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Effectiveness and safety of macrolides in bronchiectasis patients: A meta-analysis and systematic review

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ABSTRACT

Purpose: Macrolides has been studied as a potential therapeutic anti-inflammatory agent for bronchiectasis patients, which has used as an immunoregulation agent. However, the efficacy and safety results of macrolides across available randomized controlled trials (RCTs) are controversial. The aim of this systematic review is to evaluate the efficacy and safety of macrolides in bronchiectasis.
Methods: RCTs of macrolides treatment for the patients of bronchiectasis published in PubMed and Cochrane Library were searched. Two authors independently extracted data and assessment the methodological quality. The primary efficacy outcome was the impact on the number of pulmonary exacerbation. Safety outcomes included adverse events and mortality.
Results: Seven RCTs were found in the systematic review and six studies were included in the present meta-analysis. Macrolides treatment showed a significant reduced rate of pulmonary exacerbation (RR = 0.55, 95%CI = 0.43–0.70) compared with control groups. However, subgroup analysis failed to find any significant changes in total 46 patients (RR = 0.20, 95%CI = 0.03–1.58) for treatment not more than 3 months. The incidence rates of total adverse events showed no significant difference among the macrolides group and control groups.
Conclusions: Long-term treatment of bronchiectasis with macrolides can reduce incidence of pulmonary exacerbation, especially in the subgroup treatment 6 months or more. There was no evidence of increased adverse events with macrolides. However, to verify the best macrolides regimen, more studies based on larger sample size and stratified by ethnicity are still needed.
Chemical compounds studied in this article: Erythromycin (PubChem CID 12560); Azithromycin (PubChem CID: 447043); Clarithromycin (PubChem CID: 84029); Roxithromycin (PubChem CID: 5480431).

1. Introduction

Bronchiectasis is generally considered to be permanent dilation of bronchi and bronchioles, characterized as chronic bacterial infection, recurrent pulmonary exacerbations, and neutrophil airway inflammation [1]. Bronchiectasis is mostly caused by infection; the number of cases has decreased gradually since a wide range of antibiotic treatment and vaccines used. As the high-resolution computed tomography scanning was widely used in diagnosis, there was a seeming increase prevalence of bronchiectasis [2].

Structural abnormality of the bronchi and damage of bronchial epithelium would lead to deficient mucociliary clearance and retention of secretions. The result was the lower airways chronic bacterial infection and inflammation [3]. *Pseudomonas aeruginosa* was the most frequently pathogen isolated from bronchiectasis patients. Chronic respiratory infection might accompany with progressive decline in lung function [4], impaired quality of life [1,5] and increased mortality [6,7]. Thus, the aims of treatment of bronchiectasis are: treatment of primary disease, adequate drainage of sputum, reduced respiratory infection and chronic inflammation [3].

Abbreviations: RCTs, randomized controlled trials; CF, cystic fibrosis; CBM, Chinese Biomedical Literature Database; CNKI, Chinese National Knowledge Infrastructure; RR, risk rations; CRP, C-reactive protein; SGRQ, St. George's respiratory questionnaire; PFTs, pulmonary function tests; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity.

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Over recent decades, many new treatment strategies against respiratory tract infections and inflammation such as inhaled dornase alfa, and long term macrolides maintenance therapy are the most highly recommended therapies for chronic cystic fibrosis (CF) [8]. Since beneficial effects such as decrease in acute pulmonary exacerbations, improvement lung function was demonstrated with macrolides in CF, a disease with many similarities to bronchiectasis. Several studies have confirmed the benefits of macrolides in bronchiectasis, but these studies had very small sample of patients in both the treatment and placebo groups. Therefore, the efficacy and safety of macrolide therapy for non-CF bronchiectasis are examined in a systematic manner.

2. Methods

2.1. Data sources

Studies were identified from the databases of PubMed, Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Clinical Trials Gov and Cochrane Register of Controlled Trials (updated each new issue of The Cochrane Library), with the last report up to May 2013. We combined keywords macrolides or erythromycin or azithromycin or clarithromycin or roxithromycin with non-CF bronchiectasis. No language and date restrictions, limited to randomized-controlled trials (RCTs) only. In addition, abstracts presented in conferences were not searched for.

2.2. Study selection

Two reviewers independently searched the literature to be included in the meta-analysis. Any disagreement was resolved by discussion with arbitration from the third reviewer. We included randomized controlled trials that assessed the long-term effects of macrolides treatment on acute pulmonary exacerbation, lung function, and other clinical outcomes in patients with bronchiectasis. The trial was included, if it studied the role of macrolides in comparison with placebo, another antibiotic class or another macrolide. Trials that were non-randomized, focusing on pharmacokinetic or pharmacodynamic and comparing the same macrolide at different dose were excluded.

2.3. Data extraction

Two authors independently extracted data from included studies and the following data were extracted: year of publication, country of origin, characteristic of patients, antimicrobial agents and dosages, clinical events, adverse events. Any disagreements were resolved by consensus.

2.4. Quality assessment

The methods review quality of each RCT included in the analysis was according to Jaded score. This scoring system takes into account details of randomized, generation of random number, details of double-blinding procedure, allocation concealment and reporting of withdrawals or dropouts [9]. One point was awarded for the specification of each of the above criteria, with a maximum score of five. Thus, definition scored three or more points as high-quality RCTs.

2.5. Outcomes analysis

The primary efficacy outcome of this meta-analysis was the number of acute pulmonary exacerbations. The number of acute pulmonary exacerbation has been used as markers of disease severity and to predict disease progression [2]. We defined acute pulmonary exacerbation as new deterioration in pulmonary symptoms and requiring treatment with antibiotics. The secondary efficacy outcome was impact on lung function deterioration, change in the 24 h sputum volume, sputum microbiology profile, macrolides resistance, changes in inflammation markers, impact on patients' quality of life and adverse events. Outcomes on effective were analyzed group by length of follow-up.

2.6. Statistical analysis

Statistical analysis was done with Stata vision 11.0 software packages. The presence of heterogeneity between studies was evaluated with the Q- and I^2-statistics [10]. Heterogeneity was considered significant for $P < 0.10$. $I^2 = 100\% \times (Q - \mathrm{df})/Q$ [11], I^2 values of 25%, 50% and 75% were defined as low, moderate and high estimates, respectively. When a significant Q-statistic ($P < 0.10$), the random effects model was used for meta-analysis, otherwise, we used fixed effects model. Risk rations (RR) for dichotomous variables with 95% confidence intervals were calculated in this meta-analysis.

The publication bias was assessed by the Egger regression method [12], which used a linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the RR.

3. Results

3.1. Randomized controlled trial selection

The initial search of the database produced 24 potentially relevant studies. Seven articles lacked randomized control designs were excluded. Then, eight studies were excluded due to meta-analysis or review article itself. And the rest nine studies were reviewed in detail and found two of them were study protocol [13,14]. Thus, seven RCTs were included in this review (Fig. 1).

The characteristics of the seven selected studies are shown in Table 1[15–21]. All RCTs had a high jaded score more than three points; one of them was cross-over trail with one month washout period [17]. The study by Wong et al. reported treatment with azithromycin for 6 months and follow up for 12 months, the first 6 months following up results were recorded. Four RCTs included in the study used azithromycin in the treatment group, two RCTs used erythromycin and one used roxithromycin. There was no evidence showed that the efficacy had a significant difference between the different types of antibiotics; in our study, we treated them as the same kind of treatment design in the meta-analysis. Populations in the analysis were mainly adult, only one of the trails evaluated in children [15]; the period of following up ranged from 8 weeks to 52 weeks. *P. aeruginosa* and other pathogens were isolated from patients' sputum.

3.2. Primary efficacy outcome

All seven selected studies reported pulmonary exacerbation. A pulmonary exacerbation was considered to have occurred when the participant required antibiotic administration for a sustained deterioration in respiratory symptom. Acute pulmonary exacerbations were recorded in a number of ways. With data from six studies [15–20], it was possible to calculate the number of patients who had at least one exacerbation. Therefore, the number of patients was calculated from 409 patients in the six studies (Table 2, Fig. 2). Macrolides treatment group harvested statistically significant reduction in the number of pulmonary exacerbation compared with placebo group (RR = 0.55, 95%CI = 0.43–0.70). The subgroup