Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review

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Objectives: To evaluate the efficacy and safety of macrolides in cystic fibrosis (CF).

Methods: Randomized controlled trials (RCTs) of macrolides for the treatment of CF published in PubMed, the Cochrane Library and Embase were searched. Application of inclusion and exclusion criteria, data extraction, and assessment of methodological quality were independently performed in duplicate. The primary efficacy outcome was the impact on the deterioration of lung function (changes in FEV1 and FVC). Safety outcomes included adverse events and mortality.

Results: Eight RCTs (seven with azithromycin and one with clarithromycin) were found in the systematic review and six RCTs with azithromycin (654 patients) were included in the meta-analysis. Azithromycin treatment showed a significant increase in FEV1% (3.22%, 95% CI = 1.38–5.06, P = 0.0006, I² = 0%) and FVC% (3.23%, 95% CI = 1.62–4.85, P < 0.0001, I² = 0%) compared with placebo. In individuals with baseline Pseudomonas aeruginosa colonization, both FEV1% (4.80%, 95% CI = 1.66–7.94, P = 0.003, I² = 42%) and FVC% (4.74%, 95% CI = 1.92–7.57, P = 0.001, I² = 0%) increased significantly. The incidence rates of the main side effects (cough, headache, abdominal pain, vomiting, nausea and diarrhoea) were not significantly different between the azithromycin-treated group and the placebo group. The RCT of clarithromycin, involving 18 patients, showed its effects on clinical improvement; however, the small sample size made comparisons with azithromycin difficult.

Conclusions: Long-term use of azithromycin can improve lung function, especially for P. aeruginosa-colonized CF patients. There was no evidence of increased adverse events with azithromycin. More data are needed to verify the best azithromycin regimen and to evaluate other macrolides in CF patients.

Keywords: azithromycin, clarithromycin, FEV1, FVC, Pseudomonas aeruginosa

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasians. It involves multiple organ systems, among which pulmonary involvement is the most dramatic. Patients with CF are often characterized by recurrent respiratory infection and inflammation along with malabsorption of fats and micronutrient deficiency. Pseudomonas aeruginosa is the most frequently isolated microorganism from CF patients, followed by Staphylococcus aureus, Haemophilus influenzae and Stenotrophomonas maltophilia.

Prevention of bacterial infection in the lung is the primary aim for CF treatment. Over recent decades, improved antibiotic treatment strategies against respiratory tract infections have helped extend the life expectancy of patients with CF. Inhaled dornase alfa (recombinant human deoxyribonuclease) and inhaled tobramycin are the most highly recommended therapies for chronic CF. Since beneficial effects were demonstrated with erythromycin in diffuse panbronchiolitis, a disease with many similarities to CF, macrolides have received attention in treating CF patients. Several studies have confirmed the benefits of macrolides in patients with moderate to severe lung diseases associated with CF. Two meta-analyses of macrolides for CF treatment have been conducted; however, the randomized controlled trials (RCTs) in these studies were relatively old (before 2006) and only a small number of subjects focusing only on azithromycin were included. In this study, we performed an updated meta-analysis including a number of recently published RCTs to determine whether changes should be made to the recommendation of macrolides for CF treatment.
Methods

Data sources
A systematic search of the literature in PubMed (up to July 2010), the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 2, 2010) and Embase (1980 to July 2010) was conducted to identify relevant RCTs for our meta-analysis. We combined the terms ‘macrolides’ [MeSH] OR ‘azithromycin’ [MeSH] OR ‘clarithromycin’ [MeSH] OR ‘erythromycin’ [MeSH] with ‘cystic fibrosis’ [MeSH]. Searches were limited to RCTs only. In addition, references of the initially identified articles were hand searched and reviewed, including relevant review papers. Abstracts presented in scientific conferences were not searched for.

Study selection
Two reviewers (Y. C. and R. W.) independently searched the literature and examined relevant RCTs for further assessment of data on efficacy and safety. A study was considered eligible if it was a clinical RCT, if it studied the role of macrolides in comparison with placebo, another class of antibiotic or another macrolide antibiotic in the treatment of CF patients, and if it assessed the efficacy, safety or mortality of both therapeutic regimens. Trials with blinded design were included. Non-randomized studies, experimental trials and trials focusing on pharmacokinetic or pharmacodynamic variables were excluded. Studies comparing regimens of the same macrolide antibiotic at different doses were also excluded.

Data extraction
The following data were extracted from each study: (i) year of publication; (ii) patient population; (iii) number of patients; (iv) antimicrobial agents and dosages used; (v) clinical outcomes; (vi) adverse events (AEs); and (vii) mortality.

Quality assessment
The two reviewers (Y. C. and R. W.) independently extracted the relevant data. A quality review of each RCT was done to include details of randomization, generation of random numbers, details of double-blinding procedure, information on withdrawals and allocation concealment. One point was awarded for the specification of each criterion, with a maximum score of five. High-quality RCTs scored three or more points, whereas low quality RCTs scored two or fewer points, according to a modified Jadad score.16

Outcomes analysed
The primary efficacy outcome of this meta-analysis was the impact of macrolides on lung function deterioration, including percentage change in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). Because most patients with CF develop progressive pulmonary disease, measures of pulmonary involvement, in particular FEV1 and FVC, have been used as markers of disease severity and to predict survival.17,18 The secondary efficacy outcome was the number of acute pulmonary exacerbations, number of oral or intravenous additional courses of antibiotics, changes in inflammatory markers, requirement for new hospitalizations and patients’ quality of life. Outcomes on effectiveness were analysed in the following groups: (i) length of follow-up; and (ii) infected with P. aeruginosa or other pathogenic bacteria. Safety outcomes included AEs and mortality.

Data analysis and statistical methods
Statistical analysis was done with Review Manager version 5.0.17 (Cochrane Collaboration, Oxford, UK). We assessed heterogeneity of trial results by calculating a $\chi^2$ test of heterogeneity and the $I^2$ measure of inconsistency. The publication bias was assessed by examining the funnel plot. Fixed effect risk ratios (RRs) for dichotomous variables and weighted mean differences for continuous variables with 95% confidence intervals (CIs) were calculated throughout the meta-analysis.

Figure 1. Flow diagram of the randomized controlled trials reviewed.
Results

Randomized controlled trial selection

From all potentially relevant articles, eight RCTs were excluded because they either did not meet the inclusion criteria or were not consistent with the inclusion criteria (see Table S1 available as Supplementary data at JAC Online). Three of these RCTs were excluded in the meta-analysis (Figure 1). Eight RCTs were included in this meta-analysis (Figure 1).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>RCT design</th>
<th>Population</th>
<th>Pathogen</th>
<th>Drug regimen (macrolides)</th>
<th>Screened patients</th>
<th>ITT AZM macrolides versus COM</th>
<th>PP AZM macrolides versus COM</th>
<th>Mean age AZM macrolides versus COM</th>
<th>Length of follow-up</th>
<th>Study quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saiman et al. (2010)</td>
<td>DB, CS</td>
<td>Age: 6–18 years</td>
<td>uninfected with PA</td>
<td>AZM: 250 mg (18–35.9 kg) or 500 mg (≥36 kg), 3 days per week for 168 days</td>
<td>324</td>
<td>131 versus 129</td>
<td>125 versus 124</td>
<td>10.7 versus 10.6</td>
<td>168 days</td>
<td>4</td>
</tr>
<tr>
<td>Dogru et al. (2009)</td>
<td>DB, CS</td>
<td>Age: 3–14.8 years</td>
<td>NA</td>
<td>CLR: 15 mg/kg/day in two divided doses for 3 months</td>
<td>18</td>
<td>9 versus 9</td>
<td>9 versus 8</td>
<td>10.6 versus 8.4</td>
<td>3 months</td>
<td>3</td>
</tr>
<tr>
<td>Steinkamp et al. (2008)</td>
<td>DB, CS</td>
<td>Age: ≥8 years</td>
<td>infected with PA</td>
<td>AZM: 500 mg (20–29 kg), 750 mg (30–39 kg), 1000 mg (40–59 kg), 1250 mg (50 kg), once per week for 8 weeks</td>
<td>40</td>
<td>21 versus 17</td>
<td>17 versus 12</td>
<td>23.7 versus 26.3</td>
<td>8 weeks</td>
<td>4</td>
</tr>
<tr>
<td>Clement et al. (2006)</td>
<td>DB, CS</td>
<td>Age: 6–21 years</td>
<td>infected with PA</td>
<td>AZM: 250 mg (≤40 kg) or 500 mg (≥40 kg), three times a week for 12 months</td>
<td>82</td>
<td>40 versus 42</td>
<td>35 versus 37</td>
<td>10.9 versus 11.1</td>
<td>12 months</td>
<td>4</td>
</tr>
<tr>
<td>Rotschild et al. (2005)</td>
<td>DB</td>
<td>Age: 6–36.7 years</td>
<td>infected with PA or non-PA</td>
<td>AZM: 250 mg twice weekly for 3 months</td>
<td>18</td>
<td>10 versus 8</td>
<td>10 versus 8</td>
<td>NA</td>
<td>3 months</td>
<td>3</td>
</tr>
<tr>
<td>Saiman et al. (2003)</td>
<td>DB, CS</td>
<td>Age: ≥6 years</td>
<td>infected with PA or non-PA</td>
<td>AZM: 250 mg (&lt;40 kg) or 500 mg (≥40 kg), 3 days per week for 168 days</td>
<td>251</td>
<td>87 versus 98</td>
<td>85 versus 93</td>
<td>20.2 versus 20.6</td>
<td>168 days</td>
<td>4</td>
</tr>
<tr>
<td>Wolter et al. (2002)</td>
<td>DB</td>
<td>Age: ≥18 years</td>
<td>infected with PA</td>
<td>AZM: 250 mg per day for 3 months</td>
<td>60</td>
<td>30 versus 30</td>
<td>21 versus 24</td>
<td>28.1 versus 27.7</td>
<td>3 months</td>
<td>4</td>
</tr>
<tr>
<td>Equi et al. (2002)</td>
<td>DB, CS</td>
<td>Age: 8–18 years</td>
<td>infected with PA or non-PA</td>
<td>AZM: 250 mg (≤40 kg) or 500 mg (≥40 kg) per day for 3 months</td>
<td>41</td>
<td>20 versus 21</td>
<td>20 versus 21</td>
<td>13.6 versus 14.3</td>
<td>6 months</td>
<td>4</td>
</tr>
</tbody>
</table>

MC, multicentre; DB, double blind; CS, cross-over; NA, not available; AZM, azithromycin; CLR, clarithromycin; COM, comparator; ITT, intention to treat; PP, per protocol; PA, P. aeruginosa; non-PA, pathogenic bacteria other than P. aeruginosa.
Figure 2. Effects of azithromycin (AZM) on changes in (a) FEV₁% and (b) FVC% from baseline. IV, inverse variance; df, degree of freedom.
### (a) FEV₁% change in P. aeruginosa-infected patients

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM mean (SD)</th>
<th>Placebo mean (SD)</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clement 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>-8.7 (11.5)</td>
<td>-2.7 (21)</td>
<td>10</td>
<td>4.4%</td>
</tr>
<tr>
<td>Saiman 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>4.4 (13.6)</td>
<td>-1.8 (10.7)</td>
<td>98</td>
<td>77.9%</td>
</tr>
<tr>
<td>Steinkamp 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>-3.7 (13.3)</td>
<td>-5 (10.1)</td>
<td>17</td>
<td>17.8%</td>
</tr>
</tbody>
</table>

Total (95% CI) 117 125 100.0% 4.80 [1.66, 7.94]

Heterogeneity: $\chi^2 = 3.43$, df = 2 ($P = 0.18$); $I^2 = 42$

Test for overall effect: $Z = 3.00$ ($P = 0.003$)

### (b) FEV₁% change in non-P. aeruginosa-infected patients

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM mean (SD)</th>
<th>Placebo mean (SD)</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clement 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>-3 (19.3)</td>
<td>-1.1 (13.5)</td>
<td>32</td>
<td>13.0%</td>
</tr>
<tr>
<td>Saiman 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>5.4 (13.3)</td>
<td>3.4 (12.4)</td>
<td>124</td>
<td>87.0%</td>
</tr>
</tbody>
</table>

Total (95% CI) 156 156 100.0% 1.49 [-1.49, 4.47]

Heterogeneity: $\chi^2 = 0.75$, df = 1 ($P = 0.39$); $I^2 = 0$

Test for overall effect: $Z = 0.98$ ($P = 0.33$)

### (c) FVC% change in P. aeruginosa-infected patients

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM mean (SD)</th>
<th>Placebo mean (SD)</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clement 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>-4.3 (15.4)</td>
<td>-4.9 (19.4)</td>
<td>10</td>
<td>3.2%</td>
</tr>
<tr>
<td>Saiman 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>3.7 (11.8)</td>
<td>-1.3 (9)</td>
<td>98</td>
<td>85.5%</td>
</tr>
<tr>
<td>Steinkamp 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>-3.1 (15.5)</td>
<td>-7.1 (10.9)</td>
<td>17</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Total (95% CI) 117 125 100.0% 4.74 [1.92, 7.57]

Heterogeneity: $\chi^2 = 0.33$, df = 2 ($P = 0.85$); $I^2 = 0$

Test for overall effect: $Z = 3.29$ ($P = 0.001$)

### (d) FVC% change in non-P. aeruginosa-infected patients

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM mean (SD)</th>
<th>Placebo mean (SD)</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clement 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>-1 (13.3)</td>
<td>-4.3 (9.2)</td>
<td>32</td>
<td>19.7%</td>
</tr>
<tr>
<td>Saiman 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>-0.9 (11.7)</td>
<td>-2.3 (10.9)</td>
<td>124</td>
<td>80.3%</td>
</tr>
</tbody>
</table>

Total (95% CI) 156 156 100.0% 1.77 [-0.74, 4.29]

Heterogeneity: $\chi^2 = 0.35$, df = 1 ($P = 0.56$); $I^2 = 0$

Test for overall effect: $Z = 1.38$ ($P = 0.17$)

**Figure 3.** Effects of azithromycin (AZM) on changes in FEV₁% and FVC% in P. aeruginosa- or non-P. aeruginosa-infected patients. IV, inverse variance; df, degree of freedom.
## (a) Pulmonary exacerbation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM events</th>
<th>Placebo events</th>
<th>Risk ratio M–H, random, 95% CI</th>
<th>Risk ratio M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saiman 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>52 87</td>
<td>66 98</td>
<td>0.89 [0.71, 1.11]</td>
<td>0.74 [0.64, 0.86]</td>
</tr>
<tr>
<td>Saiman 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>28 131</td>
<td>50 129</td>
<td>0.55 [0.37, 0.82]</td>
<td>0.65 [0.53, 0.79]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>218</td>
<td>227</td>
<td>0.72 [0.44, 1.17]</td>
<td>0.69 [0.61, 0.78]</td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 1.32$ ($P = 0.19$)

Heterogeneity: $I^2 = 79\%$; $b^2 = 4.81$, df = 1 ($P = 0.03$)

## (b) Hospitalization

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM events</th>
<th>Placebo events</th>
<th>Risk ratio M–H, random, 95% CI</th>
<th>Risk ratio M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saiman 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>14 87</td>
<td>29 98</td>
<td>0.54 [0.31, 0.96]</td>
<td>0.74 [0.64, 0.86]</td>
</tr>
<tr>
<td>Saiman 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>12 131</td>
<td>13 129</td>
<td>0.91 [0.43, 1.92]</td>
<td>0.65 [0.53, 0.79]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>218</td>
<td>227</td>
<td>0.66 [0.42, 1.04]</td>
<td>0.69 [0.61, 0.78]</td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 1.80$ ($P = 0.07$)

Heterogeneity: $I^2 = 13\%$; $b^2 = 1.15$, df = 1 ($P = 0.28$)

## (c) Oral antibiotics

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM events</th>
<th>Placebo events</th>
<th>Risk ratio M–H, random, 95% CI</th>
<th>Risk ratio M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saiman 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>60 87</td>
<td>91 98</td>
<td>0.74 [0.64, 0.86]</td>
<td>0.74 [0.64, 0.86]</td>
</tr>
<tr>
<td>Saiman 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>65 131</td>
<td>99 129</td>
<td>0.65 [0.53, 0.79]</td>
<td>0.65 [0.53, 0.79]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>218</td>
<td>227</td>
<td>0.69 [0.61, 0.78]</td>
<td>0.69 [0.61, 0.78]</td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 5.77$ ($P < 0.00001$)

Heterogeneity: $I^2 = 24\%$; $b^2 = 1.31$, df = 1 ($P = 0.25$)

## (d) Intravenous antibiotics

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZM events</th>
<th>Placebo events</th>
<th>Risk ratio M–H, random, 95% CI</th>
<th>Risk ratio M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saiman 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>18 87</td>
<td>30 98</td>
<td>0.68 [0.41, 1.12]</td>
<td>0.68 [0.41, 1.12]</td>
</tr>
<tr>
<td>Saiman 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>11 131</td>
<td>14 129</td>
<td>0.77 [0.36, 1.64]</td>
<td>0.77 [0.36, 1.64]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>218</td>
<td>227</td>
<td>0.71 [0.46, 1.08]</td>
<td>0.71 [0.46, 1.08]</td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 1.60$ ($P = 0.11$)

Heterogeneity: $I^2 = 0\%$; $b^2 = 0.09$, df = 1 ($P = 0.77$)

---

**Figure 4.** Meta-analyses of exploratory outcomes: (a) pulmonary exacerbation; (b) hospitalization; and (c and d) new use of oral or intravenous antibiotics. AZM, azithromycin; M–H, Mantel–Haenszel; df, degree of freedom.
increased greatly in *P. aeruginosa*-infected patients in the azithromycin group (Figure 3a and 3c) compared with the placebo group. However, in patients not colonized by *P. aeruginosa*, FEV1% (P=0.33, I²=0%) and FVC% (P=0.17, I²=0%) showed no significant change after azithromycin treatment when compared with the placebo group (Figure 3b and 3d).

**Secondary efficacy outcomes**

Almost all the secondary efficacy outcomes could not be combined because of the different study designs and different types of data, except for the studies of Saiman et al. in 2003 and 2010. In these two studies, similar rates of pulmonary exacerbation were observed in the azithromycin treatment group and the placebo group during the follow-up of the 445 patients (Figure 4a; RR=0.72, 95% CI=0.44–1.17, P=0.19, I²=79%). Results also showed that there was no statistically significant reduction in the number of hospitalized participants in the azithromycin group compared with the placebo group (Figure 4b; RR=0.66, 95% CI=0.42–1.04, P=0.07, I²=13%). The azithromycin group had less risk of oral antibiotic use than the placebo group (Figure 4c; RR=0.69, 95% CI=0.61–0.78, P<0.00001, I²=24%), while no differences were found in intravenous (iv) antibiotic use (Figure 4d; RR=0.71, 95% CI=0.46–1.08, P=0.11, I²=0%).

Four out of the eight RCTs presented inflammatory marker results, including C-reactive protein (CRP) and interleukin-8 (IL-8). Steinkamp et al. reported that after 8 weeks, CRP in the placebo group was higher than that in the azithromycin group (8.2±9.9 mg/L versus 27.8±58.7 mg/L, P=0.019). Wolter et al. also reported that azithromycin treatment had a significant effect on CRP (P<0.001). Median CRP values declined steadily over time in the azithromycin group, but remained relatively constant in the placebo group. Dogru et al. reported no statistically significant difference in median IL-8 levels, both with clarithromycin and placebo treatments. In the study of Steinkamp et al., IL-8 decreased after 8 weeks of azithromycin treatment (–3.1 pg/mL) and increased after placebo (+2.9 pg/mL) treatment, and significant differences (P=0.001) were observed between the two groups. Saiman et al. found that the change in the IL-8 level was similar in the azithromycin and placebo groups.

Three trials showed that the quality of life of CF patients was significantly better when they were treated with azithromycin than with placebo, although specific indexes of quality were different in these studies.

**Safety outcomes**

Seven out of the eight RCTs presented data regarding AEs. The total number of AEs and the most frequently occurring AEs are listed in Table 2. Two cross-over studies (clarithromycin study of Dogru et al. and azithromycin study of Equi et al.) reported no AEs during the entire study. Three studies reported slightly a higher incidence of AEs in the azithromycin group and the other two studies showed a lower incidence of AEs in the azithromycin group. The most frequently reported AEs were analysed (Figure 5). Incidence of cough (RR=0.79, 95% CI=0.62–1.02, P=0.07, I²=58%), headache (RR=0.90, 95% CI=0.67–1.20, P=0.47, I²=0%), abdominal pain (RR=0.95,
Figure 5. Meta-analyses of adverse events possibly related to studied medications. AZM, azithromycin; M–H, Mantel–Haenszel; df, degree of freedom.
infections. So, the macrolide-associated properties of a thick and tight biofilm, causing chronic and intractable P. aeruginosa pathogen in CF patients is and deteriorating lung function. The most common colonizing cause of morbidity and mortality in CF are chronic lung infection P. aeruginosa direct bactericidal effects against Gram-negative bacterial pathogens; however, they have limited lides are effective against a wide range of Gram-positive and CI = 0.19, 3.50] [0.41, 1.97] [0.03, 2.37]

Discussion

Besides their well-known bacteriostatic activity as a group of antibiotics, macrolides modulate inflammation and immunity in eukaryotes without affecting homeostatic immunity. Macrolides are effective against a wide range of Gram-positive and Gram-negative bacterial pathogens; however, they have limited direct bactericidal effects against P. aeruginosa. The main causes of morbidity and mortality in CF are chronic lung infection and deteriorating lung function. The most common colonizing pathogen in CF patients is P. aeruginosa, which often forms a thick and tight biofilm, causing chronic and intractable infections. So, the macrolide-associated properties of impaired bacterial biofilm synthesis, attenuation of bacterial virulence factors and immunoregulation might lead to their use in treating CF.

This systematic review with meta-analysis compared the efficacy and safety of macrolides with placebo in CF patients. Only one RCT compared clarithromycin with placebo. Some improvements in clinical status, such as decrease in acute pulmonary exacerbations, have been shown after 3 months of clarithromycin treatment. However, this RCT had a very small sample of patients in both the treatment and placebo groups, and the results could not be combined with those of other RCTs because of different data types (median versus mean). Another seven RCTs focused on azithromycin; no RCT of other macrolides, such as erythromycin or roxithromycin, in CF patients was found in our study. The possible reasons why azithromycin is the most widely used macrolide in CF patients are: (i) its prolonged half-life in blood (≏68 h) allows for daily dosing and reduces the pill burden for patients already on multiple medications; and (ii) it is metabolized through the liver and is not induced or oxidized by cytochrome P450 enzymes, making it less interactive with other drugs. Clarithromycin, a commonly used macrolide with fewer AEs (compared with other kinds of macrolides, except azithromycin) and excellent uptake by respiratory tissues, also deserves further studies on its effect and role in CF treatment. Next, we focused on azithromycin, because all meta-analyses were based on azithromycin RCTs. Azithromycin was associated with a statistically significant increase of FEV1% and FVC%. However, this increase had clinical importance. Long-term (≏3 months) azithromycin treatment greatly improved the lung function of the patients, while short-term (≤3 months)
azithromycin or placebo treatment made no difference to the changes in FEV1% and less of a difference to the changes in FVC compared with long-term treatment. Azithromycin treatment improved FEV1% and FVC% in P. aeruginosa-colonized subpopulations, while no significant change was found in non-P. aeruginosa-colonized subpopulations. These suggested that P. aeruginosa-colonized CF patients might receive the most benefit with long-term azithromycin treatment.

The similar study designs of Saiman et al. in 2003 and 2010 enabled the combination of the results of pulmonary exacerbation, hospitalization, and oral and iv antibiotic use. Rate enabled the combination of the results of pulmonary exacerbation, hospitalization, and oral and iv antibiotic use. Rate of oral antibiotics use in azithromycin group was significantly lower than placebo group. Rate of pulmonary exacerbation, hospitalization and iv antibiotic use in the azithromycin group showed no statistically or clinically significant difference compared with placebo group. However, each of these two studies showed that azithromycin had less risk of causing exacerbations than placebo. Such a contradiction might be due to the high heterogeneity (I² = 79%), which was most probably caused by different pathogens (P. aeruginosa or others) in CF patients. This suggests that when pulmonary exacerbations are analysed it will be appropriate to divide them into subgroups according to different pathogens.

Azithromycin treatment also caused the decrease of some inflammatory markers, such as CRP, and IL-8. One exception was that Saiman et al. failed to detect a significant change in the IL-8 level during their study.

The safety data of the most frequently reported AEs (cough, headache, abnormal pain, vomiting, nausea and diarrhoea) showed that azithromycin and placebo had almost the same rate of AEs, while Florescu et al. reported that azithromycin treatment had a significantly higher risk of the main AEs (nausea and diarrhoea) than placebo treatment. Because Florescu et al. did not provide data on AE analyses, we could only speculate that different sample sizes and more accurate dosing of azithromycin in the new RCTs might have led to the lower rate of AEs.

There were some limitations of our meta-analysis. First, there was heterogeneity in some of the relevant aspects (time of follow-up, drug dosage and pathogens), which made some results difficult to interpret. However, differences among trials were inevitable and heterogeneity did not preclude pooling of the results, because individual patients were directly compared only with other patients within the same trial and not across trials. Moreover, subgroup analysis was performed to reduce uncertainty resulting from clinical heterogeneity. Second, two studies comparing azithromycin at different doses were not included. One of them compared azithromycin at 5 mg/kg/day with 15 mg/kg/day and the other compared 250 mg daily with 1200 mg weekly treatments. It was difficult to include these RCTs, because the dose regimens of even these two RCTs were not comparable. Azithromycin plays an important role in CF patients; however, more RCTs to determine the best regimen are still needed.

In conclusion, we present the largest meta-analysis and systematic review of studies of macrolides for the treatment of CF patients to date. We conclude that azithromycin has favourable efficacy outcome (lung function index: change in FEV1% and FVC%) and similar incidence rates of AEs compared with placebo therapy for CF. Benefit was most apparent for individuals who received >3 months of azithromycin treatment. However, well-designed RCTs focusing on azithromycin treatment at different dosages and intervals, as well as macrolides other than azithromycin are still required.

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**Transparency declarations**

None to declare.

**Supplementary data**

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

**References**


