Long-term Azithromycin Treatment in Pediatric Primary Ciliary Dyskinesia: A Retrospective Study

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Abstract

Objectives: Primary ciliary dyskinesia (PCD) is a rare genetic disease mainly involved in lung dysfunction. PCD patient outcomes after azithromycin (AZM) treatment have rarely been reported. This study was aimed to assess AZM treatment effects on disease progression of pediatric PCD patients. Study design: This retrospective follow-up study involved PCD patients diagnosed from December 2009 to December 2020. Changes of clinical outcomes, pulmonary function, and chest computed tomography findings were compared between untreated and AZM-treated patients. Results: Of 63 enrolled patients (median follow-up duration of 3.1 years), 30 received AZM (AZM-treated group) and 33 received no AZM (AZM-untreated group). At diagnosis, no significant intergroup differences in age, sex, height, weight, respiratory infection frequency, and FEV1% and FVC% predicted values were found, although FEF25-75% predicted was lower in AZM group. Between treatment initiation and follow-up, patients in AZM-treated group had less respiratory infection frequency than that of controls (1.4 ± 0.8 VS 3.0 ± 2.1 times/year, respectively, P = 0.001) and fewer AZM-treated group patients exhibited exercise intolerance. Increases above baseline of AZM-treated group FEV1% and FVC% predicted values exceeded corresponding control increases, but intergroup differences were insignificant (FEV1% predicted: 5.3 (-13.4, 9.4) VS 1.8 (-12.1, 9.5), P = 0.477; FVC% predicted: 6.7 (-7.6, 18.8) VS 1.6 (-5.6, 7.6), P = 0·328). Conclusions: Long-term AZM treatment can reduce respiratory infection frequency and may maintain pulmonary diseases stable in pediatric PCD patients.

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ABSTRACT

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in age, sex, height, weight, respiratory infection frequency, and FEV1% and FVC% predicted values were found, although FEF_{25-75}% predicted was lower in AZM group. Between treatment initiation and follow-up, patients in AZM-treated group had less respiratory infection frequency than that of controls (1.4 ± 0.8 *VS* 3.0 ± 2.1 times/year, respectively, $P = 0.001$) and fewer AZM-treated group patients exhibited exercise intolerance. Increases above baseline of AZM-treated group FEV1% and FVC% predicted values exceeded corresponding control increases, but intergroup differences were insignificant (FEV1% predicted: 5.3 (-13.4, 9.4) *VS* 1.8 (-12.1, 9.5), $P = 0.477$; FVC% predicted: 6.7 (-7.6, 18.8) *VS* 1.6 (-5.6, 7.6), $P = 0{\cdot}328$).

Conclusions: Long-term AZM treatment can reduce respiratory infection frequency and may maintain pulmonary diseases stable in pediatric PCD patients.

Keywords

Primary ciliary dyskinesia, pediatric, azithromycin

Abbreviation

PCD Primary ciliary dyskinesia

AZM Azithromycin

FEV1 Forced expiratory volume in one second

FVC Forced vital capacity

FEF_{25-75} Forced expiratory flow at 25-75%

CF Cystic fibrosis

BEAT-PCD Better Experimental Approaches to Treat PCD

Introduction

Primary ciliary dyskinesia (PCD), a rare genetic disorder that is characterized by recurrent respiratory infection and pulmonary dysfunction, has historically been viewed as a mild respiratory condition [1]. However, recent data suggest that PCD disease can seriously impair lung function in children of preschool age. In fact, in some children PCD can worsen rapidly and lead to greater decline in lung function during childhood than occurs in pediatric cystic fibrosis (CF) patients [2-4]. Frequent respiratory tract infections appear to be important factor of pulmonary disease progression in PCD patients [5], while also causing repeated hospitalizations that adversely affect quality of life of patients. Moreover, results of one European study revealed that 70% of PCD patients who did not receive regular treatment accumulated more than 50 outpatient visits before diagnosed[6].

Respiratory management of PCD patients is critical in order to prevent irreversible lung damage and appropriate treatment will likely prevent or slow progression of lung damage once a diagnosis is established[5]. Current PCD treatment mainly follows CF and non-CF bronchiectasis treatment recommendations, with azithromycin (AZM) maintenance therapy known to exert beneficial anti-inflammatory effects when use to treat CF and non-CF bronchiectasis [7, 8]. RCTs examining azithromycin versus placebo demonstrated increases of percent predicted forced expiratory volumes (ranged from 2.95% to 6.2%) in AZM-treated CF patients and two studies of azithromycin treatment in adult non-CF bronchiectasis lasting 6 and 12 months showed similar results [9, 10]. For a long time, there were only anecdotal reports of benefit from macrolide antibiotic (Clarithromycin, erythromycin, and azithromycin) in PCD patients[11, 12]. Recently, an international BEAT-PCD consensus statement for infection prevention and control was published in order to improve diagnosis and treatment [13]. Besides, the recently well-designed randomized, placebo-controlled trial showed that significantly improvement of pulmonary exacerbations in PCD patients that received 6-month AZM treatment regimens as compared to those receiving a placebo, while measurements of pulmonary function indicators revealed no significant intergroup differences in changes of predicted FEV1, FVC and FEF_{25-75}

values[14]. Nonetheless, treatment outcomes of pediatric PCD patients receiving AZM are unclear, since studies abovementioned conducted to date have been focused either on adults or included both children and adults.

Here, we describe clinical outcomes of AZM-treated pediatric PCD patients based on longitudinal follow-up periods of 3.1 years on average (4 months to 9.4 years). The aim of the study was to evaluate effects of long term AZM treatment on pulmonary disease status of pediatric PCD patients through retrospective analysis of clinical follow-up data conducted at the largest pediatric pulmonary treatment center in China.

Subjects and Methods

Subjects:

This study was conducted in order to provide a retrospective analysis of clinical data obtained from a group of PCD pediatric patients who were diagnosed in the Department of Respiratory Medicine in Beijing Children's Hospital between January 2009 and December 2020. PCD patients enrolled in this study had received definitive PCD diagnoses and consented to receive follow-up care. The study was approved by the Beijing Children's Hospital Ethics Committee. Verbal and written consent was obtained from all parents and patients older than 8 years of age enrollment in the study.

Data Collection:

Collection of disease-specific clinical data was collected using a pre-designed form. Baseline clinical data that were collected included demographic information: name, sex, date of birth, age at diagnosis, height at diagnosis, weight at diagnosis, medical history, diagnostic information, lung function, and chest imaging results, history of hospitalizations and drug treatments, antibiotics used to treat acute infections (dosage, treatment duration), prophylactic antibiotics (antibiotic drugs, dosage, start date), other prescribed medications (e.g., mucolytic agents, corticosteroids), and surgeries. Follow-up data that were collected included the annual frequency of respiratory infection-associated exacerbations, lung function test results, chest computed tomography (CT) imaging findings, growth measurements, days off from school due to PCD, sports endurance, etc. Clinical data were retrospectively analyzed and assessed.

Clinical data of patients were compared according to AZM treatment duration. Patients treated regularly with AZM at a dose of 10 mg/kg administered 3 times per week for longer than 3 months were assigned to the AZM-treated group, while those who did not take AZM or less than 3 months were assigned to AZM-untreated group. Clinical changes, frequency of respiratory tract infections, changes in height and weight, lung function changes, and changes in chest imaging findings were compared between the two groups.

Statistics:

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc, Chicago, IL). Continuous data were expressed as the mean ± standard deviation or median. The normality of each variable distribution was assessed using the Kolmogorov-Smirnov test. Comparisons of quantitative data between AZM-treated and AZM-untreated groups were conducted using the T-test or Mann-Whitney U test, while X^2 or Fisher's exact tests were used to compare proportions. Statistical tests were two-sided and were deemed statistically significant for $P < 0.05$.

Results

Demographics and Clinical Characteristics of Patients at Baseline

From January 2009 to December 2020, a total of 75 patients with definitive PCD diagnoses were admitted to the Department of Respiratory Medicine, Beijing Children's Hospital. Clinical and genetic characteristics of patients were collected and analyzed during the follow-up period. Of the total of 75 PCD patients, 63 patients received follow-up care, 7 patients were lost to follow-up, 4 refused to participate, and 1 patient died of severe complex congenital heart disease at 1 year of age. In summary, follow-up data were obtained from a total of 63 patients, of which 35 patients were males and 28 were females; the overall median duration of

the follow-up period after diagnosis was 3.1 years (ranging from four months to 9.4 years) and the average age at diagnosis was 7.6 +- 3.3 years.

Age, sex and clinical characteristics between AZM-treated and AZM-untreated groups of PCD patients were very similar at baseline (Table 1, partly reported in previous studies[12]) except for FEF_{25-75}% predicted values, which were lower in the AZM-treated group than in the AZM-untreated group (46.9 +- 20.8 *VS* 70.8 +- 28.0, $P = 0.008$, respectively).

PCD Management

In this study, routine therapies used to treat PCD patients included long-term AZM administration, airway clearance (daily chest physiotherapy), inhaled hyperosmolar agents, and corticosteroids. Treatment during acute infection included antibiotics, with AZM administered most often, followed by ceftriaxone, ceftazidime, cefoperazone sodium, sulbactam sodium, and meropenem. PCD patients presenting with wheezing as the major symptom were also treated with intravenous or oral corticosteroids.

Treatment management details of 63 patients are shown in Table 2. Although long-term oral AZM was recommended for 90% of patients with definite PCD diagnosis, only about 50% of patients were able to adhere to long-term oral AZM administration, of which 46% complied with recommended airway clearance physiotherapy.

Ultimately, the average duration of oral AZM treatment was 14 months (range 0.5 to 29 months). Notably, in the total of follow-up patients, 30 (48%) of patients continually took AZM for longer than 3 months, including 8 patients who took AZM for 3-6 months and 22 patients for more than 6 months. The remaining 33 (52%) patients who either did not regularly take AZM or took AZM for less than 3 months were assigned in the AZM-untreated group included, including 22 patients who did not take AZM, 4 patients who regularly took AZM for 2 weeks, 4 patients who took AZM for 1 month, and 2 patients who took AZM for two months. Aside from AZM treatment, there were no significant differences in other treatment measures between the two groups (Table 2).

In the AZM-treated group, 3 patients experienced transient nausea and abdominal pain that ceased after oral AZM administration timing was changed. No other serious adverse reactions were observed. Moreover, testing at intervals during follow-up revealed that no patients suffered from leucopenia or neutropenia, and no patients had abnormal alanine transaminase levels, or abnormal electrocardiogram findings.

Clinical Outcomes

Growth Changes

Average percentage-based increases in height of children were 9.6% and 6.9% for AZM-treated and AZM-untreated groups, respectively, between the time of initial diagnosis to the final follow-up visit, with percentage change in height increasing in 75% of AZM-treated group patients as compared to 64% of AZM-untreated group patients. Meanwhile, BMI percentile increases did not significantly differ between AZM-treated and AZM-untreated groups [(1.5, 1.0-2.0) *VS* (1.7, -6.4-17.9), respectively], while the average AZM-treated group weight increased by only 5.1% as compared to 10.2% for the AZM-untreated group (Table 3) also with no significance of difference.

PCD Manifestations

The mean frequency of infections was significantly reduced in the AZM-treated group as compared to the AZM-untreated group (1.4 +- 0.8 *VS* 3.0 +- 2.1, respectively, P =0.001). In addition, significantly decreased sputum volumes were observed in AZM-treated group patients as compared to those of AZM-untreated group (93% *VS* 70%, respectively, P =0.043). Moreover, the percentage number of AZM-treated group patients with exercise intolerance was lower than that of the AZM-untreated group (12% *VS* 24%, respectively,P =0.009).

Changes in Chest CT Findings and Pulmonary Function Test (PFT) Results

Only 28 patients (16 in AZM-treated group and 12 in the AZM-untreated group respectively) received repeated chest CT scans. Scans of 1 patient in AZM-treated group revealing aggravation of lung damage with pathological involvement of new bronchiectasis, while, results obtained for 5 patients showed signs of lung improvement and results for 10 patients showed no obvious change in CT findings, number of which in the AZM-untreated group were 3, 2 and 7 (Table 3) respectively.

Results of cross-sectional analysis of lung function-based measurements collected during the follow-up period are shown in Table 3. The first measured FEV1% predicted of patients at baseline varied widely between normal and subnormal values (i.e., <80% of predicted), with a substantial number (n=10; 33%) demonstrating subnormal values (59%–79% of predicted). Importantly, lung function indicator values seemed increased after AZM treatment, but of no significance of difference, with increases by 5.3% and 1.8% respectively in AZM-treated and AZM-untreated groups respectively. Meanwhile, although the FEF_{25-75}% predicted value in the AZM-treated group was significantly lower than that of the AZM-untreated group at baseline, intergroup FEF_{25-75}% predicted change differences were of no statistically significance [6.0 (-7.6-18.8) *VS* -2.8 (-20.3, 11.2), respectively, P =0.594].

Microbiology Data

Numbers of positive sputum culture results varied among patients.*Streptococcus pneumoniae* was the most commonly isolated pathogen (65% of sputum specimens resulted in at least one isolation), followed by *Haemophilus influenzae* and *Staphylococcus aureus* (Table 3). *Pseudomonas aeruginosa* was isolated at least once from sputum only obtained from 5 different subjects (2 cases in AZM-treated group and 3 in AZM-untreated group). Among patients with positive sputum culture results, sputum of only 8 patients were retested, including 1 patient whose sputum yielded a new *P. aeruginosa* isolate and 2 patients whose sputum tested negative for *S. pneumoniae* . Due to the small number of patients with repeated sputum culture test results, the differences between AZM-treated and AZM-untreated groups were insignificant.

Discussion

PCD is a lifelong disease that can promote occurrence of recurrent airway infections that finally resulted in bronchiectasis and declining lung function that, in turn, support development of respiratory infections and perpetuate a vicious cycle of disease. Interrupting this vicious cycle is vital in order to delay disease progression. In fact, results of several studies have shown that AZM treatment of patients with CF and non-CF bronchiectasis for 3-6 months improved lung function and nutritional status, while also reducing C-reactive protein levels, pulmonary exacerbations and hospitalization rates[7-10], but only one multicenter phase 3 trial study was performed that showed similar results included both pediatric and adult PCD patients [14]. Here, we retrospectively studied a school-age pediatric population with a mean age at baseline of 8.0 years and a mean age at follow-up of 11.03 years, parts of baseline data had been reported in previous study[15]. Our results revealed that pediatric PCD patients with long-term AZM use experienced significantly fewer respiratory infections than those who had not taken AZM, as observed in the previous study [14].

Azithromycin is currently widely used in chronic respiratory diseases including PCD [16], due to its ability to alleviate both infection and inflammation. More specifically, AZM plays an anti-infective role by inhibiting synthesis of bacterial proteins that can interfere with bacterial biofilm generation and production of other virulence factors [17]. Concurrently, AZM plays an anti-inflammatory role by inhibiting host production of IL-8 and tumor necrosis factor-α (TNF-α) [18-19]. Notably, the decreased frequency of respiratory infections in the AZM-treated group as compared to the control group may be related to relatively reduced daily sputum volume associated with AZM treatment effects on mucus properties and mucus production[20]. In addition, our results also revealed that PCD patients who received long-term AZM therapy exhibited less exercise intolerance as compared to control group. Which indicated that a history of long-term AZM use administered three times per week reduced the frequencies of respiratory infection-triggered inpatient and/or outpatient doctor visits, while also improving school attendance and overall quality of life.

Studies have shown that early in life, impairment of PCD patient lung function begins and increases with age, with magnitudes of PCD disease-induced effects on FEV1 and FVC values eventually resembling those

reported in studies of CF patients [21-22]. However, few studies have investigated macrolide antibiotic treatment effects on FEV1 values of non-CF bronchiectasis produced conflicting results [23-25], with only one of the studies indicating improvement of FEV1 after treatment[23]. In this study, lung function varied widely among our patients and the mean follow-up time was 3.1 years and longest follow-up duration was 9.4 years. Importantly, baseline FEF_{25-75} of patients in the AZM-treated group were lower than that in corresponding control group. Moreover, AZM-treated group lung function improved slightly more than that of the control group, although the intergroup difference was of no apparent difference, due to small numbers of patients in both groups with both baseline and follow-up pulmonary function test results. Ultimately, the results collectively suggest that regularly long term AZM use may stabilized FEV1, FVC, and FEF_{25-75} in patients with poor lung function or more severe disease resulting from frequent infections.

In fact, that lung spirometry is less sensitive than high-resolution computed tomography (HRCT) at detecting functional and structural lung damage induced by PCD disease [26]. Thus, CT scans were used here to assess lung damage in our PCD patient cohort. Results of this study, which were of no statistically significant between-group differences at baseline, revealed that about 90% of patients in the AZM-treated group exhibited signs of stable or improved lung function as compared to about 75% of that in control group patients. However, this change did not differ apparently between the two groups which need to be confirmed by more detailed and rigorously designed studies due to the evaluation complexity of imaging changes.

Importantly, Goutaki M et al investigated a large group of over 3000 PCD patients, which indicated that both growth and nutrition are affected adversely in PCD patients from early life with delayed diagnosis[28]. However, other studies showed preschool referral to a PCD center was not associated with better BMI[29]. Our results revealed that BMI was a little lower in both groups at baseline which may be associated with late diagnosis in this cohort, while the mean heights were in normal range. Notably, although the average follow-up duration of the AZM-treated group was shorter than that of the control group, the percent increase in height of the AZM-treated group was slightly greater than that of controls, but the intergroup difference was of no statistical significance. Indeed, at first measurement, most PCD patients in this study were of normal height and weight. Thus, these indicators would not likely increase further with AZM treatment during follow-up.

The most common adverse reactions associated with AZM treatment which were observed in this study were that occasional and mild gastrointestinal reactions experienced only in three patients who received regular AZM treatment. Importantly, such reactions improved after patients adjusting the timing of AZM administration. Although hearing decrements were observed to be more common in the azithromycin group in a 12-month RCT in patients with chronic obstructive pulmonary disease [30], no serious adverse reactions, such as ototoxicity and cardiotoxicity, were observed.

A limitation of this retrospective study that lung function tests, chest CT scans, and sputum cultures were not regularly conducted during follow-up duration, which indicate that inadequate patient education and inconsistencies of disease management was exist in China. In the future, establishment of PCD follow-up treatment programs at medical research centers with standardized prospective collection of data related to characteristics and factors associated with PCD phenotypes may help to provide more scientifically based and comprehensive disease management evidence.

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Conflict of interest

The authors declare no conflicts of interest.

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