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Macrolide antibiotics for treatment of asthma in adults: A meta-analysis of 18 randomized controlled clinical studies

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ABSTRACT

Mounting studies have been showed that long-term macrolides used in patients with asthma could improve the lung function and symptoms. However, a large number of studies have reported inconclusive results. The aim of this meta-analysis was to investigate the effect of macrolide antibiotics in patients with asthma. We have performed a search in PubMed, Embase, China National Knowledge Internet (CNKI), and Wanfang databases. The weighed mean difference (WMD) or standardized mean difference (SMD) was used to evaluate the pooled effect. Statistical analysis was performed by STATA 11.0 software. Totally 1306 patients were included in the meta-analysis. The overall results indicated that statistically significance of long-term macrolides therapy in patients with asthma on forced expiratory volume in 1 s (FEV1) (WMD: 0.11, $P < 0.01$), peak expiratory flow (PEF) (SMD: 0.25, $P = 0.001$), airway hyper-responsiveness (AHR) (SMD: 0.90, $P = 0.04$), forced vital capacity (FVC) (WMD: 0.18, $P = 0.05$) and FEV1/FVC (WMD: 1.93, $P < 0.001$), but no statistically significance on FEV1/predict, FVC/predict, symptom scores, quality of life scores (QOL), reliever inhaler puffs per 24 h, and cell counts in sputum and blood. The subgroup analysis indicated macrolides could increase FEV1 and PEF in Caucasian and Asian, decrease AHR in Caucasian, while cells counts of sputum improvement among Asian. Therefore, the study suggested that long-term marolides therapy in asthma may improved the FEV1, PEF, AHR, FVC, FEV1/FVC and cells counts in sputum, but it can't improve other lung function (FEV1/predict and FVC/predict) and clinical outcomes (such as symptom, quality of life etc.).

1. Introduction

Asthma is characterized by chronic airway inflammation and airway hyper-responsiveness (AHR), and always considered a heterogeneous disease [1]. The symptoms of asthma mainly include wheeze, chest tightness, shortness of breath, and cough with variable expiratory airflow limitation [2]. It is estimated that 1–18% of population has been influenced on the asthma in different countries [2]. In 2004, Global Initiative for Asthma (GINA) program reported that there were almost 300 million people currently having asthma in the worldwide [3]. Recent years, although lots of drugs including inhaled corticosteroids (ICS), long acting β-agonist (LABA), and theophylline could effectively managed the asthma, there is still a high morbidity and mortality of asthma [3]. It is considered that asthma accounts for about 1 per 250 deaths in the world, and there may be an additional 100 million people with asthma by 2025 [3].

Abbreviations: CNKI, China national knowledge internet; WMD, weighed mean difference; SMD, standardized mean difference; PEF, peak expiratory flow; AHR, airway hyper-responsiveness; FEV1/FVC, the ratio of forced expiratory volume in 1 s and forced vital capacity; GINA, global initiative for asthma; ICS, inhaled corticosteroids; LABA, long acting β-agonist; CAP, community acquired pneumonia; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; SD, standard deviation; CI, confidence interval; QOL, quality of life; LTRA, leukotriene receptor antagonist.

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Macrolide antibiotics are often used as the first-line drugs in the treatment of acute respiratory tract infection, such as acute bronchitis and community acquired pneumonia (CAP) [4]. In addition to direct anti-microbial activity, increasing evidences have indicated that macrolides also have immune modulatory and anti-inflammatory effects [5,6]. In the previous studies, many patients with chronic respiratory diseases have gained benefits from long-term macrolides therapy (more than 3weeks), such as the chronic obstructive pulmonary disease (COPD) [7,8], bronchiectasis [9,10] and cystic fibrosis (CF) [11]. Furthermore, lots of studies also have focused on the efficacy of long-term macrolide used in patients with asthma in recent decades. Simpson et al. reported a reduction in wheeze and significant improvements in asthma quality of life (QOL) scores in refractory asthma patients [12]. After therapy with clarithromycin for 8 weeks, a significant reduction on AHR in patients with asthma was found by Kostadima and co-workers, however there was no significant increase on the forced expiratory volume in 1 s (FEV1) [13]. Besides, a study conducted by Cameron et al. indicated that there was no improvement in FEV1, symptoms control and peak expiratory flow (PEF) when prolonged macrolides administration in patients with asthma [14].

Since the results of previous studies are inconclusive, and a small sample sizes of each study may lack the power to provide percise conclusions, we performed a meta-analysis to investigate whether long-term macrolides used in patients with asthma can improve the asthma symptoms, quality-of-life and increased the clinical or laboratory outcomes, such as lung function, and cell counts of sputum etc. To our knowledge, this is most comprehensive meta-analysis to assess the effect of prolonged treatment with macrolide antibiotics in patients with asthma.

2. Materials and methods

2.1. Study selection

Two reviews (Xiang Tong and Tingting Guo) performed a comprehensive search about long-term macrolides used to treat asthma in PubMed, Embase, China National Knowledge Internet (CNKI), and Wanfang databases, with last updated search being conducted in May, 2014. The searching words used were as follows: 'macrolides', 'macrolide antibiotics', 'azithromycin', 'roxithromycin', 'clarithromycin', 'telithromycin', 'erythromycin' and 'asthma' or 'wheeze'. There was no language restriction. The following inclusive criteria were used: 1) the study should be designed as a randomized-controlled study; 2) the study should be to evaluated efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma; 3) the study should be provided available data for extracted or calculated the mean, standard deviation (SD), *P* value and 95% confidence interval (CI); 4) the studies should be focused on human subjects; 5) the methodology quality assessment used by Jadad score (5-points) in each study should be equal or more than two. The following exclusive items were used: 1) the study was not designed as a randomized-controlled study; 2) the participants of study included children; 3) the study is only abstracts, reviews or overlapping study; 4) the study have insufficient data for extracting or calculating the pooled results; 5) the Jadad score (5-point) was less than two.

2.2. Date extraction

According to the inclusive items, the information of studies was independently collected by two reviewers (Xiang Tong and Tingting Guo). If there is a disagreement, a third author (Sitong Liu) could assess those articles again. For each study, first author, publication year, country, ethnicity, mean age of participant, sample size of experimental and placebo group, asthma type, macrolides type, each dose and daily frequency of macrolides, duration of therapy, and end-point outcomes. These information was summarized in Tables 1 and 2.

2.3. Statistical analysis

The meta-analysis was performed by the STATA 11.0 software (STATA Corporation, Texas State, USA, http://www.stata.com/). Weighed mean difference (WMD) or standardized mean difference (SMD) was used to measure the efficacy of long-term macrolides therapy in patients with asthma. The SMD was performed when studies reported different scales or units of outcomes; otherwise, the WMD would be applied. Heterogeneity of the studies was assessed by the χ^2-based Q statistic and I-squared (I^2) test. It was considered that studies lacked the significant heterogeneity when $P > 0.10$ for the χ^2 test and I^2 <50%, thus the WMD or SMD was

Table 1
Characteristics of included studies in the present meta-analysis.

First author	Year	Country	Ethnicity	Age	Sample size	Asthma type	Jadad score
				Experiment/placebo	Experiment/placebo		
Amayasu H	2000	Japan	Asian	NA[a]	17/17	Adult	3
Black PN	2001	Muti-center[b]	Caucacian	40 ± 11.6/42 ± 11.9	105/114	Adult	4
Brusselle GG	2013	Belgium	Caucacian	53/53	53/49	Adult	5
Cameron EJ	2013	England	Caucacian	46.4 ± 8.8/42.8 ± 9.4	38/39	Adult	3
Hahn DL	2012	America	Caucacian	45.7 ± 15.5/47.±14.2	23/32	Adult	5
Hahn DL	2006	America	Caucacian	50 ± 14/45 ± 12	19/17	Adult	5
He J	2009	China	Asian	35 ± 7.3/34 ± 5.6	20/20	Adult	2
Kostadima E(BID)	2004	Greece	Caucacian	48 ± 16/41 ± 16	22/21	Adult	4
Kostadima E(TID)	2004	Greece	Caucacian	42 ± 12/41 ± 16	20/21	Adult	4
Kraft M	2002	England	Caucacian	NA	26/26	Adult	3
Shoji T	1999	Japan	Asian	NA	14/14	Adult	3
Simpson JL	2008	Australia	Caucacian	60/55	23/22	Adult	5
Sutherland E	2010	America	Caucacian	NA	41/39	Adult	4
Wang T	2014	China	Asian	28.44 ± 15.98/29.56 ± 14.21	29/29	Adult	2
Wang Y	2012	China	Asian	NA	23/22	Adult	3
Xiao KA	2013	China	Asian	34.5 ± 7.2/33.7 ± 8.3	106/104	Adult	2
Yan XQ	2008	China	Asian	38 ± 12/39 ± 12	20/20	Adult	3
Zhang LY	2013	China	Asian	NA	30/30	Adult	2

[a] Not available.
[b] Muti-center: Australia, New Zealand, Italy, and Argentina.