Editorial

Advantages and drawbacks of long-term macrolide use in the treatment of non-cystic fibrosis bronchiectasis

Li-Chao Fan, Jin-Fu Xu

Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China
Correspondence to: Jin-Fu Xu, MD, PhD. Shanghai Pulmonary Hospital, Tongji University School of Medicine, No. 507 Zhengmin Road, Shanghai 200433, China. Email: jfxucn@gmail.com.

Abstract: Non-cystic fibrosis (non-CF) bronchiectasis is a respiratory disease characterized by persistent airway inflammation and dilation of bronchial wall driven by various causes. Patients with bronchiectasis suffer from excessive sputum production, recurrent exacerbations, and progressive airway destruction. Major therapy for bronchiectasis is focused on breaking the "vicious cycle" of mucus stasis, infection, inflammation, and airway destruction. Growing evidences have been shown that macrolides possess immunoregulatory and anti-inflammatory functions beyond their antimicrobial effects. Macrolide antibiotics have been effectively used in the treatment of diffuse panbronchiolitis, CF and bronchiolitis obliterans syndrome. Currently a number of clinical trials were performed to assess macrolide treatment in the management of non-CF bronchiectasis. The purpose of this paper is to review the efficacy and potential risks of these recent studies on the use of macrolides in non-CF bronchiectasis.

Keywords: Macrolides; bronchiectasis; advantages; drawbacks

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Non-cystic fibrosis (non-CF) bronchiectasis is an inflammatory respiratory disease characterized by chronic bacterial infection, and irreversible dilation of the bronchial walls. Some patients with bronchiectasis often suffer from chronic cough, excessive sputum production, and recurrent exacerbations. Left untreated, non-CF bronchiectasis is always associated with a very poor prognosis (1).

In clinical practice, the prevalent access to high-resolution computed tomography (HRCT) has resulted in the increased diagnosis of non-CF bronchiectasis cases. Trends in bronchiectasis diagnoses in the United States indicated the detection of 1,106 cases per 100,000 individuals, with an annual percentage increase of 8.74% (2). Further, the average annual hospitalization rate was 9.4 per 100,000 residents in Germany during 2005-2011, with the highest rates, 39.4 hospitalizations per 100,000 individuals, apparent among men aged 75-84 years (3). Until now, no accurate prevalence data was available to quantify the incidence of bronchiectasis in developing countries. However, morbidity rates in developing countries are typically elevated due to the inherently high burden of infectious disease.

Interventions for the management of bronchiectasis include treatment of the underlying disease, management of infections, promotion the clearance of mucus stasis, and the bolstering of immunity to break the "vicious cycle" (4). Evidence has indicated that 14- and 15-membered ring macrolides possess immunomodulation and anti-inflammatory functions beyond their antimicrobial properties (5). The underlying mechanisms that account for the anti-inflammatory actions of macrolides have not yet to be elucidated, and the activities do not appear to be controlled by a single mechanism. Nevertheless, investigations have shown that macrolides down-regulate cytokine production by blocking the activation of nuclear factor kappa B (NF-kappaB), and the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2). Likewise, the ability of macrolides to mediate the innate and adaptive immune responses by inhibiting neutrophil activation has been demonstrated (6).

As early as 1984, the effectiveness of macrolides for the treatment of inflammatory disease was apparent, as the

administration of erythromycin to patients with diffuse panbronchiolitis (DPB) led to dramatic increases in 10-year survival rates from 10-20% to over 90% (7). Further, published reports have demonstrated that macrolides provide compelling benefits in the treatment of DPB, CF, COPD and bronchiolitis obliterans syndrome (8-11). Currently, a number of clinical trials have elucidated the effects of macrolides in the treatment of non-CF bronchiectasis. Findings from studies have shown that when used as chronic maintenance therapies, macrolides could reduce the frequency and duration of infectious exacerbations, as well as decrease the volume of sputum production, improve quality of life, and attenuate lung function deterioration. However, prior studies have also indicated that the number of side effects, as well as resistance to macrolides, increased among treatment groups.

Studies have reported that long-term treatment with macrolides can decrease the frequency of pulmonary exacerbations. A randomized, doubled-blind, placebo-controlled trial involving the administration of azithromycin (500 mg) 3 times a week for 6 months resulted in a 62% relative reduction in the rate of exacerbations, compared to rates apparent following treatment with a placebo. The improvements continued for a 12-month period, and corresponded to a 42% relative reduction in the annual rate of exacerbations following treatment with azithromycin (P<0.0001). Additionally, the median time to a first exacerbation was 239 days in the azithromycin treatment group and 85 days in the placebo group (RR =0.44; 95% CI, 0.29-0.65; P<0.0001) (12). Another randomized, doubled-blind, placebo-controlled study reported that the number of exacerbations was significantly diminished following the daily administration of azithromycin (250 mg) for 12 months. The percentage of patients who had at least one exacerbation was reduced 33.5% in the azithromycin-treated group compared to treatment with the placebo (13). The time to a first exacerbation was also prolonged in the azithromycin group. In the pivotal Bronchiectasis and Low-dose Erythromycin Study (BLESS) conducted by Serisier and colleagues (14), 117 patients (58 placebo, 59 erythromycin) were randomized into groups that received either erythromycin ethylsuccinate 400 mg (250 mg erythromycin base) twice daily, or a placebo for 48 weeks. The results of the study demonstrated a significant reduction in the incidence of protocol-defined pulmonary exacerbations (PDPEs) in the erythromycin-treated group (1.29 in the treatment group *vs.* 1.97 in the placebo group, P=0.003). A well designed multicenter study involving 99 children who had been diagnosed with either bronchiectasis or chronic suppurative lung disease, and received either azithromycin (30 mg/kg) or a placebo once a week for up to 24 months, found improvement in pulmonary exacerbations (15). A limited number of clinical studies involving a small number of samples also investigated macrolides in bronchiectasis. The results of a recent meta-analysis that assessed the long-term use of macrolides for the treatment of non-CF bronchiectasis revealed a decrease in the number of participants with exacerbations (RR =0.70; 95% CI, 0.60-0.82), as well as a reduction in the average number exacerbations per participant of –1.01 (16). Taken together, the evidence has suggested that long-term treatment of bronchiectasis with a macrolide may be associated with an attenuated frequency of exacerbations.

At present, whether prolonged macrolide therapy possess beneficial effects on the improvement of pulmonary function is ambiguous. Erythromycin significantly attenuated the decline in the post-bronchodilator forced expiratory volume at the end of the first second of forced expiration (FEV1) percent predicted value (change from baseline =–1.6 in the erythromycin group and –4.0 in the placebo group, P=0.04) (14). In the bronchiectasis and long-term azithromycin treatment (BAT) randomized controlled trial, the percent of predicted FEV1 increased 1.03 per 3 months in the azithromycin group, and decreased 0.10 per 3 months in patients receiving the placebo (P=0.047). Additionally, the changes in percent of predicted forced vital capacity (FVC) were directly correlated to changes apparent in FEV1 (13). The results of the EMBRACE study also suggested a trend in the attenuation of lung function deterioration associated with azithromycin treatment, despite the lack of statistical significance (12). Interestingly, Diego and colleagues (17) did not detect significant improvement in FEV1 or FVC in patients treated with azithromycin compared to controls. As well, a small open-label, crossover-design study involving eleven patients who received routine medications and azithromycin 500 mg twice weekly for 6 months, reported no significant difference in lung function during azithromycin therapy, or in the control phase (18). Differences in macrolide doses, duration of treatment, and sample size could explain the discrepancies apparent in previously published findings. Results of prior studies suggest the efficacy of macrolide therapy in the improvement of pulmonary function was modest. Future, well-designed, studies that involve a large number of participants are required to assess macrolide effectiveness to lung function. Additional considerations

include the potential stratification of patients with different exacerbations, as well as including individuals with persistent *Pseudomonas aeruginosa* infections.

The results of macrolide clinical trials also suggested an improvement in sputum characteristics. The mechanism by which macrolides inhibit mucus secretion is thought to be through the suppression of mucin synthesis by inhibition of MUC5AC and MUC2 genes (19). In associated studies, the administration of 250 mg of azithromycin 3 times per week for 3 months in 30 patients with stable non-CF bronchiectasis resulted in a significant decrease in sputum volume [mean (SD), –8.9 (1.8) *vs.* 2.1 (3.4) mL] (17). In the BLESS trial, erythromycin significantly reduced the 24 h sputum volume from baseline values, compared with volumes in the placebo group (median difference =–4.3 g, IQR =–7.8 to –1, P=0.01). Further, the results of a randomized, double-blind, placebo-controlled study involving 25 children (1:1 ratio) treated for 12 weeks with roxithromycin (4 mg/kg, twice a day), or a placebo, indicated treatment with roxithromycin significantly improved the sputum purulence and leucocyte scores after 6 weeks (20). Another randomized double-blind study involving 21 patients who received erythromycin (500 mg) or a placebo twice daily, reported improvement in 24 h sputum volume, but no change in sputum pathogens, leukocytes, interleukin-1α (IL-1α), IL-8, tumor necrosis factor-α (TNFα), or leukotriene B4 (21).

The clinical effects of macrolide treatment on quality of life assessments were varied. In the BAT randomized controlled trial, quality of life, when measured by the St. George Respiratory Questionnaire (SGRQ) and the lower respiratory tract infection visual analog scale (LRTI-VAS) score, was significantly improved in patients receiving azithromycin compared to those receiving only a placebo (13). Similarly, a meta-analysis suggested that the SGRQ total scores were significantly reduced in the macrolide treated group compared with controls (weighted mean difference =–5.39; 95% CI, –9.89 to –0.88; P=0.02) (16). Conversely, in the EMBRACE study, a significant reduction in SGRQ component scores of azithromycin group symptoms was observed at 6 months when compared with symptoms associated with placebo administration, but no significant differences were noted at 12 months (12). Finally, the administration of erythromycin did not significantly alter Leicester cough questionnaire scores, or SGRQ scores, in the BLESS study (14). Consequently, the need for further investigations to determine the optimal duration of macrolide therapy to achieve maximal anti-inflammatory properties is patently clear.

In addition to varied outcomes related to efficacy, there are existing safety concerns associated with the use of macrolides for maintenance therapy. The main adverse events reported include nausea, vomiting, diarrhea, and abdominal pain. In the EMBRACE trial, there was a significantly increased number of complaints regarding gastrointestinal symptoms in the azithromycin group compared to the placebo group (P=0.005). Similarly, in the BAT trial, patients receiving azithromycin exhibited a higher risk of developing diarrhea (relative risk =8.36; 95% CI, 1.10-63.15) and abdominal pain (RR =7.44; 95% CI, 0.97-56.88). Other adverse effects including rash, auditive complaints, itching, heart palpitations, hearing decrement and headaches were comparable between the treated and placebo groups.

Macrolide use also raises concerns over the associated induction of prolonged QTc intervals, which serve as an indicator of ventricular tachyarrhythmias, including Torsades de pointes (Tdp). In the BLESS trial, no differences existed between the placebo and erythromycin groups in terms of prolonged QTc intervals or induced cardiac arrhythmia over the course of the study. However, electrocardiograms (ECG) should be closely monitored, and the co-administration of other known QT-prolonging agents (such as ciprofloxacin, moxifloxacin) should be avoided during the use of macrolides, in order to prevent the development of potential cardiovascular events.

Another primary concern that limits the long-term use of macrolides is the introduction of potential selective pressures for the development of resistant strains of bacteria. In the BLESS trial, the percentage of macrolide resistant commensal oropharyngeal streptococcal species was significantly increased in patients receiving erythromycin treatment. Likewise, azithromycin exhibited a high associated risk of macrolide resistant pathogens in the BAT trial (88% *vs.* 26%, P<0.001). Although macrolide resistance was not routinely tested in the EMBRACE trial, 4% of participants still developed macrolide-resistant *Streptococcus pneumoniae* in the azithromycin treatment group. The proportion of azithromycin-resistant bacteria in Valery's trial (15) was of 46% compared 11% in the placebo group (P=0.002). Consequently, a potential apprehension related to the increased use of long-term macrolides therapy is the risk of the emergence of drug resistant pathogens in the surrounding community (22). Although macrolides are the most important regimens in the treatment of NTM, macrolides monotherapy was not recommended owing to the risk for developing macrolide resistance (23,24). Patients with bronchiectasis should excluded NTM infection

for the use of long-term macrolides treatment. Thus, attention should be directed to EM703 and CYS0073, the new class of macrolides currently in development that possess anti-inflammatory actions but lack anti-bacterial properties (25,26).

In conclusion, macrolide maintenance therapy could improve the frequency of exacerbations, sputum volume, and lung function in patients with inflammatory respiratory disease. Considering the published evidence, the potential for using long-term low-dose macrolides to treat non-CF bronchiectasis is patently clear. However, the introduction of selective pressures for microbial resistance, and the adverse effects associated with macrolide maintenance therapy, may ultimately limit the use of macrolide antibiotics in clinical practice. A balance between apparent clinical benefits, and the potential development of pathogen resistance to macrolides and associated adverse events should be weighed carefully. Regarding the long-term treatment of chronic inflammatory respiratory diseases, investigations are needed into the application of novel, synthetically derived macrolides that retain the anti-inflammatory function, but reduce the risk of microbial resistance. Additional randomized controlled trials involving larger patient populations are likewise warranted, to confirm the appropriate dosage and duration of macrolide therapy, and to benefit non-CF bronchiectasis patients.

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