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Improved lung function and body mass index associated with long-term use of Macrolide antibiotics

Omar M. Pirzada, Jean McGaw, Christopher J. Taylor, Mark L. Everard*

Cystic Fibrosis Service, Department of Respiratory Medicine, Sheffield Children's Hospital, Western Bank, Sheffield, S10 2TH, UK

Abstract

Background: A number of studies have suggested that the non-antimicrobial actions of macrolide antibiotics may be valuable in treating patients with cystic fibrosis. The use of long-term macrolide antibiotics for the management of CF patients colonised by *Pseudomonas aeruginosa* and progressive pulmonary disease was introduced into our clinic in 1997. A retrospective study was undertaken to assess of the impact of this therapy. *Methods:* Twenty patients with progressive pulmonary disease (>10% fall in FEV_1 over 12 months despite optimising conventional therapy) were commenced on Azithromycin, 250 mg daily during a 21-month period. At the time of assessment they had remained on therapy for a mean of 0.9 years. Changes in lung function, weight, body mass index (BMI) and frequency of pulmonary exacerbations were assessed. A group of 20 patients with stable lung function and matched as far as possible for age and sex was identified for comparison. *Results:* Pulmonary function increased significantly in the Azithromycin group with FEV1% predicted increasing from a mean of 50.2–59.1% ($P=0.001$) while FVC% predicted increase from 64.5 to 76.1% ($P=0.002$). There was small but non-significant fall in lung function in the comparison group. Body mass index increased by a mean of 1.1 in the Azithromycin group but remained unchanged in the comparison group. The number of pulmonary exacerbations requiring intravenous antibiotics declined by 48.3% in macrolide treated subjects compared to the pre-treatment period ($P<0.025$); frequency of exacerbations in the control group was unchanged. *Conclusion:* Long-term Azithromycin treatment in patients with progressive deterioration in lung function appears to have led to an improvement in pulmonary function, increased body mass index and decreased the frequency of pulmonary exacerbations requiring intravenous antibiotics.

Keywords: Cystic fibrosis; Macrolide antibiotics; Pulmonary function

1. Introduction

Progressive pulmonary damage, frequently associated with chronic endobronchial infection by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is the major cause of morbidity and mortality in cystic fibrosis (CF). There are many factors contributing to this progressive lung damage including the release of inflammatory mediators and free proteases from neutrophils (PMN) and exo-products released by *P. aeruginosa* [1,2].

Diffuse pan-bronchiolitis [3,4] is a chronic respiratory disease of unknown aetiology that is relatively common in Japan. It is also characterised by chronic inflammation and infection in small airways with progressive pulmonary damage, eventually resulting in respiratory failure and death. Chronic *Pseudomonas aeruginosa* infection is common in patients with this disease. Bronchial lavage reveals increased numbers of neutrophils and these cells have been implicated in the causation of the progressive lung disease. Traditionally, the disease was treated with oral steroids and antibiotics. However, the introduction of long-term erythromycin (200 mg tds) therapy in the 1980s led to an increase in 10-year survival from 12.4 to 90% [5]. Investigators have suggested that this effect is due to anti-inflammatory properties of the antibiotic rather than any anti-microbial effect [3–7]. This suggestion is supported by studies showing improvement accompanied by a fall in IL-8, neutrophil derived elastase and PMN numbers in bronchoalveolar lavage fluid [6].

A number of antibiotics have non-antimicrobial actions that may be of value in conditions characterised by chronic endobronchial infection [6]. These actions

*Corresponding author. Tel.: +44-114-271-7400; fax: +44-273-0522.
E-mail address: m.l.everard@sheffield.ac.uk (M.L. Everard).

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could explain clinical improvement seen in patients colonised by organisms that are apparently resistant to specific antibiotic groups. A pilot study demonstrated that low dose erythromycin administered for 1 month led to a reduction in IL-8 and neutrophil elastase levels in the sputum of CF patients [8]. More recent clinical studies have suggested that the introduction of low dose macrolide antibiotics may have a beneficial therapeutic effects in non-CF bronchiectasis and cystic fibrosis [9–11].

On the basis of these reports we reviewed the impact of the introduction of once daily Azithromycin in CF patients with aggressive chronic endobronchial infection. In particular we assessed the effect of this intervention on lung function, pulmonary exacerbations and nutrition.

2. Methods

During the period July 1997 to March 1999 a total of 20 CF patients colonised by *Pseudomonas aeruginosa* and progressive pulmonary disease ($>10\%$ fall in FEV_1 over 12 months) despite conventional therapy were commenced on long-term Azithromycin therapy. Subjects were identified from a clinic population of 160 CF patients attending the Sheffield Cystic Fibrosis Centre. Diagnosis was confirmed by genotype analysis, sweat test ($Na^+ > 60$ mmol/l) and typical clinical presentation. All patients were colonised by *Pseudomonas aeruginosa* defined as at least three positive bacteriological cultures over a 6-month period. They received the macrolide antibiotic, Azithromycin 250 mg daily, for a minimum period of 3 months.

Data on 20 patients with stable lung function ($<5\%$ change in FEV_1 and FVC) and Shwachman score over the previous 12 months was obtained for comparison. These patients were all colonised by *Pseudomonas aeruginosa* and matched as far as possible for age, sex and lung function. Data were obtained from matched time periods. Two patients in each group were also infected with *B. cepacia.*

The primary end-point of the study was FEV_1% predicted since it is acknowledged as the closest predictor of morbidity and mortality [12]. Secondary outcome measures included FVC%, weight gain, body mass index (BMI), sputum microbiology and infective exacerbations. Clinical status, sputum culture and weight were evaluated on a monthly basis. Lung function was monitored on a Vitalograph 2120 spirometer and results expressed according to age/height matched standards. The number of pulmonary exacerbations was noted in both groups and compared to the pre-trial period. All standard CF treatments were continued for both groups.

Results were analysed by Student's *t*-test test with a value of $P<0.05$ taken to indicate statistical significance. The change in pulmonary exacerbation frequency within groups was analysed using the Wilcoxon Rank sum test.

3. Results

The median age at the start of Azithromycin treatment was 18.6 years. The median age of the comparison group was 18.8 years. Fifteen of the 20 patients in each group were male. Azithromycin treated patients completed a mean of 0.9 ± 0.5 years therapy. One subject, excluded from the analysis, developed abdominal pain after 2 weeks, which resolved when the drug was discontinued.

Pulmonary function improved significantly in those patients treated with Azithromycin. Their FEV1% predicted increased from a mean of 50.2% prior to introduction of treatment to 59.1% ($P=0.001$) while FVC% predicted increase from 64.5 to 76.1% ($P=0.002$). In the comparison group no such improvement was observed. A small but non-significant fall in FEV1% predicted from a mean of 58.7 to 57.2% ($P>0.3$) and FVC% predicted 74.1 vs. 73.2% ($P>0.5$) was observed in these subjects.

The frequency of pulmonary exacerbations requiring intravenous antibiotics declined in the Azithromycin treatment group by 48.3% ($P<0.025$). In the comparison groups there was no significant change in intravenous antibiotic use over time with a reduction of 3.5% ($P>0.5$) being observed. Macrolide treated patients gained, on average, significantly more weight than controls, (3.9 kg vs. 1.3 kg, $P=0.040$). A corresponding increase in BMI was noted in the macrolide treated group (1.1 vs. 0.1, $P<0.05$).

Sputum microbiology was unchanged at the end of the treatment period although one individual in the treatment group colonised by *S. aureus* eradicated this organism. Atypical mycobacteria were sought but were not isolated in any patient.

4. Discussion

This review of our experience would support the suggestion that long-term macrolide therapy with Azithromycin is associated with a significant improvement in lung function and a reduction in intravenous antibiotic use in CF patients colonised by *Pseudomonas aeruginosa*. The significant improvement in lung function after commencing Azithromycin is similar to that reported in two small studies involving paediatric patients [10,11]. The overall improvement in lung function in Azithromycin treated patients contrasts with essentially static lung function in the comparison group and the expected decline in FEV_1 and FVC that might be anticipated from reviewing the results of large CF population studies [13]. Since completing this review the suggestion that the long-term use of macrolide antibiotics maybe bene-

ficial in the treatment of cystic fibrosis has been further strengthened by the publication of a randomised trial suggesting that Azithromycin improved a number of parameters including quality of life and reduced the rate of decline in lung function [15].

Our experience would also suggest that the use of Azithromycin is associated with an increase in mean body weight and BMI. BMI is considered a good marker of nutritional status, which, in turn, predicts survival [12]. The combination of poor weight and pulmonary function combine to predict a worse prognosis [16]. The increase in weight gain and BMI in macrolide treated patients may reflect enhanced intestinal motility and improved nutrient absorption. An alternative and perhaps more likely explanation is that the improvement in BMI resulted from reduced calorie demand as a result of improvements in the patient's pulmonary status.

The observed improvements are unlikely to reflect an antimicrobial effect as the macrolides have MICs $>$ 128 ug/ml against most strains of *P. aeruginosa* and thus not bactericidal at therapeutic concentrations [7]. Macrolides have been shown to disrupt the formation of Pseudomonal biofilms [4], diminish *Pseudomonas aeruginosa* alginate expression [14], reduce the production of bacterial virulence factors in vitro and alter PMN activity [4,7,14]. These antipseudomonal effects occur at sub-MIC ranges but it is at present unknown whether they account for clinical efficacy [14].

Effective gene transfection fully restoring ion transport and function remains an elusive goal in CF [17]. Therefore, alternative treatments are being sought, especially for those with established lung disease. Clinicians have started to use macrolides as an adjunct to other therapies based on anecdotal reports of efficacy. This open retrospective study provides further support for the suggestion that macrolide antibiotics may be of value in CF patients colonised by *Pseudomonas aeruginosa* whose clinical status is deteriorating despite optimising conventional therapy.

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