ORIGINAL ARTICLE

ROLE OF LONG-TERM INTERMITTENT USE OF ORAL AZITHROMYCIN ON PULMONARY EXACERBATIONS IN CYSTIC FIBROSIS CHILDREN

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Background: Pulmonary exacerbation is the most common acute event occurring in a patient with cystic fibrosis and *Pseudomonas aeruginosa* is the most commonly involved organism. Azithromycin has antimicrobial and immunomodulatory effects on the lungs and our study aimed to determine the role of long-term intermittent use of oral azithromycin on pulmonary exacerbations in children with cystic fibrosis. **Methods:** A retrospective cohort study was conducted from January 2012 to December 2016 at a tertiary care hospital, Aga Khan University Hospital, Karachi. The criteria for enrolment included cystic fibrosis patients aged 3–18 years who were classified into two groups based on their antibiotic use. The Azithromycin group included those CF patients who were on three days per week oral Azithromycin (10 mg per Kg per day) for 6 months. The non-azithromycin group included CF patients who were not on long term oral azithromycin. Our primary outcome was to assess the reduction in the number of exacerbations. **Results:** Sixty-three patients with a mean age (10.06±3.80) and mean pulmonary exacerbations of (3.67±1.58) in the 6 months before enrolment were included in our study. Out of these, 30 patients were included in the azithromycin group and 33 patients in the non-azithromycin group. Overall, 180 exacerbations were documented during the study period. The one-way ANOVA ($F(1,61) = 8.033$, $p<0.05$) demonstrated a statistically significant difference in the mean number of exacerbations between the azithromycin (2.70±1.72) and non-azithromycin group (3.81±1.40) however, the mean length of stay between the groups was not significant ($p=0.582$). *P. aeruginosa* was found to be the most predominant colonizer of the airways. **Conclusion**: Long term low dose azithromycin therapy is beneficial in young patients with cystic fibrosis. It is an effective prevention strategy for pulmonary exacerbations.

Keywords: Cystic Fibrosis, pulmonary Exacerbation, Macrolide

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INTRODUCTION

Cystic fibrosis is an autosomal recessive multisystem disease that presents with severe manifestations of the respiratory, urogenital, and gastrointestinal systems. The overall symptoms have a debilitating effect on the quality of life of these patients and the requirement of multiple hospitalizations throughout their disease process. Studies show that the majority of hospitalizations are due to pulmonary manifestations and this further adds to the burden of the disease.[1,2] Among other autosomal recessive diseases, it is the most common cause of early mortality in the Caucasian population in the world.[3] The prevalence of cystic fibrosis in Pakistan is difficult to determine and the disease goes mostly underdiagnosed due to the limited availability of diagnostic tools and neonatal screening programs.[4] The diagnosis largely depends on history, physical exam supported by sweat chloride tests, and genetic analysis.

Pulmonary exacerbation is the most common acute event occurring in a patient with cystic fibrosis.[5] Abnormally hyper viscous secretions and impaired mucociliary clearance promote bacterial overgrowth. This is followed by the release of a large amount of pro-inflammatory cytokines by neutrophils which damage the airways and further weaken host defences. Chronic inflammation also promotes a change of flora colonizing the airways, predominantly *Staphylococcus aureus,* and *Pseudomonas aeruginosa* in the early and later stages respectively.[6] Clinical trials have found *Pseudomonas aeruginosa* to be the most commonly involved organism in acute exacerbations.[7,8]

Although many studies have tried to develop standard definitions and scoring systems for diagnosis and classification of pulmonary exacerbations based on severity, most of these have not been validated and their accuracy is unknown. A lack of specific diagnostic criteria makes the diagnosis and management mostly clinician-decision based. Existing definitions encompass symptoms and laboratory studies with common features like acute worsening of chronic cough with increased production of sputum, chest pain, shortness of breath,

weight loss, and abrupt decline in lung function test levels.[9–11]

Given the adverse outcomes associated with exacerbations, it is imperative to develop a treatment strategy that prevents these exacerbations from occurring so frequently. Clinical trials have been done in the past which examined common prevention strategies used namely inhaled antibiotics, mucolytics, and azithromycin with rates of exacerbation being the outcome variable and each study showed significant and clinically important reductions in exacerbation rates defined by the investigator as compared to control groups.[12,13]

Since clinical trials have also established that azithromycin may have some role in altering the course of disease in cystic fibrosis given its antimicrobial and immunomodulatory effects, we would like to extrapolate the findings of previous research into our settings. This will help us to maximize the survival benefit of this debilitating disease and further yield in the evolution of this complex disease spectrum in a developing country. The present study aimed to determine the role of long-term intermittent use of oral azithromycin on pulmonary exacerbations in children with cystic fibrosis.

MATERIAL AND METHODS

This was a retrospective cohort study conducted from January 2012 to December 2016 at a tertiary care hospital, Aga Khan University Hospital, Karachi. Ethical approval was obtained from the Ethical review committee of the university.

Sweat was stimulated through pilocarpine iontophoresis and sweat collection done by Wescor macroduct sweat collection system as adopted by the chemical pathology laboratory of the hospital

These included Cystic fibrosis patients aged 3–18 years who presented to the aforementioned hospital during the study period. The patients were then categorized into two groups namely Azithromycin group (AZM) exposed and non-azithromycin group (NAZM) unexposed based on their antibiotic use. The Azithromycin group included those CF patients who were on three days per week oral Azithromycin (10 mg per Kg per day) for 6 months. Non-azithromycin group included CF patients who were not on long term oral azithromycin.

Patients who were on inhaled antibiotics or Dornas Alpha were excluded from the study. Similarly, patients who had used oral azithromycin for treating exacerbations for more than 3 days per week were excluded from the study. The criteria used to define pulmonary exacerbation used in our study was of those CF patients who were admitted in the ward or started on intravenous antibiotics and presented with respiratory distress, increased frequency of cough, increased sputum production, increased work of breathing, and/or new crackles on auscultation or new radiological finding on chest x-rays as new consolidations ± collapse or infiltrates.[9,14]

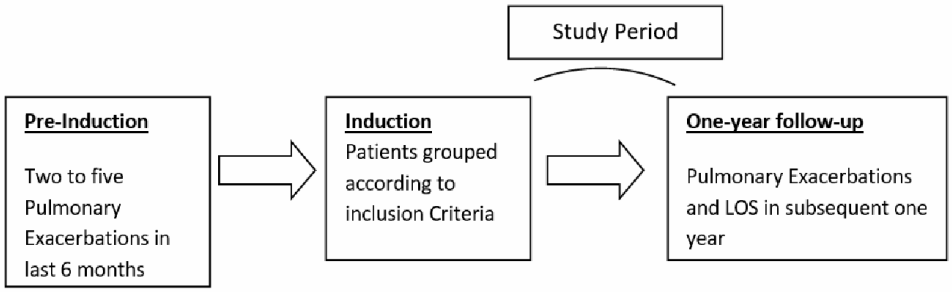

Figure-1: Study Design

To match the characteristics of both the groups, all patients who experienced at least 2–5 pulmonary exacerbations in the last six months before inclusion in the study were enrolled. The number of pulmonary exacerbations and the average length of stay in the subsequent year was noted. Both the groups were compared for these variables and their data was analyzed to compare responses between the groups and identify possible associations (Figure-1).

Pulmonary function tests were not available for the entire whole cohort hence that data was excluded from the study. Tracheal swab or sputum cultures were documented for the growth of organisms during the study period.

Data was collected from patient charts, online admission data, and e-pharmacy register. Mean and standard deviation were reported for continuous variables. Frequencies and percentages were reported for categorical variables. One-way ANOVA was used to assess significance between the two groups.

RESULTS

A total of 63 cystic fibrosis patients were enrolled, 30 (47.61%) were on long term intermittent oral Azithromycin therapy and were included in the

Azithromycin group (AZM) whereas 33 (52.38%) patients were not found to be on long term azithromycin therapy and they were included in the Non-Azithromycin group (NAZM). The baseline characteristics of patients with and without azithromycin. (Table-1) The mean age of our study population was 10.06±3.80 years. The male to female ratio was 1.6:1. There was no significant difference concerning age, gender, mean sweat chloride, mean weight, mean height, and mean pulmonary exacerbations in the 6 months before enrolment in both the groups. Overall, 180 exacerbations were documented during the study period. The Azithromycin group (AZ) was noted to show a significant decrease in the number of exacerbations in the subsequent year as compared to the non- Azithromycin group (NAZ). However, there was no significant difference between the groups in terms of their length of stay (LOS) as shown in Table-2.

One-way ANOVA was also used to find any significant difference between mean exacerbations and length of stay in the two groups as depicted in Table III. The one-way ANOVA (F (1, 61) = 8.033, p=0.006) demonstrated a statistically significant difference in the mean number of exacerbations between the azithromycin and non-azithromycin group however, the mean length of stay between the groups was not significant (p=0.582).

During the one-year post intermittent azithromycin therapy, these patients were also followed up for their sputum cultures. Results showed that *Pseudomonas aeruginosa* was the most common isolated organism growing in the sputum culture followed by Staph Aureus. (Table-5)

Comparing the number of exacerbations with sputum culture growths in both groups also showed some significant trends. It is observed that during the one-year post azithromycin therapy, the number of exacerbations are decreased in patients with *P. aeruginosa* colonization in their airways. The data was too small to find a statistically significant difference between the groups. This data has been graphically represented in figure-2.

Table-1: Demographic Data of two groups

	Azithromycin Group (AZ) 30	**Non-azithromycin Group (NAZ)** 33	**Total**
Mean Age	10.16±4.09	9.96±3.57	10.06±3.80
M:F	1.5:1	1.7:1	1.6 :1
Mean Sweat chloride	75 .36±6.91	80.23±9.21	77.51±7.81
Mean Weight (KG)	18.35±7.81	16.45±8.23	17.49±8.12
Mean Height (cm)	135.35±55.39	129.55±38.75	119.37±45.45
Mean PE in the last 6 months before enrolment in the study	3.58±1.75	3.73±1.86	3.67±1.58

Table-2: Exacerbations and length of stay

	Azithromycin Group (AZ) (30)	**Non-azithromycin Group (NAZ) (33)**	**Total n=63**
Exacerbations	2.70±1.72	3.81±1.40	3.28±1.65
Length of Stay	4.03±1.37	4.24±1.60	4.14±1.49

Table-3: ANOVA Table

		Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**	**Sum of Squares**
Exacerbations	Between Groups (Combined)	19.648	1	19.648	8.033	**.006**	19.648
	Within Groups	149.209	61	2.446			
	Total	168.857	62				
Length of Stay (LOS)	Between Groups (Combined)	.687	1	.687	.306	**.582**	.687
	Within Groups	137.027	61	2.246			
	Total	137.714	62				

Table-4: Sputum cultures

	Azithromycin Group n= 30	**Non-Azithromycin Group n=33**
Pseudomonas	11 (36.66%)	13 (39.39%)
Staph aureus	5 (16.66%)	4 (12.12%)
No Growth	4 (13.33%)	6 (18.18%)
klebsiella pneumonia	2(6.66%)	3 (9.09%)
Hemophilus influenza	4 (3.33%)	2(6.06%)
Burkholderia cepacia	2 (6.66%)	2 (6.06%)
Streptococcus species	2 (6.66%)	3 (9.09%)

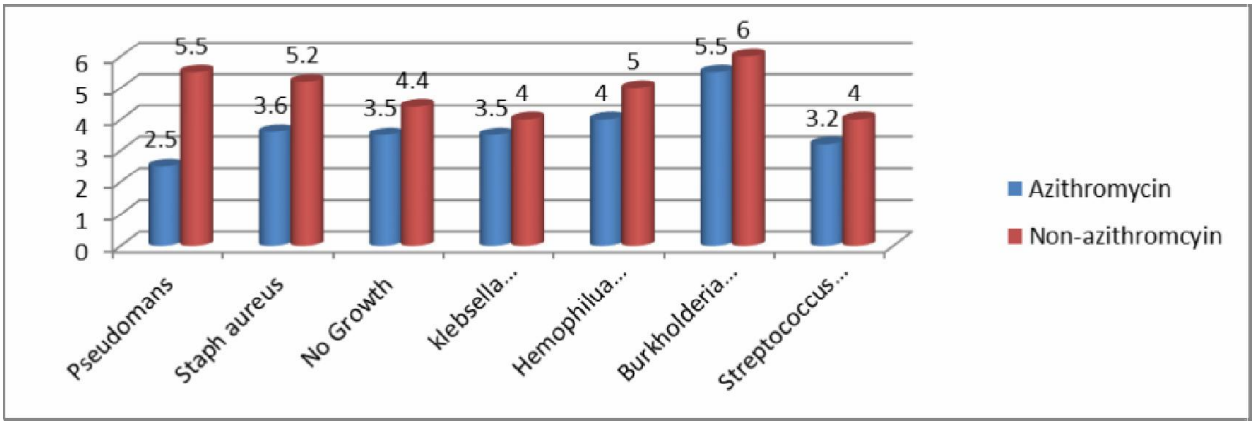

Figure-2: Number of exacerbations and sputum culture growths in two groups

DISCUSSION

In this retrospective cohort study of 63 patients at a tertiary care center in Pakistan, we studied the effect of long-term azithromycin therapy on rates of pulmonary exacerbation in cystic fibrosis. The results provide evidence that the 6-month intermittent use of azithromycin 3 days per week has significantly reduced the number of exacerbations. In our cohort, there was no significant difference noticed in the mean length of hospital stay (LOS) between the AZ group (4.03±1.37) and the NAZ group (4.24±1.60).

Our study suffered some limitations due to inadequate data availability of pulmonary function tests for these patients and the lack of FEV1 values to document their pulmonary exacerbations. We overcame this limitation by basing our decision for exacerbations on clinical and microbiological studies and radiological definitions derived through literature evidence.

Pulmonary exacerbations are associated with higher rates of mortality. A study conducted in France showed increased admissions for pulmonary exacerbations between 1 and 5 years of age to be negatively associated with lung function and risk of death at the 8-year follow-up evaluation.[12]

A multicentre double-blind placebo-controlled randomized trial done in the US studied the effect of 24 weeks of azithromycin therapy on CF patients with chronic *P. aeruginosa* infection. It showed a mean increase in FEV1 and lesser rates of pulmonary exacerbation with better nutritional status of the patients at the end of their study period.[15] Another retrospective cohort study done in the US compared chronic azithromycin users to matched controls based on their FEV1 levels and rates of intravenous antibiotic use to treat the exacerbations in cystic fibrosis patients. Results showed that the percent per year decline in fev1 was 40% lesser in patients with *Pseudomonas aeruginosa* infection and azithromycin use as compared to matched controls. In cases not infected with *Pseudomonas aeruginosa*, long term azithromycin therapy was found to have no association with preserved lung function throughout the study.[13] The results of these trials are in line with our findings and further, confirm that *P. aeruginosa* is the organism most extensively studied during long term azithromycin therapy clinical trials and has the most clinical benefits recorded.[15]

Our study mainly focusses on the beneficial impact of long-term azithromycin in terms of reduction in pulmonary exacerbations which has mostly been studied as a secondary outcome in most clinical trials so far. The reason for this being inconsistency across different trials as to how pulmonary exacerbation is defined. In our study pulmonary exacerbations were defined as CF patients who were admitted in the ward or started on intravenous antibiotics presented with respiratory distress, increased frequency of cough, increased sputum production, increased work of breathing, and/or new crackles on auscultation or new radiological finding on chest x-rays as new consolidations ±collapse or infiltrates. The existing scoring systems developed by some trials are not validated yet and there is a need for further research to establish a standard criterion for defining pulmonary exacerbation. Moreover, the use of IV antibiotics cannot be accurately quantified because of the use of antibiotics at home which may not have been recorded accurately.[12]

The effect of long-term low dose azithromycin therapy on the airways can be explained by several theories. The most widely studied mode of action is the antimicrobial activity of the drug in both intracellular as well as extracellular regions. Azithromycin is derived from erythromycin; it is a 15 membered ring azalide molecule whose unique structure allows for enhanced intracellular penetration and accumulation in the tissues. Azithromycin is also known to have anti-

inflammatory and tissue reparative effects. Other effects of macrolides that are reported include, inhibition of pro-inflammatory mediator release, less influx of neutrophils in the lungs, regulation of mucus secretion, and alteration of the biofilm matrix. This shows macrolides greatly benefit the AZ group by inhibiting the growth of *P. aeruginosa* and modulating host defences and interacting with all the different types of cells present in the airways to reduce inflammation.[16]

Saiman and colleagues found that sputum neutrophil elastase activity increased in the placebo group over 6 months but remained the same in the azithromycin group.[13] By contrast, Equi and colleagues could not document any changes in airway interleukin (IL)-8 and neutrophil elastase concentrations in the subgroup of patients who were sputum tested. This discrepancy can be explained by the fact that it is often difficult to obtain reliable measurements of inflammatory mediators in the sputum of CF patients.[17] Culic *et al* found that the immunomodulatory effect of azithromycin is also known to depend on the time duration and stages of inflammation being encountered. Studies performed in both human and animal models have shown that azithromycin has a positive immunomodulatory effect when it is administered early in the phase of bacterial infection whereas its effect is significantly reduced when used later in the inflammatory process, leads to an increase in the concentration of inflammatory mediators. This further explains why pre-treatment is a better strategy for the prevention of exacerbations.[18]

Azithromycin is established as the most appropriate type of antibiotic therapy for the prevention of exacerbations. Therefore, in 2017 the Cystic Fibrosis Foundation reviewed its guidelines after studying five randomized control trials three out of which showed absolute improvement in lung function tests and four out of five showed a decreased rate of exacerbations and recommended chronic use of the drug in CF patients 6 years and older with persistent *P. aeruginosa* in cultures to reduce exacerbations and improve lung function. There was a high certainty of net benefit in this recommendation whereas the certainty of net benefit was rated to be moderate in case of patients not infected with *P. aeruginosa* with a small net estimate of benefit. However, the guideline did not recommend for children aged less than 6 years which has been adequately covered in our study.[19]

CONCLUSION

Azithromycin has antimicrobial and immunomodulatory effects and can be given to cystic fibrosis patients as long-term therapy to decrease the number of pulmonary exacerbations. This reduces the morbidity and mortality associated with the disease. We recommend a prospective cohort study with a larger sample size to further establish the role of azithromycin in patients with cystic fibrosis.

AUTHORS' CONTRIBUTION

DA: Concept and design of study, main article. writing, final approval of version. SS: Data collection. HI: Statistical analysis. FM revising and final proof reading.

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