Macrolide Therapy Decreases Chronic Obstructive Pulmonary Disease Exacerbation: A Meta-Analysis

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Key Words

Chronic obstructive pulmonary disease · Exacerbation · Macrolide · Meta-analysis

Abstract

Background: Macrolide antibiotics have anti-inflammatory effects, and long-term administration may reduce chronic obstructive pulmonary disease (COPD) exacerbations. **Objective:** To investigate the effects of long-term treatment of macrolide therapy for COPD. **Methods:** We searched the PubMed and Embase databases to identify randomized controlled trials that evaluated the effect of macrolide therapy (of at least 2 weeks) for COPD. The primary outcome assessed was the frequency of acute exacerbations during follow-up. **Results:** Six trials involving 1,485 COPD patients were included in the analysis. Analysis of the pooled data of all 6 trials showed that macrolide administration reduced the frequency of acute exacerbations of COPD [risk ratio (RR) = 0.62; 95% CI 0.43–0.89, $p = 0.01$]. Subgroup analysis showed that only erythromycin might be associated with decreased COPD exacerbations (erythromycin: $p = 0.04$, azithromycin: $p = 0.22$, clarithromycin: $p = 0.18$). Moreover, macrolide therapy for 3 months did not significantly reduce the number of exacerbations ($p = 0.18$), whereas a beneficial effect was conclusive in

the 6-month ($p = 0.009$) and 12-month ($p = 0.03$) treatment subgroups. In addition, nonfatal adverse events were more frequent in the macrolide treatment groups than in the controls (RR = 1.32; 95% CI 1.06–1.64, $p = 0.01$). However, related clinical factors had no influence on the overall result ($p = 0.19$). There was no publication bias among the included trials. **Conclusions:** Macrolide therapy was effective and safe in decreasing the frequency of exacerbations in patients with COPD. Treatment might provide a significant benefit but only when therapy lasts more than 6 months.

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Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways characterized by airflow limitation which is progressive and not fully reversible [1]. Standard therapies for COPD include bronchodilators and anti-inflammatory agents such as high-dose inhaled corticosteroids. Long-term use of a bronchodila-

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tor improves symptoms and the ability to exercise but may not slow down progressive reduction in lung function. High-dose corticosteroid inhalation may reduce exacerbation frequency (an acute worsening of symptoms) [2, 3] but has little effect on the improvement of FEV₁ (the volume of exhaled air at the end of the first second of forced expiration) and the long-term outcomes of COPD [4].

Macrolides are a class of antibiotics all of whom contain a macrocyclic lactone ring. Their effectiveness in treating infectious respiratory diseases has been confirmed [5]. In addition, recent research has reported that macrolides such as erythromycin, roxithromycin, clarithromycin, and azithromycin play a role in immunoregulation [6–8]. The immunoregulation effect restricts tissue destruction by neutrophils, reduces mucous secretion, and inhibits angiogenesis; this is the theoretical basis for applying macrolides in chronic inflammatory airway diseases [7]. Furthermore, long-term and small-dose macrolide therapy can improve the prognosis of diffuse pan-bronchiolitis [9], a chronic inflammatory airway disease. Systematic reviews have also indicated the benefits of macrolides in the treatment of cystic fibrosis [10] and noncystic fibrosis bronchiectasis [11].

Given the association between chronic inflammation in COPD patients and acute exacerbations, macrolides may be able to ameliorate the pathogenic process of the disease [12]. However, the efficacy of macrolide therapy for COPD has not been definitively established. For the present study we performed a meta-analysis using published randomized controlled trials to investigate the feasibility and safety of macrolide therapy in COPD patients.

Methods

Search Strategy

A systematic literature search of PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Embase (<http://www.embase.com/>) databases was performed. The terms used (Medical Subject Headings; <http://www.nlm.nih.gov/mesh/>) were *chronic obstructive pulmonary disease* and *macrolide*. Searches were limited to humans only and to English-language literature. The last search date was October 1, 2012.

Inclusion Criteria

Studies that met the following criteria were eligible for the meta-analysis: (1) randomized controlled trials that enrolled patients with COPD in the stable stage, as defined by the Tiffeneau-Pinelli index [FEV₁/forced vital capacity (FVC)] <70%, FEV₁ <80% predicted, and an increase in FEV₁ <12% (or 200 ml) after inhaling bronchodilators [1]; (2) drugs were administered orally; (3) macrolide therapy lasted ≥2 weeks, and (4) clinical efficacy or safety

was reported, such as the information on acute exacerbation of COPD (AECOPD) or drug adverse effects. Studies targeting patients with asthma, cystic fibrosis, or bronchiectasis were excluded in this meta-analysis.

Study Selection

To identify potentially eligible studies, the author-investigators Yao and Zhang considered all citations in duplicate. Both investigators obtained the full text of relevant articles and independently reviewed them using the predefined eligibility criteria. The reviewers resolved differences through consensus, and the senior physician author-researcher (Ma) resolved any disagreements.

Data Extraction and Quality Assessment

For the articles that passed our screening criteria, we extracted details on study and patient characteristics, treatment information, duration of follow-up, and AECOPD and drug adverse effects (e.g. gastrointestinal reactions, ototoxicity, rash, and liver injury). The author-reviewers Yao and Zhang extracted the data independently. A Jadad score was assigned as a measure of the quality of the study design of randomized trials [13].

Statistical Analyses

We pooled treatment effects and calculated risk ratios (RR) with 95% CI for all clinical end points using random-effects models. Sensitivity analyses were performed to examine the robustness of the effect by deleting trials with the highest weight or low Jadad scores (<3) and thereafter computing overall estimates for the remaining studies. Statistical heterogeneity was measured using the I² statistic on a scale of 0–100% (>50% indicated a statistical between-study inconsistency, and >75% represented a very large degree of heterogeneity). Data stratified according to the specific antibiotics (erythromycin, azithromycin, or clarithromycin), type of control (placebo or nonplacebo), and macrolide therapy duration (3, 6, or 12 months) were analyzed by subgroup analyses. Publication bias was assessed using the funnel plot method. Pooling analyses were performed with RevMan 5.1 software (Cochrane Collaboration, Copenhagen, Denmark). *p* < 0.05 was considered statistically significant.

Results

Literature Selection

A flow diagram of the selection process for potentially eligible trials and reasons for exclusion is illustrated in figure 1. Briefly, 1,327 published articles were initially identified (1,202 from Embase and 125 from PubMed). Among them, 6 met the prespecified inclusion criteria (table 1) [14–19]. These trials included 1,485 COPD patients, with a mean follow-up ranging from 3 to 12 months. Of the 1,485 patients, 738 had been randomly allocated to a macrolide (erythromycin, clarithromycin, or azithromycin) treatment group and 747 to the control group (patients treated with riboflavin, standard therapy, or placebo; table 1). All of the enrolled trials [14, 15, 17–

Fig. 1. Flowchart for the selection of studies for inclusion in the meta-analysis.

Table 1. Clinical characteristics of the 6 trials included in the meta-analysis

Literature source	Total subjects n	Treated subjects n	FEV ₁ , l/s at baseline ^a		Therapy strategy	Dose per week mg	Concomitant medication to treat COPD	Course of therapy months	Jadad score
			control group	macrolide group					
Suzuki et al. [14]	109	55	1.30 (0.08)	1.47 (0.15)	Erythromycin 200–400 mg/day compared with riboflavin 10 mg/day	1,400–2,800	Sustained release theophylline and inhaled anticholinergic agents, except corticosteroids	12	2
Banerjee et al. [15]	67	31	1.12 (0.07)	1.13 (0.07)	Clarithromycin 500 mg/day compared with placebo	3,500	Inhaled corticosteroids	3	3
Seemungal et al. [16]	109	53	1.36 (0.55)	1.27 (0.51)	Erythromycin 250 mg/b.i.d. compared with placebo	3,500	Inhaled corticosteroids	12	5
Blasi et al. [17]	22	11	Not applied ^b	Not applied ^b	Azithromycin 500 mg 3 times/week compared with standard therapy	1,500	Not mentioned	6	3
He et al. [18]	36	18	1.02 (0.41)	1.12 (0.47)	Erythromycin 125 mg t.i.d. compared with placebo	2,625	Inhaled corticosteroids, theophylline, inhaled anticholinergic agents, inhaled β-adrenergic agents	6	4
Albert et al. [19]	1,142	570	1.10 (0.50)	1.12 (0.52)	Azithromycin 250 mg/day compared with placebo	1,750	Inhaled corticosteroids, inhaled anticholinergic agents, inhaled β-adrenergic agents	12	3

^a Values are given as means (SE). ^b Severe COPD patients with tracheostomy were included in the study.

Fig. 2. Forest plot of relative ratios for the frequency of AECOPD in patients treated with macrolides compared with the control groups. The size of the square is proportional to the weight of the individual studies. M-H = Mantel-Haenszel method.

Table 2. Subgroup analyses based on data on acute exacerbation frequency of COPD and drug adverse effects

	Exacerbation frequency of COPD			Drug adverse effects		
	studies, n	RR (95% CI)	p	studies, n	RR (95% CI)	p
Erythromycin	3	0.48 (0.24–0.96)	0.04	2	0.92 (0.21–4.01)	0.91
Azithromycin	2	0.65 (0.33–1.29)	0.22	2	2.03 (0.41–10.12)	0.39
Clarithromycin	1	2.90 (0.61–13.93)	0.18	1	2.90 (0.61–13.93)	0.18
Placebo	4	0.79 (0.65–0.96)	0.02	3	1.30 (1.05–1.61)	0.02
Nonplacebo	2	0.28 (0.13–0.58)	0.0007	2	5.51 (0.67–45.28)	0.11
Three-month treatment	1	2.90 (0.61–13.93)	0.18	1	2.90 (0.61–13.93)	0.18
Six-month treatment	2	0.56 (0.36–0.87)	0.009	2	1.94 (0.14–26.69)	0.62
Twelve-month treatment	3	0.59 (0.37–0.95)	0.03	2	1.30 (1.04–1.62)	0.02

19] reported the number of patients who had at least one exacerbation. The duration of macrolide therapy was more than 6 months in 5 studies [14, 16–19]. These 5 studies [14, 16–19] used the COX proportional hazards model to evaluate the hazard ratio for AECOPD with the corresponding 95% CI. In the study of Banerjee et al. [15], the RR was calculated as: $RR = \text{frequency of AECOPD in the treatment group} \times \text{follow-up period} / \text{frequency of AECOPD in the control group} \times \text{follow-up period}$.

In addition, 5 of the 6 trials [14, 15, 17–19] reported the number of patients in the treatment groups who experienced adverse side effects, which was used in the present meta-analysis.

Quantitative Data Synthesis

Meta-analytic pooling for COPD exacerbations showed that macrolide therapy significantly decreased the frequency of AECOPD compared with the control groups ($RR = 0.62$; 95% CI 0.43–0.89; $p = 0.01$, $I^2 = 75\%$; fig. 2). However, the beneficial effect was not shown consistently in subgroup analyses of the specific drug, the type of control, or the observed period (table 2). Only erythromycin was found to be associated with decreased COPD exacerbation (erythromycin: $p = 0.04$, azithromycin: $p = 0.22$, clarithromycin: $p = 0.18$). In addition, macrolide therapy for 3 months did not yield significant improvements in COPD exacerbations ($p = 0.18$), whereas the beneficial effect was conclusive in the 6-month and 12-month treatment subgroups ($p = 0.009$ and 0.03 , re-

Fig. 3. Forest plot of relative ratios for drug adverse effects in COPD patients treated with macrolides compared with the control. The size of the square is proportional to the weight of the individual studies. M-H = Mantel-Haenszel method.

spectively; table 2). Of note, the current study did not demonstrate the pronounced impact of the type of control on the overall results in this meta-analysis. However, the above statistical heterogeneity vanished when the factor was considered (placebo: $p = 0.02$, $I^2 = 34\%$; nonplacebo: $p = 0.0007$, $I^2 = 0\%$; table 2). It suggested that the type of control might be an essential factor responsible for the heterogeneity.

Moreover, the administration of macrolides to COPD patients seemed likely to increase the incidence of nonfatal adverse effects compared to the controls (RR = 1.32; 95% CI 1.06–1.64; $p = 0.01$, $I^2 = 0\%$; fig. 3). However, in subgroup analysis according to the specific antibiotic, there were no statistical differences between the treated and control groups. Furthermore, there was an increased occurrence of nonfatal adverse effects in the macrolide group compared with the placebo controls ($p = 0.02$), but not with the nonplacebo controls ($p = 0.11$). In addition, only in the 12-month treatment subgroup was there a significant increase in drug adverse effects associated with the use of macrolides ($p = 0.02$; table 2). Mortality could not be analyzed because it was reported only in two trials [17, 19].

Sensitivity Analysis and Publication Bias

Sensitivity analysis based on nonfatal drug adverse effects was performed by deleting trials with the highest weight [17, 19] or a low Jadad score [14, 15, 17–19]. The results showed significant influences on the overall result (p value changed to 0.19). It suggested that there was only a nominal increase in the risk of nonfatal drug adverse effects in our meta-analysis. Nevertheless, sensitivity analy-

sis based on the incidence of COPD exacerbations did not show any relevant influence on the overall result. In the analysis of publication bias, funnel plots showed an essential symmetry regarding overall results in AECOPD and drug adverse effects (online suppl. material; see www.karger.com/doi/10.1159/000350828), indicating that there was no significant publication bias among the included trials.

Discussion

In this meta-analysis we found that macrolide therapy significantly lowered the risk of acute exacerbations for COPD patients compared with no macrolide treatment. In subgroup analyses, only erythromycin or therapy duration of 6 months or more showed a beneficial effect of macrolide treatment on the exacerbation frequency of COPD. In addition, there was a tendency toward increase in the occurrence of drug adverse effects in the macrolide treatment groups compared with the control. The incidence of nonfatal adverse effects might be associated with therapy duration of no less than 12 months.

The present study found that macrolide treatment was beneficial for decreasing the occurrence of COPD exacerbations. Only erythromycin was found to be associated with decreased COPD exacerbation. The immunoregulation effect is demonstrated not only for erythromycin but also for other 14- and 15-membered ring macrolides (clarithromycin, roxithromycin, and azithromycin, respectively) [8]. A decrease in the frequency of infectious

exacerbations was also demonstrated after treatment with azithromycin in patients with cystic fibrosis [10]. The heterogeneity of the two studies [17, 19] may explain the absence of significant differentiation between the azithromycin treatment groups compared with the control.

However, the optimal duration of macrolide therapy for COPD is not well established. The results indicated that significant benefits required no less than 6 months of treatment in COPD subjects. Therefore, a therapy course of macrolides in COPD patients should be maintained for at least 6 months. According to the guidelines for treatment of diffuse panbronchiolitis published by the Ministry of Health, Labor, and Welfare of Japan [20], although many cases attain clinical remission after 2–3 months' treatment, the therapy should last no less than 6 months; serious cases should receive longer-term therapy. These are the recommendations for the treatment of diffuse panbronchiolitis based on previous evidence, but when treating COPD the best course of treatment should be determined after future clinical trials.

It is of great importance to monitor for adverse side effects when using macrolides for long-term therapy in COPD. Our analysis showed that the use of macrolides led to a nominal increase in nonfatal adverse effects. The main adverse effects were gastrointestinal reactions, ototoxicity, rash, and liver injury. The most common adverse effect during short-term treatment was gastrointestinal reactions [21]. A meta-analysis of long-term, small-dose azithromycin therapy in cystic fibrosis [10] showed that gastrointestinal reactions (nausea, diarrhea) were more frequent in the treatment group than in the control group. Some patients in the study of Albert et al. [19] experienced hypoacusis, with a statistical significance between the azithromycin (25%) and control (20%) groups. How-

ever, this was not reported in the other 5 studies. A previous study also confirmed a positive correlation between reversible ototoxicity and macrolide dosage [22].

Methodologically, the use of a random effects model and no publication bias among the included trials ensured the robustness of conclusions from the current study. Moreover, the sensitivity analyses further confirmed the credibility of the meta-analysis estimates. However, the power of the subgroup analyses might be restricted by the limited study number and population size, and the conclusions drawn should be considered carefully. Further randomized controlled trials with larger sample sizes and longer-term follow-ups are required to attain more robust clinical evidence and to verify the true effects of macrolide therapy in COPD subjects.

In conclusion, treatment with macrolides significantly lowered the frequency of AECOPD. The benefit gained might be time dependent; macrolide treatment for no less than 6 months was needed to exert a favorable effect in COPD subjects. Moreover, the use of macrolides in COPD trended toward increasing the incidence of non-fatal adverse effects.

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Financial Disclosure and Conflicts of Interest

There are no conflicts of interest.

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