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ORIGINAL ARTICLE AIRWAY DISEASES

Macrolides for the long-term management of asthma – a meta-analysis of randomized clinical trials

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Abstract

Background: Macrolide antibiotics, which have anti-inflammatory and immune modulatory effects, have been studied as adjuncts for the management of asthma. However, results have been contradictory and trials underpowered. We therefore sought to conduct a meta-analysis of randomized controlled trials (RCT).

Methods: All RCT of prolonged macrolides (3+ weeks) for asthma treatment, published up to January 2013 in MEDLINE, Scopus, CINAHL, Highwire, and The Cochrane Collaboration Library, were included. Fixed- or random-effects models were used to calculate pooled weighted or standard mean differences (WMD or SMD, respectively).

Results: A total of 12 studies were included for analysis. The pooled effect of macrolides on FEV1 (eight trials, 381 subjects) was not significant (SMD 0.05, 95% CI −0.14–0.25), but there was a significant increase in peak expiratory flow (four trials, 419 subjects; WMD 6.7, 95% CI 1.35–12.06). Pooled analysis also showed significant improvements in symptom scores (eight studies, 478 subjects; WMD −0.46, 95% CI −0.60 to −0.32), quality of life (five trials, 346 subjects; WMD 0.18, 95% CI 0.001–0.37), and airway hyper-reactivity (two trials, 131 subjects; SMD 1.99, 95% CI 0.46–3.52). *Post hoc* evaluation showed limited statistical power to detect significant differences in FEV1.

Conclusions: Macrolide administration for asthma for three or more weeks was not associated with improvement in FEV1, but produced significant improvements in peak expiratory flow, symptoms, quality of life, and airway hyper-reactivity. Macrolides may therefore be beneficial as adjunct asthma therapy. Future trials, focusing on long-term safety and effectiveness, should use standardized outcomes and procedures.

Asthma is a disease characterized by chronic airway inflammation and hyper-responsiveness resulting in episodes of airflow obstruction. In several westernized countries, it affects well over 20% of children and 10% of adults (1), and its prevalence has risen significantly over the last several decades (1, 2). Inhaled corticosteroids (ICS) have become the mainstay of the long-term treatment of persistent asthma (3). However, asthma morbidity remains high; as evidenced by patients whose asthma is steroid dependent or steroid resistant (4), there may be specific asthma phenotypes for which novel treatment approaches or adjunct therapies may be necessary.

Macrolide antibiotics have been shown to have anti-inflammatory and immune modulatory effects in addition to their antimicrobial effects (5). They are beneficial in several pulmonary conditions including cystic fibrosis (6), diffuse panbronchiolitis (7), chronic obstructive pulmonary disease (8), post-transplant bronchiolitis obliterans (9), and bronchiectasis (10). As such, they may represent an alternative for difficult-to-control asthma. Furthermore, chronic symptoms

and acute exacerbations may be associated with bacterial infections, such as *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* (11), which can be treated using macrolides.

Several trials have been conducted to evaluate the effectiveness of macrolides as adjunct approach to asthma treatment. However, results from single studies have been contradictory and many such analyses may have been underpowered to detect statistically significant differences. In the present study, we sought to conduct a meta-analysis of randomized, controlled trials to assess whether prolonged therapy with macrolides is effective at improving clinical measures of asthma, such as lung function, symptom scores, quality of life, and airway hyper-reactivity.

Methods

Data sources and searches

We conducted a comprehensive search in MEDLINE, Scopus, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), Highwire, and The Cochrane Collaboration Library, published up to January 2013, evaluating the effect of prolonged asthma treatment with macrolides (defined *a priori* as 3 weeks or longer). Additionally, we screened the reference lists of the papers identified through database search for additional studies. The following search strategies were used:

1. In MEDLINE, The Cochrane Collaboration Library, Scopus, and CINAHL: (Macrolide* OR Azithromycin OR Erythromycin OR Clarithromycin OR Roxithromycin OR Troleandomycin) AND (Asthma* OR Wheez*) (Limits "Humans").
2. In Highwire: Macrolide* asthma*(all words in title or abstract); Azithromycin* asthma*(all words in title or abstract); Erythromycin* asthma*(all words in title or abstract); Clarithromycin* asthma*(all words in title or abstract); Roxithromycin* asthma*(all words in title or abstract); Troleandomycin* asthma*(all words in title or abstract).

Study selection

We included all randomized clinical trials on macrolide administration for three or more weeks to treat asthma, controlled with placebo or standard therapy, and published in or with abstract in English with sufficient information to extract required data. We excluded nonrandomized or nonblinded clinical trials, ineligible interventions (treatment other than macrolides *vs* placebo or standard therapy), ineligible outcomes, and insufficient data to perform a pooled analysis. Two authors (JR and ND) independently screened all references according to the selection criteria. Agreement between the reviewers on study selection was assessed using Cohen's kappa statistic (κ). Differences of opinion regarding inclusion were resolved by mutual agreement and arbitration of a third author (EF).

Data extraction and quality assessment

Using a standardized data extraction spreadsheet, JR and ND independently excerpted from full-text articles' data on references (first author, publication year); sample characteristics (participants' age, number of participants per treatment arm); type of macrolide, dose, and duration of therapy; and outcome definitions. Disagreements on data extraction were resolved through discussion and by arbitration of a third author (EF). When possible, we obtained data from the original manuscripts; when incomplete, we attempted contacting the authors or obtained estimates from the previous meta-analysis on the topic if available (12). The reporting quality of the individual studies was evaluated using the Jadad scale (13), a widely used and validated system to evaluate the methodological quality of clinical trials (14).

Data analysis

Data collected were pooled to calculate summary estimates. Each study was weighted by its inverse effect size variance (13). We calculated weighed or standardized mean differences (WMD or SMD, respectively); SMD were used when studies reported different units or scales for the outcome. Heterogeneity was quantified using I^2 (15). Fixed-effects models were used when heterogeneity between studies was nonsignificant, and random-effects were used for analyses with significant heterogeneity. Random-effects analyses include within- and between-study variances, providing a more conservative estimate (16). When possible, meta-regression was performed to explore potential sources of heterogeneity and test the effect of different available factors (e.g., age-group, type of macrolide, dose, duration of treatment, or study design) on the treatment outcomes. Egger tests were used to assess for potential publication bias. All analyses were performed in STAT (v12; STATA Corporation, College Station, TX), and a P-value <0.05 was considered statistically significant.

Results

A total of 553 manuscripts were identified (Fig. 1): 264 from PubMed, 143 from Scopus, 65 from CINAHL, 14 from Highwire, 66 from The Cochrane Library, and one from study references. After removal of duplicates, we evaluated 288 studies. Based on title/abstract and full-text screening, the authors agreed on 285 of the 288 articles (inter-reader $\kappa = 89.1\%$). Of these 288, 12 studies (831 participants) were included in the meta-analysis (Table 1) (17–28).

Studies' characteristics

Studies included were published between 1993 and 2013. Of 13 trials, 10 were performed in adults (17–20, 22, 23, 25–28) and two in children (21, 24), five trials used clarithromycin (17, 20, 22, 23, 27), four azithromycin (19, 21, 25, 26), two roxithromycin (18, 28), and one troleandomycin (24). Duration of treatment ranged from 3 to 26 weeks (median 8 weeks, mean 9.8 weeks, SD = 5.9). Most trials involved

Table 1 Characteristics of randomized clinical trials included in the meta-analysis

Reference	Number of subjects	Age-group	Antibiotic and dose	Duration of treatment	Outcome (s) analyzed	Note (s)	Quality score*
Kamada 1993 (24)	11 (6 treatment, 5 placebo)	Children	Troleandomycin 250 mg	12 weeks	PEF, symptom score		5
Shoji 1999 (28)	56 (28 subjects, crossover)	Adults	Roxithromycin 300 mg	8 weeks	FEV_1, symptom score	Crossover design, FEV_1 in liters	3
Amayasu 2000 (17)	68 (34 subjects, crossover)	Adults	Clarithromycin 400 mg	8 weeks	FEV_1, symptom score, AHR	Crossover design, FEV_1 in liters, AHR as PC_{20}	3
Black 2001 (18)	219 (105 treatment, 114 placebo)	Adults	Roxithromycin 300 mg	6 weeks	PEF		3
Kraft 2002 (27)	52 (26 treatment, 26 placebo)	Adults	Clarithromycin 1000 mg	6 weeks	FEV_1	Crossover design, FEV_1 in liters	3
Kostadima 2004 (20)	63 (22 BID treatment, 20 TID, 21 placebo)	Adults	Clarithromycin 500 mg (BID) or 750 mg (TID)	8 weeks	FEV_1, AHR	FEV_1 as percent of predicted, AHR as PD_{20}	4
Hahn 2006 (26)	36 (19 treatment, 17 placebo)	Adults	Azithromycin 600 mg	6 weeks	Symptom score, QOL	AQLQ for QOL	5
Piacentini 2007 (21)	16 (8 treatment, 8 placebo)	Children	Azithromycin	8 weeks	FEV_1, AHR	FEV_1 as percent of predicted, AHR as PC_{20}	4
Simpson 2008 (22)	46 (23 treatment, 23 placebo)	Adults	Clarithromycin 1000 mg	8 weeks	FEV_1, symptom score, QOL	FEV_1 as percent of predicted, AQLQ for QOL	5
Sutherland 2010 (23)	80 (41 treatment, 39 placebo)	Adults	Clarithromycin 1000 mg	16 weeks	FEV_1, PEF, symptom score, QOL, AHR	FEV_1 in liters, AQLQ for QOL, AHR as PC20	4
Hahn 2012 (25)	75 (38 treatment, 37 placebo)	Adults	Azithromycin 600 mg	12 weeks	Symptom score, QOL	AQLQ for QOL	5
Brusselle 2013 (19)	109 (55 treatment, 54 placebo)	Adults	Azithromycin 250 mg	26 weeks	PEF, symptom score, QOL	AQLQ for QOL	5

*Quality score using Jadad scale (13), which ranges from 0 (lowest quality) to 5 (highest), and evaluates the randomization, blinding, and withdrawals and dropouts as described in the original study.

two parallel arms (macrolide *vs* placebo), but Kostadima et al. had two treatment arms (clarithromycin twice daily [BID] and three times daily [TID]) plus a placebo arm; this study was analyzed as two comparisons (BID *vs* placebo, TID *vs* placebo). Shoji et al. and Amayasu et al. (17, 27, 28) were crossover trials, whereas the rest were parallel-arm trials. Outcome reporting varied as well: FEV_1 was reported in liters in three trials, as percent of predicted in another three (20–22), and as both in one study (23). Airway hyper-reactivity was reported as the dose of methacholine required to produce a 20% drop in FEV_1 (PD_{20}) in one trial (20) and as the concentration (PC_{20}) in another (17). Symptom score systems were diverse; however, all studies used the validated Asthma Quality of Life Questionnaire (AQLQ) to report quality of life. Five studies included mild, mild to moderate, or moderate asthmatics (17, 23, 25, 27, 28); three included severe asthmatics (19, 22, 24); and the remaining studies did not specify severity (18, 20, 21) or included a broad range of asthma severity (26). Similarly, baseline asthma therapy varied among studies (Table S1 (Supporting Information) for details on baseline severity and treatment).

FEV_1

Eight trials totaling 381 subjects were included (17, 20–23, 27, 28). The pooled effect of macrolides on FEV_1 was not significant (SMD 0.05, 95% CI −0.14 to 0.25, $P = 0.60$) (Fig. 2). There was no significant heterogeneity among included studies (I^2 0.0, $P = 0.44$). No significant effects were found in subgroups by age or FEV_1 units utilized (liters *vs* percent predicted). Clarithromycin was used in six studies (17, 20, 22, 23, 27) with no significant effect (SMD 0.01, 95% CI −0.20 to 0.23, $P = 0.91$). Both azithromycin (SMD −0.41, 95% CI −1.40 to −0.58, $P = 0.42$) (21) and roxithromycin (SMD 0.43, 95% CI −0.10 to 0.96, $P = 0.11$) (28) were used in only one study each. Egger test showed no evidence of publication bias ($P = 0.26$).

Peak expiratory flow

Four trials ($N = 419$) were included (18, 19, 23, 24). Overall, macrolide administration produced a significant increase in PEF (peak expiratory flow) when compared to placebo (WMD 6.70, 95% CI 1.35–12.06, $P = 0.014$) (Fig. 3). Heterogeneity was not statistically significant (I^2 0.40, $P = 0.17$). Among subgroups, PEF improved in trials involving adults (WMD 6.68, 95% CI 1.32–12.04, $P = 0.015$) (18, 19, 23) but not children ($P = 0.76$) (24). Egger test showed no evidence of publication bias ($P = 0.41$).

Asthma control and symptom scores

Eight studies ($N = 478$) were included: five reported mean symptom scores at the end of the trial (17, 22–24, 28) and three reported mean change from baseline (19, 25, 26). Symptom scales and asthma control measures utilized differed among studies (see Table S1, Supporting Information, for details). Macrolides produced a significant reduction in

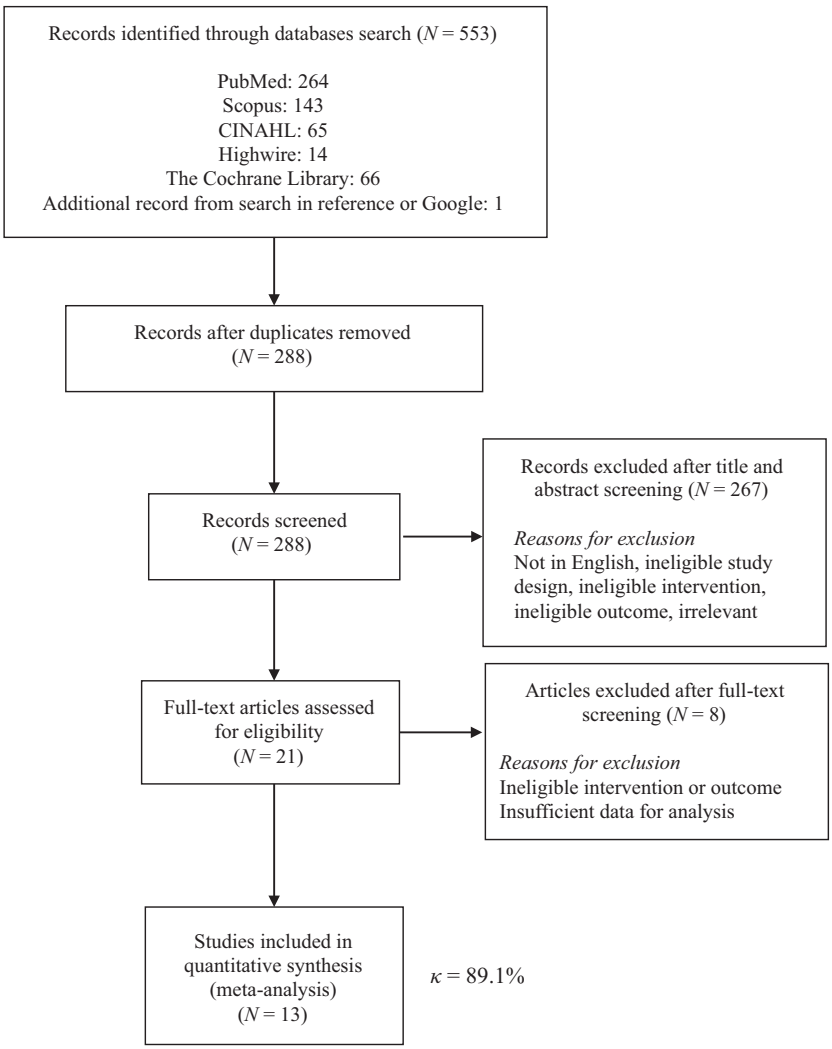

Figure 1 Flowchart of study selection. Adapted from: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (49).

symptoms in studies reporting change from baseline (WMD −0.26, 95% CI −0.50 to −0.03, $P = 0.028$) (Fig. 4) and in those reporting final scores (WMD −0.56, 95% CI −0.73 to −0.39, $P < 0.001$); the overall effect was also significant (WMD −0.46, 95% CI −0.60 to −0.32, $P < 0.001$). Studies reporting change from baseline were homogeneous (I^2 0.34, $P = 0.22$), but those reporting final scores were significantly heterogeneous (I^2 0.62, $P = 0.03$). Meta-regression showed that study design explained the heterogeneity among studies ($P = 0.003$, residual I^2 0.0): crossover studies showed a significant improvement ($P < 0.001$) but parallel-design studies did not ($P = 0.24$). There was no evidence of publication bias ($P = 0.66$).

Quality-of-life (QOL) scores

Five trials ($N = 346$) were included (19, 22, 23, 25, 26). Overall, macrolides produced a significant improvement in QOL (WMD 0.18, 95% CI 0.001–0.37, $P = 0.048$) (Fig. 5). Studies were highly homogeneous (I^2 0.0, $P = 0.99$). All studies were performed in adults; when looking at subgroups, there were no differences by antibiotic (clarithromycin *vs* roxithromycin) or by reported measure (final score *vs* change from baseline). Egger test showed no evidence of publication bias ($P = 0.31$).

Airway hyper-reactivity

Three comparisons from two trials ($N = 131$) were included (17, 20). Airway hyper-reactivity (AHR) was measured by the dose or concentration of methacholine required to produce a 20% decrease in FEV_1 (PD20 or PC20, respectively); higher PD20 or PC20 represents lower AHR. Overall, macrolides led to a decrease in AHR, measured by higher PD20 or PC20 (SMD 1.99, 95% CI 0.46–3.52, $P = 0.011$) (Fig. 6). Studies included were significantly heterogeneous (I^2 0.93, $P < 0.001$); given the small number of studies, we were

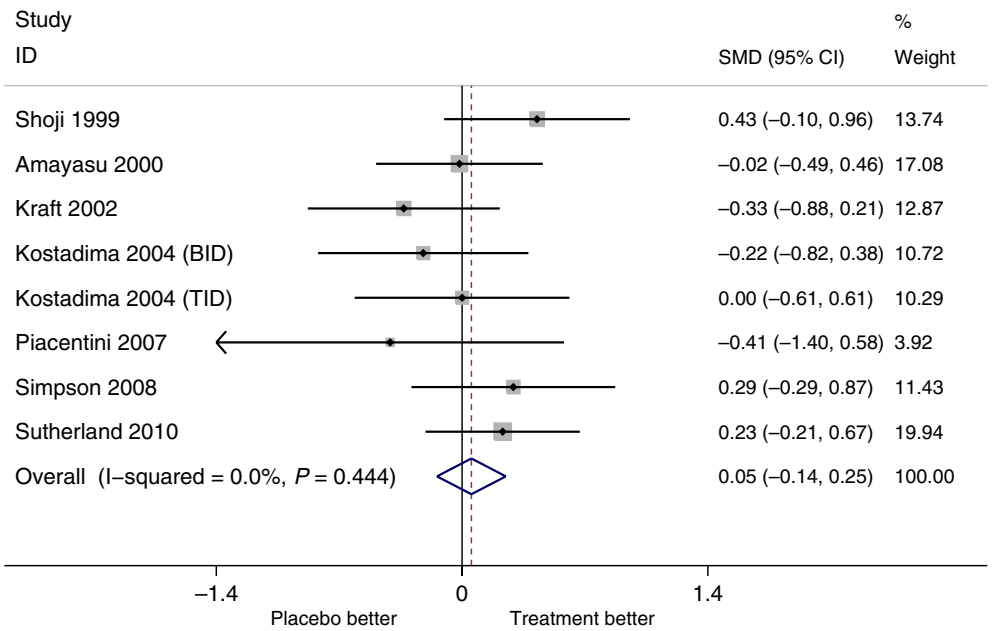

Figure 2 Effect of macrolides on FEV_1.

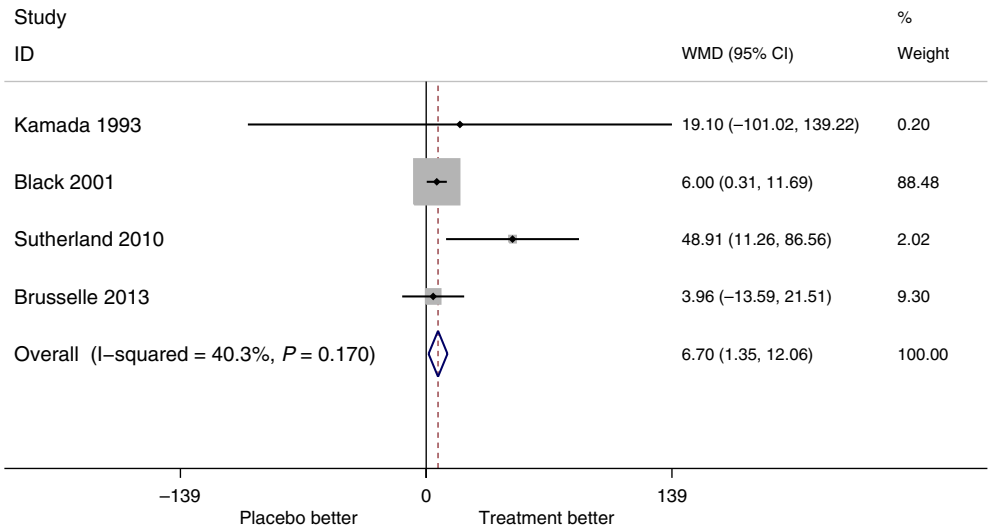

Figure 3 Effect of macrolides on peak expiratory flow (PEF).

unable to perform meta-regression to assess potential reasons for the heterogeneity.

Exacerbations

Insufficient data were available for pooled analysis of asthma exacerbations. One trial reported no significant difference in the rate of severe exacerbations between the treatment and placebo arms (19). On subgroup analysis, however, the rate of exacerbations decreased in subjects with noneosinophilic severe asthma treated with azithromycin (19). Two other studies reported either no significant differences in the rate of exacerbations (18, 25) but neither reported data.

Side-effects

Three studies reported comparable gastrointestinal side-effects (nausea, diarrhea, and abdominal pain) (18, 19, 25). Patients receiving macrolides reported significantly more nausea ($P = 0.012$) than patients in the placebo arm, but there were no differences for diarrhea or abdominal pain (Fig. S1, Supporting Information). Most other studies reported varied

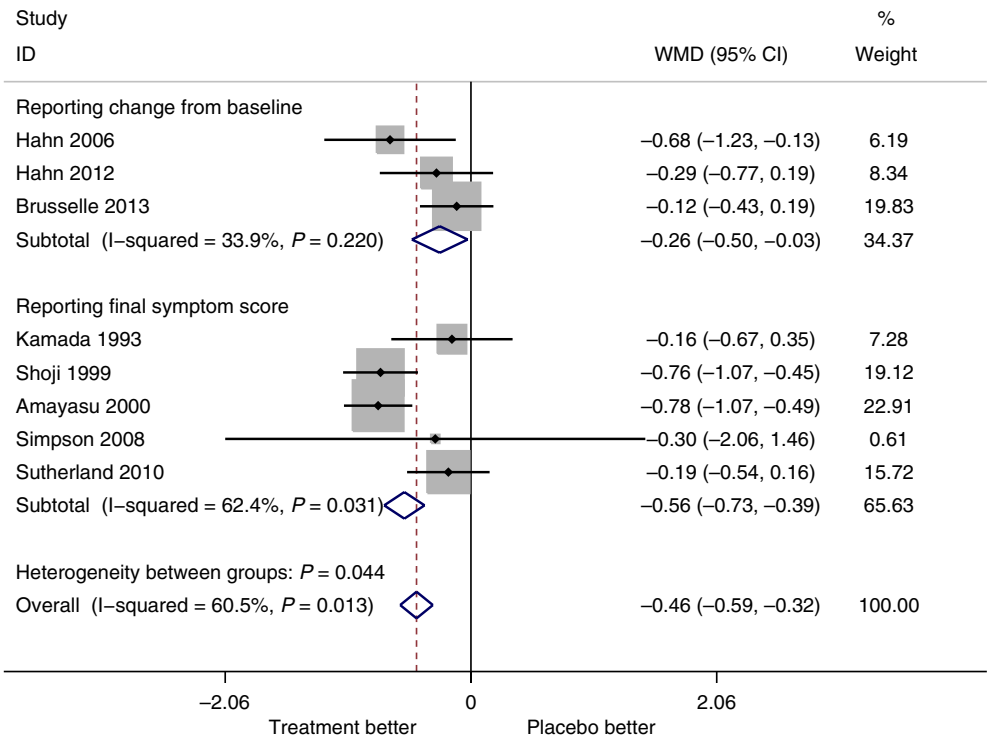

Figure 4 Effect of macrolides on symptom scores.

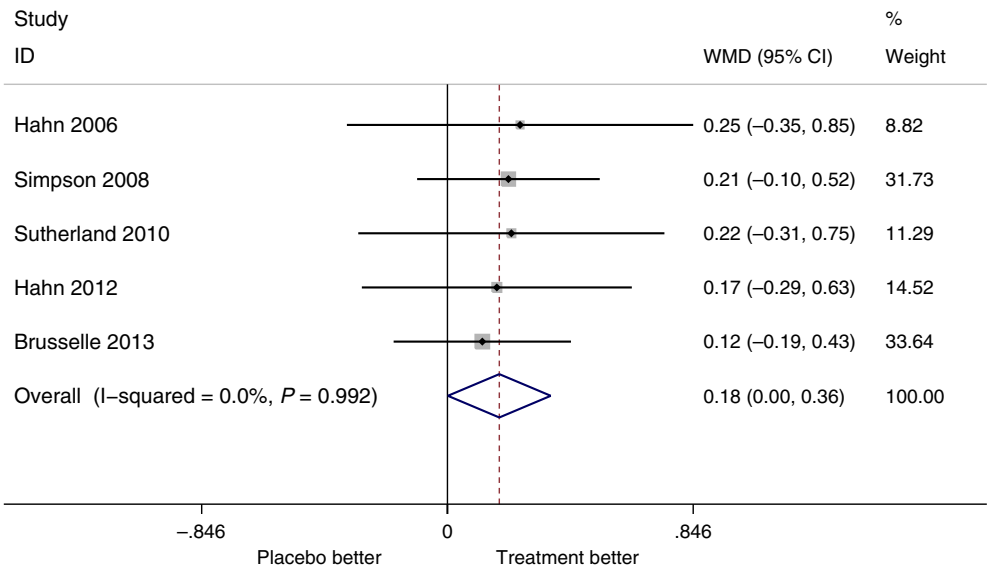

Figure 5 Effect of macrolides on quality-of-life (QOL) score.

side-effects and therefore could not be pooled for analysis: Hahn et al. (26) reported five instances of 'GI symptoms' in the treatment arm and two in the placebo arm; Hahn et al. (25) reported similar proportions in each arm of vomiting, rash, swelling, and hearing loss, and one case of acute coronary syndrome in the placebo group, which was the only reported instance in which the trial medication was stopped. Brusselle et al. (19). reported very small and similar numbers in each arm of allergic reaction, vertigo, headache, and other side-effects; two patients in the placebo arm and one in the treatment arm discontinued the trial medication. Three of the studies reported a small number of patients with a reversible

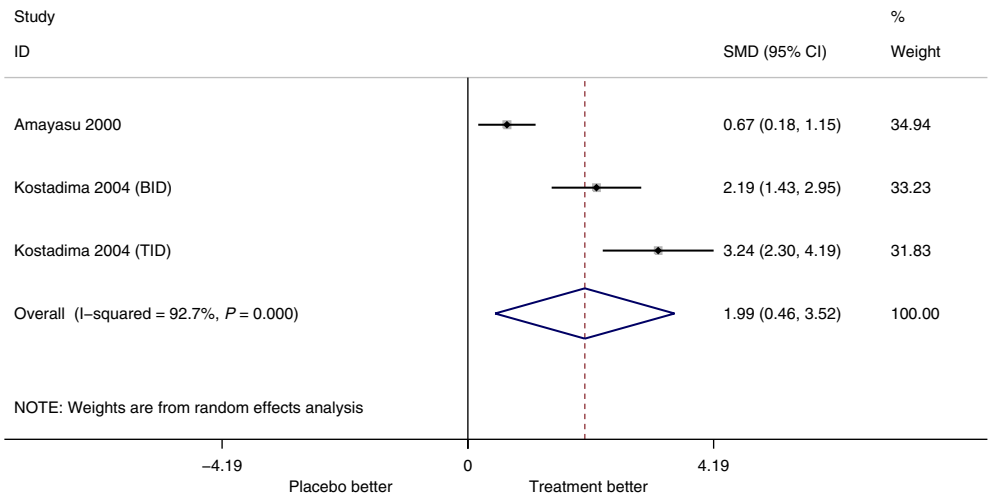

Figure 6 Effect of macrolides on airway hyper-reactivity (AHR).

increase in liver function tests while on the macrolides (18, 19, 24). Sutherland et al. (17, 20–22, 27, 28) noted that the treatment arm patients were not more likely to experience drug-related adverse events. The rest of studies did not report side-effects.

Discussion

In this meta-analysis, we found that prolonged therapy with macrolides led to significant improvement in several clinical asthma outcomes – including peak expiratory flows, symptoms, quality of life, and airway hyper-reactivity – but yielded no changes in FEV_1.

Asthma affects over 235 million people worldwide (29). It is a chronic inflammatory disorder of the airways, which in many cases requires long-term anti-inflammatory therapy (30). Not all patients achieve asthma control even with high doses of ICS in combination with other medications (31). These patients with severe or difficult to treat asthma represent a small proportion of the total number of asthmatic patients (<15%) but account for substantial morbidity, mortality, and cost and continue to be an important public health problem (32).

Erythromycin, the first macrolide antibiotic, was discovered in 1952. Thenceforth, many beneficial effects have been attributed to these antibiotics (33). Some macrolides concentrate intracellularly and have been shown to modulate various cell functions, even when given at non-antimicrobial doses (34). Macrolides attracted researchers' attention for asthma treatment, particularly as a steroid sparing agent, as early as the late 1950s (35). Reports in the late 1980s of beneficial responses in patients with diffuse panbronchiolitis, an idiopathic inflammatory disease principally affecting the respiratory bronchioles (7) spawned new attention toward the use of macrolides in the treatment of various chronic inflammatory pulmonary diseases.

Several clinical trials have been performed evaluating the role of macrolides in different aspects of asthma therapy such as acute asthma (36), refractory asthma (22), and as steroid sparing agents (37, 38). Most of these comprised small sample sizes and were likely underpowered. A 2005 Cochrane Report on use of macrolides for chronic asthma failed to show a significant effect (12), likely due to the small number of trials analyzed. Moreover, given the small numbers of studies and due to their different methodologies, many studies were not comparable and several outcomes were not analyzed. In the present study, we found a total of nine additional randomized controlled trials, of which seven met the final inclusion criteria for analysis, thereby increasing sample size and power, and allowing the meta-analysis of several outcomes.

We did not find a significant improvement in FEV_1 following macrolide administration, either in studies reporting FEV_1 in liters or in those reporting percent-of-predicted values. Although the pooled analysis included eight trials and 381 patients, *post hoc* calculations showed only 5–8% power to detect a significant difference, given the pooled effect estimates and variances. The lack of significant difference could also reflect inadequacy of FEV_1 as a sensitive clinical outcome in asthmatic patients (39, 40), given its specificity for larger rather smaller airways (41). Furthermore, FEV_1 may reflect the degree of bronchoconstriction but may be an inadequate surrogate marker for airway inflammation, particularly in subjects with long-standing, persistent asthma. This is in line with studies showing reductions in inflammatory markers with treatment but no improvement in FEV_1 (19, 38). For example, trials of mepolizumab (an anti-interleukin-5 [IL-5] monoclonal antibody) for refractory asthma also showed lack of FEV1 response despite improvements in clinical and inflammatory outcomes (42). Improvements, if any, may be small, and it may be difficult for future studies to be adequately powered to detect clinically and statistically significant changes in FEV_1.

While results for FEV_1 were nonsignificant, macrolide administration led to improvements both in PEF and in AHR. Methacholine assesses AHR by acting directly on

airway smooth muscle; it has been postulated that its effect has a variable component, which tends to improve with the use of ICS, and a 'fixed' component that does not improve with ICS and is likely related to neutrophilic inflammation and airway remodeling (43). Macrolides play a role in neutrophilic airway diseases such as diffuse panbronchiolitis, cystic fibrosis, and noncystic fibrosis bronchiectasis (10). Few studies have looked specifically at the neutrophilic asthma phenotype. Simpson et al. (22) reported a significant decrease in IL-8, sputum neutrophil counts, and sputum neutrophil elastase. Similarly, Brusselle et al. (19) reported a significant decrease in severe asthma exacerbations in a subgroup of patients with noneosinophilic asthma.

Beyond measures of lung function and AHR, our results show significant improvement in symptom scores and quality of life among asthmatics treated with macrolides. The discrepancy between the lack of improvement in FEV_1 and the significant effect of macrolides on symptomatology and quality of life further highlights the importance of choosing clinically relevant outcomes for future trials. Multiple *in vitro* studies have shown an anti-inflammatory effect of macrolides on the airways (44); this effect may result in clinical relief without or before a bronchodilatory effect.

Not all studies reported adverse events. Pooled analysis of side-effects for which enough information was available demonstrated only an increased risk of nausea among patients receiving macrolides. Importantly, adverse events were infrequent, mostly minor and rarely led medication discontinuation. There were no reported serious cardiovascular side-effects in patients treated with macrolides, which has been the topic of significant controversy recently (45, 46), and should warrant caution when using azithromycin in patients with high risk of cardiovascular disease.

There are several limitations to our study. Despite the pooled sample size, we cannot conclude whether the lack of a statistically significant change in FEV_1 was due to inadequate power or due to a true lack of effect. Asthma severity and baseline asthma therapy varied among studies (Table S1). There also was significant heterogeneity among studies evaluating symptom scores and AHR; although we used a random-effects model to account for this heterogeneity, this correction is only partial. Given the small number of studies, we were unable to assess factors that may modify the effects of macrolides, such as antibiotic used, dose, and duration of treatment. On the other hand, an important strength of the current analysis is the increased number of trials and patients included as compared to previous literature (12). Thus, the current report provides more information on different outcomes and provides insight on the effect of macrolides on different asthma phenotypes. This is important because asthma treatment is moving in the direction of phenotype-directed treatment, accepting the vast variability of the underlying pathology (47). Recent trials on monoclonal antibodies against IL-5, for example, have shown improvement in clinical outcomes and inflammatory markers in patients with persistent airway eosinophilia refractory to corticosteroid treatment (48).

In summary, prolonged treatment with macrolides led to significant improvements in several asthma outcomes, including quality of life and symptoms, although there was no improvement in FEV_1. Macrolides may therefore be beneficial as adjunct asthma therapy, particularly in certain asthma phenotypes such as noneosinophilic or neutrophilic asthma. Further trials are necessary to assess long-term safety and effectiveness, should use standardized outcomes and procedures, and, to the extent feasible, should consider including asthma phenotypes that may benefit most from this intervention.

Author contributions

JR and ND performed the literature searches, selected the studies, extracted the data, participated in the data analysis, and wrote the manuscript draft; AM aided in the data analysis and critically reviewed the manuscript for important intellectual content; JG, ERV, AC, and AQ critically reviewed the manuscript for important intellectual content; EF was responsible for the study concept and design, supervised data extraction, and participated in the analysis and manuscript preparation. All authors approved the final version of the manuscript as submitted.

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This study did not receive any funding.

Conflict of interest

The authors declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Asthma severity and treatment at baseline.

Figure S1. Reported side effects with macrolide therapy *vs* placebo.

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