

Macrolides for treatment of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a common disease characterized by continued airflow limitation that is caused by inflammation and autoimmune response. Acute exacerbation of COPD (AECOPD) will increase risk of death, result in a more rapid decline of lung function, and reduce quality of life. COPD inflammation is not only limited to the lungs, but also involves multiple organs, leading to coronary heart disease, depression, skeletal muscle atrophy, and other systemic complications. Clinical study showed that long-term macrolide could reduce the frequency of AECOPD.^[1] However, there are still some controversies and concerns on side effects such as drug resistance, cardiac toxicity, and hearing impairment caused by long-term macrolide therapy for COPD.

Clinical Studies on Effects of Macrolides on COPD

The idea of long-term macrolide therapy for COPD was derived from the successful treatment in reducing exacerbation and improving lung function of cystic fibrosis, diffuse panbronchiolitis, and other chronic respiratory diseases.^[2-7] Some randomized trials showed that macrolide therapy reduced AECOPD.^[8-10] A systematic review summarized evidences on effectiveness and safety of prophylactic or erythromycin for reducing the frequency of AECOPD.^[11] A retrospective study found that azithromycin significantly reduced AECOPD and hospitalizations of severe COPD patients.^[12] Our study showed that long-term use of low-dose erythromycin could reduce the interleukin-8 level in sputum of COPD patients and significantly reduce the number of acute exacerbations.^[13] Han *et al*^[14] found that azithromycin seemed to be more effective in older patients who had milder disease and there was no effective treatment for inactive smokers. In 2014, a systematic review showed that long-term antibiotic therapy reduced AECOPD but it remained unclear which kind of COPD patients to be the target.^[15] In clinical subgroups

study, taking azithromycin (250 mg daily) was more effective in elder COPD patients and the patients with milder Global Initiative for COPD stages. Gender or oxygen therapy had no significant efficacy on COPD.^[14]

Anti-inflammatory Mechanism of Macrolides on COPD

The mechanism of COPD inflammation is complex and remains unclear.^[16,17] Kanoh *et al*^[18] reported that macrolides decreased mucus secretion and the levels of neutrophils and macrophages in airway through inhibiting production of proinflammatory cytokines, adhesion molecules, and chemokines.

Besides, our study found that erythromycin could reduce inflammatory effect of COPD and inhibit corticosteroid resistance induced by cigarette smoke extract through inhibition of phosphatidylinositol 3'-kinase- δ /Akt pathway and increased histone deacetylase 2 expression.^[19] Besides, recent studies showed that there was imbalance of T lymphocyte in COPD patients and the abnormal immune response in cigarette-induced mice were partly corrected by macrolides.^[20,21] These abnormal immune responses of mice exposed to cigarette smoke could be partly corrected by erythromycin.^[22] Therefore, these results indicated that macrolides could inhibit inflammatory interleukins and immunomodulatory effects and reduce corticosteroid resistance in COPD treatment. However, the mechanism of macrolides is complex and remains unclear. Deeply exploring and confirming the mechanism can bring benefit for COPD patients.

Macrolides in Guidelines

Long-term use of macrolides has been recommended by recent society guidelines for COPD treatment. Recent guideline of European Respiratory Society and American Thoracic Society recommended that long-term macrolides

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therapy could be used for the COPD patients who have more than once moderate-to-severe acute exacerbation in the past year to reduce acute exacerbations besides inhalation therapy. The 2017 Global Initiative for COPD suggested that the patients of group D with smoking history have exacerbations despite appropriate therapy, macrolides can be considered (evidence B), and azithromycin (250 mg/d or 500 mg three times per week) or erythromycin (500 mg two times per day) for 1 year reduces the risks of exacerbations in patients prone to exacerbations.^[23] In our study, we treated COPD patients with erythromycin (125 mg/d) and found that the treatment could inhibit airway inflammation and reduce AECOPD.^[13] Macrolides can be given to prevent AECOPD in the patients who have a history of many/repeated acute exacerbations. However, there are still some problems on the clinical application of macrolides in COPD, which needs further and deeper studies.

Controversy of Long-Term Use of Macrolides in COPD Patients

Current evidences supported that continuous macrolides prophylaxis is associated with a clinically significant reduction in COPD exacerbations, and it appears to be a cost-saving strategy. However, long-term adoption of macrolides in COPD has attracted concerns and controversies regarding its adverse effects such as hearing impairment, arrhythmia, and antibiotic resistance.

Safety of Long-Term Use of Macrolides

A retrospective cohort study showed that during 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths. Compared with amoxicillin, there were 47 additional cardiovascular deaths per 1 million courses of azithromycin therapy; for patients in the highest decile of baseline risk of cardiovascular disease, there were 245 additional cardiovascular deaths per 1 million courses.^[24] Thus, the US Food and Drug Administration recommended careful review of patient-level risk factors for ventricular arrhythmias when using azithromycin.^[25] The other side effects of macrolides are gastrointestinal symptoms such as hearing decrement and diarrhea.^[26] Hearing decrement is the leading cause of early withdrawal from the study, however, hearing as assessed by audiometry returned to baseline in about one-third of patients.^[10] Considering the side effects of macrolides, we recommended to use smaller dose to treat COPD patients.

Incidence of Adverse Effects

For long-term use of azithromycin in COPD, the incidence of adverse effects is unknown. Albert *et al*^[10] demonstrated no increased risk of cardiac arrhythmias over a study period of 1 year with use of daily azithromycin compared with placebo. Published study indicated that the large majority of patients experiencing cardiac arrhythmias from macrolides had coexisting risk factors and that the incidence of arrhythmias in the absence of coexisting risk factors was very low, perhaps less than one in 100,000 patients.^[27] This risk has been overestimated and

suggested an approach to patient evaluation that should reduce the relative risk and the incidence of arrhythmias to the point that chronic macrolides can be used safely in the majority of patients for whom they are recommended.^[25]

Long-Term Use of Macrolides and Microbial Resistance

Another considered that the wide use of maintenance macrolides therapy in COPD would result in microbial resistance in community populations. In view of large patient population affected by COPD, the widespread use of macrolides, especially azithromycin, may greatly affect population macrolides resistance in the community, but published studies showed that no evidences indicated the spread of drug-resistance bacteria, which needs longer and further studies to monitor the macrolides resistance in patients with severe COPD and determine their effects on the microbial as a whole and on the lower airway inflammatory response.

Perspective

Macrolide therapy could reduce the rate of COPD exacerbations, increase the time to next exacerbations, and improve quality of life. There is uncertainty about the risk of serious adverse effects of long-term macrolide therapy in COPD. The mechanism of macrolides therapy on COPD is anti-inflammatory effect, but some researchers believed that macrolides had antibacterial effect and could regulate airway microbiota. Besides, drug resistance in China is different from European and American countries. Resistance rate of macrolides has been up to 80%. For these reasons, further clinical researches are needed to better understand the mechanism of macrolide therapy in COPD patients and their effects on the lower airway inflammatory response.

The pathogenesis of COPD is airway and lung inflammation. Theoretically, anti-inflammatory drugs can fundamentally control the progression of COPD, but glucocorticoids are far from achieving this goal. Therefore, long-term use of macrolides may be beneficial for COPD patients. The future direction of COPD study is developing a kind of macrolides that can modify the immune response without antibiotic effects.

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Conflicts of interest

None.

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