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Effects of prolonged use of azithromycin in patients with cystic fibrosis: A meta-analysis

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ABSTRACT

Azithromycin has been studied as potential therapeutic anti-inflammatory agent for cystic fibrosis (CF) patients. Azithromycin (AZM) has been used as an immunomodulating agent, based on few small studies. Considering the cost and potential side effects of long-term azithromycin therapy, it is important to identify the group of patients that would benefit the most. Weighted mean difference was used for pulmonary function tests, and risk ratios for all other variables. The random-effects model was applied for all reports. Combining four studies ($N = 368$), azithromycin showed increase in FEV_1 (3.53%, 95% CI 0.00, 7.07, $p = 0.05$; $I^2 = 38\%$) and FVC (4.24%, 95% CI 2.02, 6.45, $p = 0.0002$; $I^2 = 0\%$). When trials were analyzed by baseline *Pseudomonas* sputum colonization, the heterogeneity decreased ($I^2 = 0\%$), FEV_1 significantly increased to 4.66% (95% CI 1.18, 8.15, $p = 0.009$), and FVC increased to 4.64% (95% CI 2.11, 7.17, $p = 0.0003$). The GI side effects were 72% higher with azithromycin use (RR 1.72, 95% CI 1.33, 2.21, $p = 0.00003$), the main side effects being nausea (RR 2.04, 95% CI 1.19, 3.45, $p = 0.009$), and diarrhea (RR 2.12, 95% CI 1.10, 4.08, $p = 0.02$). Azithromycin improves lung function of CF patients, especially in the subgroup colonized with *Pseudomonas*. However, nausea and diarrhea are significantly more frequent with azythromycin.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease primarily affecting the lungs. The median survival of CF patient has been steadily increasing to 36.9 years [1] as a result of better antibiotic treatment, standardization of care, and establishment of multidisciplinary CF Care Centers [2,3]. CF physicians primarily follow lung disease quarterly by measurement of the forced expiratory volume at 1 s (FEV_1), with increased frequency during pulmonary exacerbations of disease.

The pathophysiology of cystic fibrosis lung disease is related to the abnormal cystic fibrosis transmembrane receptor (CFTR) present in the apical cell membrane of airway epithelial cells. Abnormal CFTR results in excessive efflux of sodium from the airway surface layer with resultant loss of chloride and water from the airway mucus layer [4,5]. Dehydration of mucus compromises ciliary clearance resulting in airway obstruction. Patients with CF have cough as the sole mechanism to clear the abnormally thick sputum.

Retained mucus in the lungs of these patients serves as a growth medium for many bacteria, mainly *Pseudomonas aeruginosa*. The neutrophilic response to this infection creates an inflammatory milieu in airways, causing damage to the airway walls and development of progressive bronchiectasis, contributing further to impaired mucus clearance. The cycle of airway obstruction combined with recurrent infections, inflammation and bronchiectasis progresses to end stage lung disease and death or the need for lung transplantation.

Standard therapies for CF include chest physiotherapy to augment clearance of abnormal mucus [6], DNAse to decrease the viscosity of airway secretions [7], inhaled anti-pseudomonal antibiotics (tobramycin or colistin) to decrease the density of *Pseudomonas* colonization [8] and nebulized hypertonic saline [9]. Azithromycin has also recently become part of the standard CF maintenance therapy [10] despite limited supporting evidence, and it has been given a strong recommendation by the Cystic Fibrosis Foundation. We intend to perform a systematic review and meta-analysis to evaluate the efficacy and safety of azithromycin in CF patients.

Abbreviations: CF, cystic fibrosis; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity; CFTR, cystic fibrosis transmembrane receptor.

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2. Methods

2.1. Search strategy and inclusion criteria

We searched Cochrane Register of Controlled trials and PubMed database from inception to April 2008. No language or date restrictions were applied. The keywords used were cystic fibrosis, azithromycin, macrolides, randomized, and clinical trial. Two reviewers independently performed the search and disagreements were resolved by consensus among authors.

2.2. Inclusion criteria

We included randomized placebo controlled trials that assessed the long-term effects of azithromycin treatment on pulmonary function tests, respiratory infections, antibiotic use, and hospitalizations in patients with CF. We included trials that compared different regimens of azithromycin only with placebo.

2.3. Exclusion criteria

Trials that were not randomized, or that compared azithromycin against active control were excluded.

2.4. Primary and secondary outcomes

The primary outcome assessed was the impact of azithromycin on lung function deterioration (percentage change in FEV_1 and FVC). All selected trials reported $FEV_{1\%}$ and FVC% predicted values pretreatment and predicted change with placebo and azithromycin treatment.

Secondary outcomes included: number of acute pulmonary exacerbations, number of oral or intravenous additional courses of antibiotics, changes in inflammatory markers, impact on the frequency of the newly positive sputum cultures, requirement for new hospitalizations, adverse effects from azithromycin, and patients' quality of life.

2.5. Statistical analysis

Outcomes analyzed by weighted difference in means included: forced expiratory volume at 1 s (FEV_1); forced vital capacity (FVC); number of IV antibiotics courses for acute exacerbations; number of hospital days. Side effects were analyzed by risk ratios. Because of the different follow up length of time among trials, all results were reported with the random-effects model by DerSimonian and Laird [11]. Heterogeneity was analyzed by I^2 and Cochran Q statistics. QUOROM Guidelines were used for meta-analysis reporting (Fig. 1), and the Jadad scale was used for the quality of each clinical trial (Table 1). The Egger regression method was used to evaluate publication bias [12]. The software used was Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ).

3. Results

The initial search of the database produced 18 potentially relevant studies (Fig. 1). Nine studies were selected as randomized placebo controlled trials involving treatment with azithromycin in patients with CF. One article was excluded because it was a meta-analysis of three previously published studies [13]. The rest of the articles were reviewed in detail and only four studies qualified as randomized placebo controlled studies [10–16]. The study by Equi et al. had a cross-over design [15], but based on the first 6 months follow up and results reported in another manuscript [13], we were able to keep this study in our meta-analysis. Table 1 contains summary information concerning the four included trials, including the quality score assigned (Jadad scale).

3.1. Demographic characteristics

The demographic characteristic of the patients in the control and treatment arms were similar (Table 1). We included a total of 368 patients, 191 patients in the placebo arm and 177 in the azithromycin arm, 190 patients male and 178 female. The mean age of patients in the placebo group was 18.5 years and in the azithromycin group 18.1 years. Two of the studies were conducted in young adults [10,16], and the other two were conducted in children [14,15]. The patients were treated for 13–52 weeks (mean 28.25 weeks) (Table 1). Two studies aimed to enroll patients with *Pseudomonas* colonization [10,16]: Saiman et al. (90% positive) and Wolter et al. (83% positive). Most of the patients enrolled in Clement study were not colonized with *Pseudomonas* [14], but we were able to extract the data for patients colonized with *Pseudomonas* and combine with the other two trials [10,16] to evaluate the effect of azithromycin in trials with high proportion of patients colonized with *Pseudomonas*. The patients not colonized with *Pseudomonas* from the Clement study were combined with the ones from Equi study [15] (only 50% colonized) to evaluate the effect of azithromycin in trials with no (or low proportion of) patients colonized with *Pseudomonas*.

3.2. Primary efficacy outcome

Azithromycin showed an overall significant 3.53% increase in FEV_1 (95% CI 0.00, 7.07, $p = 0.05$; $I^2 = 38\%$) (Fig. 2). No significant FEV_1 changes were observed in the first 3 months of follow up. When FEV_1 changes were analyzed by the baseline *Pseudomonas* sputum colonization (Fig. 3), heterogeneity decreased, and the FEV_1 increase to 4.66 (95% CI 1.18, 8.15, $p = 0.009$; $I^2 = 22\%$) for trials with high proportion of *Pseudomonas* colonization.

The overall FVC increase with azithromycin was also significant (4.24%; 95% CI 2.02, 6.45, $p = 0.0002$; $I^2 = 0\%$) (Fig. 4) compared to that of placebo. No significant FVC changes were observed in the first 3 months of follow up. The FVC increase in trials with low proportion of *Pseudomonas* (Fig. 5) was 3.0 (95% CI 1.45, 7.45, $p = 0.186$; $I^2 = 0\%$), and with higher proportion of *Pseudomonas* colonization was 4.64% (95% CI 2.11, 7.17, $p = 0.0003$; $I^2 = 0\%$).

3.3. Secondary efficacy outcomes

Because of different study design and different study periods, the following outcomes from the four studies data could not be combined: number of days of hospitalization, number of acute pulmonary exacerbations, number of days of hospitalization, inflammatory markers, adverse effects, quality of life. Three trials showed a significant decrease in the number of antibiotic courses (oral and/or intravenous courses of antibiotics) [10,14,16]. Only two of these studies reported non-statistically significant reduction in hospital days [10,14,16].

3.4. Safety outcomes

The risk of gastrointestinal side effects was 72% higher with azithromycin use (RR 1.72, 95% CI 1.33, 2.21, $p = 0.00003$). The main side effects reported were nausea (RR 2.04, 95% CI 1.19, 3.45, $p = 0.009$), and diarrhea (RR 2.12, 95% CI 1.10, 4.08, $p = 0.02$), both significantly higher with azithromycin compared to placebo. Mortality could not be analyzed because it was not reported in any of the included trials.