that *Mycoplasma pneumoniae* infection may worsen asthma symptoms and can produce wheezing in individuals who do not have asthma.[6] Among 51 children with a first asthmatic attack, acute *M. pneumoniae* infection was found in 50%. At follow-up, the patients infected with *M. pneumoniae* were more likely to have recurrent asthma than those without these infections. Among infected patients, recurrences tended to be rapid if the patient was not treated with a macrolide.[7]

The global initiative for asthma guidelines suggested to add macrolides as add-on treatment in patients who are nonallergic asthmatics (low type II inflammation).[8] The Saudi initiative for asthma guidelines has advocated the use of long-term macrolides in steroid-resistant asthmatics or those who are not eligible or able to use biological agents.[9]

Reiter *et al.* published a meta-analysis in 2013 on macrolides for the long-term management of asthma.[10] They concluded that there is a significant improvement in the peak expiratory flow, symptoms, quality of life, and airway hyperreactivity but not forced expiratory volume in one second. However, in this study, an exacerbation was not included.

In 2015, a Cochrane systematic review was done on the use of long-term macrolides in bronchial asthma.[11] Authors found 23 studies that had been published for the past similar review in 2007. They reported that 1513 participants received either macrolide or placebo. There were major concerns about the difference between methods and results among different studies which were reflected on the quality and reliability of the outcomes. However, the authors showed that macrolides were not better than placebo for most of the important outcomes they looked at such as exacerbations requiring hospital admission or treatment with oral steroids. However, they may have some benefits on symptom scale and lung functions. There were no reports of serious side effects of macrolides, but 16 studies did not say whether any occurred.

Brusselle *et al.* published a multicenter randomized, double-blind, placebo-controlled trial on the use of azithromycin for the prevention of exacerbations in severe asthma known as AZISAST.[12] Over 26 weeks and using azithromycin at a dose of 250 mg twice weekly on 109 patients, they noted a significant improvement in the Asthma Quality of Life Questionnaire score. There was no significant difference between

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the control and treated group for the primary endpoints (rate of severe exacerbations and lower respiratory tract infections). However, when they considered only patients with noneosinophilic asthma, there were less exacerbations in this group.

More recently, Gibson *et al*. have published another randomized, double-blind, placebo-controlled trial on the effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma known as AMAZES study.[13] Over 48 weeks and using 500 mg twice a week for 420 patients, authors found that compared to placebo, the treated group have shown a significant reduction in the number of exacerbation rate, annual asthma exacerbations rate, and the percentage of exacerbation free days that is better in eosinophilic patients. They also showed improved asthma-related quality of life. The study excluded patients with hearing impairment or the QT interval prolongation. Diarrhea was the most common side effect reported (34% in the treatment group vs. 19% in the placebo group).

In our view, azithromycin is effective in preventing asthma exacerbations when inhaled corticosteroids and long-acting beta 2-agonists are not enough, and the use of biologic drugs is not feasible or ineffective. Benefits include the reduction of reported symptoms, improved quality of life scores, and reduction of exacerbations as well as improved pulmonary function tests. These benefits are likely to be mediated by preventing respiratory infections, enhancing viral inactivation, and anti-inflammatory effects of macrolides. Long-term azithromycin therapy is to be reserved for patients at highest risk for exacerbations and preferably restricted to months of autumn and winter when most respiratory viral infections occur. It is best used for patients with frequent exacerbations who are not candidates for biologics therapy; for example, neutrophilic asthma, and in situations where biologic drugs are not available or unaffordable.

The long-term antibiotics resistance is a concern and needs to be addressed in future studies.[14] Azithromycin is a safe drug with diarrhea as the most frequently reported side effect. Before the initiation of the drug, a precautionary measure is to exclude patients with prolongation of QT interval and/or hearing impairment. The ideal dose is 500 mg three times per week for 48 weeks.

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Conflicts of interest
There are no conflicts of interest.

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