Respiratory Medicine 117 (2016) 1–6

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Long-term effects of azithromycin in patients with cystic fibrosis

Clémentine Samson [a, b], Aline Tamalet [a], Hoang Vu Thien [c], Jessica Taytard [a, f], Caroline Perisson [a], Nadia Nathan [a], Annick Clement [a, d], Pierre-Yves Boelle [d, e], Harriet Corvol [a, d, f, *]

[a] AP-HP, Hôpital Trousseau, Pediatric Pulmonology Department, Paris, France
[b] Besançon Hospital, Pediatric Department, Besançon, France
[c] AP-HP, Hôpital Trousseau, Bacteriology Department, Paris, France
[d] Sorbonne Universités, UPMC Univ Paris 06, Paris, France
[e] AP-HP, Hôpital Saint Antoine, Biostatistic Department, INSERM U1136, Paris, France
[f] INSERM, Centre de Recherche Saint-Antoine (CRSA), F-75012, Paris, France

ARTICLE INFO

Article history:
Received 24 August 2015
Received in revised form
17 May 2016
Accepted 23 May 2016
Available online 24 May 2016

Keywords:
Children
Cystic fibrosis
Azithromycin
Lung function
Respiratory exacerbation
Bacteria resistance

ABSTRACT

Background: Low-dose azithromycin has beneficial effects on severity of the lung disease in cystic fibrosis (CF) patients for a period of 6–12 months after initiation of the treatment. Although its impact in the longer term is uncertain, this treatment is frequently used chronically. The aim of this retrospective study was to investigate the effects of low-dose azithromycin treatment on the progression of CF lung disease in patients treated for more than 12 months.

Methods: All of the CF patients followed in our pediatric center and who had been on low-dose azithromycin for more than 12 sequential months were included. The clinical data were collected for one year before and three years after the initiation of the azithromycin treatment. These data comprised lung function analyses, rates of exacerbations and of antibiotic courses, and changes in the airways' bacterial colonization.

Results: A total of 68 patients were included (mean age: 9.95 yrs (3.61)). After 12 months, significant reductions in the numbers of pulmonary exacerbations and antibiotic courses were present. However, this effect was not maintained in the subsequent periods, during which increased rates of both pulmonary exacerbations and antibiotic courses were observed. The lung function decline was not modified during the treatment, and a decreasing time-dependent trend typical of CF was observed for the various parameters. No differences in the airway colonization by pathogens such as *Pseudomonas aeruginosa* and methicillin-sensitive and/or -resistant *Staphyloccocus aureus* were observed during the treatment. However, isolated *Staphyloccocus aureus* strains became resistant to macrolides after 6 months of azithromycin and remained resistant thereafter.

Conclusions: No clinical benefits of low-doses azithromycin were present after one year of treatment in young CF patients. Selection for macrolide-resistant strains of bacteria occurred, which should lead to a reconsideration of the duration of azithromycin treatment in CF.

1. Introduction

Cystic fibrosis (CF) is the most common severe autosomal recessive genetic disease in Caucasians. CF is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (*CFTR*), a chloride channel expressed in the epithelial cells throughout the body [1]. The disease affects many organs including the pancreas, the liver, the intestine, and, most critically, the lungs. CF lung disease still remains the major cause of morbidity and mortality in CF, with a progressive decline of the lung function due to a vicious cycle of airway infection and inflammation [2,3]. The inflammation in the lungs of CF patients is persistently neutrophilic and is associated with an up-regulation of neutrophil chemotactic mediators [4,5]. The accumulation of activated neutrophils in the airways and the resulting release of toxic

* Corresponding author. AP-HP, Hôpital Trousseau, Pediatric Pulmonary Department, 26 Avenue du Docteur Arnold Netter, 75012 Paris, France.
E-mail address: harriet.corvol@aphp.fr (H. Corvol).

http://dx.doi.org/10.1016/j.rmed.2016.05.025
0954-6111/

products impair the host defense and contribute to infection and subsequent chronic colonization by microorganisms such as *Pseudomonas aeruginosa* (*P. aeruginosa*).

Because inflammation is a central contributor to the pathogenesis of CF pulmonary disease, limiting the excessive production of inflammatory mediators represents a major therapeutic strategy for slowing the decline in lung function and improving the overall survival. Worldwide, one of the most frequently prescribed anti-inflammatory drugs in CF is azithromycin, despite the fact that this is an off-label use of the drug. Azithromycin is a macrolide antibiotic that is recognized as having not only antimicrobial but also anti-inflammatory and immunomodulatory properties [6,7]. It is an erythromycin-derived 15-membered ring azalide, structurally modified to increase its half-life and enhance its intracellular accumulation with greater tissue penetration as well as to increase its intra-cellular and extra-cellular antimicrobial activity [8]. Therefore, low doses and infrequent dosing schedules (such as three times a week) are possible, making it attractive as a long-term oral therapy. Azithromycin has also been reported to inhibit the release of pro-inflammatory mediators, to limit the pulmonary influx of neutrophils, to regulate mucus secretion, and to alter the formation of the *P. aeruginosa* biofilm matrix [7]. In CF, it has also been shown *in vitro* to restore the chloride efflux [9].

The first success of macrolides in lung diseases was observed in patients with diffuse panbronchiolitis. With long-term treatment using macrolides, the survival of patients with diffuse panbronchiolitis increased remarkably from 25 to 95% at 5 years [10–13]. Because diffuse panbronchiolitis and CF share many similarities including neutrophil airway inflammation and *P. aeruginosa* infections, macrolides, and more specifically azithromycin, have since been evaluated in several trials in CF patients. A Cochrane Database systematic review has further ascertained that administration of low-dose azithromycin for 6–12 months has beneficial effects on the lung function, the occurrence of exacerbations, the need for other antibiotics, and on the weight gain in CF patients [14]. Thus, azithromycin, despite its off-label use, is frequently prescribed to CF patients aged more than 6 years throughout the world, but the treatment is rarely interrupted, leading to very long treatment durations, *i.e.,* > 12 months, without any evidence of maintained beneficial effects. We therefore conducted a retrospective study to investigate the effects of prolonged (>12 months) low-dose azithromycin treatment on the progression of CF lung disease.

2. Material and methods

2.1. Patients

This retrospective study took place in a pediatric CF center in Paris, which cares for 150 CF patients. We queried our Electronic Health Record system for all CF patients under 18 years old who had started azithromycin at anti-inflammatory doses (250 or 500 mg 3 times a week for patients under or above 40 kg respectively) between November 1st, 1999 and December 31st, 2013 and had been treated for more than 12 subsequent months. The clinical data were retrospectively collected from the electronic patient records, supplemented when necessary with data from the paper patient records. For each individual patient, the date of the initiation of the azithromycin therapy was designated time T0. The clinical data were subsequently collected 12 months before the start of azithromycin treatment (T-12), at T0, and every 12 months following T0 (T12, T24, T36) or up to discontinuation of treatment. We documented:

- *CFTR* genotypes and pancreatic status, *i.e.,* sufficient or insufficient
- Body Mass Index (BMI) z-score measurements
- Pulmonary function tests, expressed as percent-predicted values, using the modified Knudson equations [15]: Forced Expiratory Volume in 1 s (FEV_1), Forced vital capacity (FVC) and Forced expiratory flow 25%–75% (FEF_{25-75})
- Arterial blood gas (partial pressure of oxygen, PaO_2, and partial pressure of carbon dioxide, $PaCO_2$);
- Annual rate of acute respiratory exacerbations. A respiratory exacerbation was defined as an acute exacerbation of CF respiratory symptoms that in the opinion of the patient's physician required administration of new oral or intravenous (IV) antibiotics, according to the criteria published by the 1994 CF Foundation Microbiology and Infectious Disease Consensus Conference [16,17].
- Number of IV and of oral antibiotic courses
- Microbiological analyses of sputum and throat cultures for the common CF pathogens and for nontuberculous mycobacteria as previously described [18–20].

2.2. Statistical analysis

The data were expressed as the means ± SD for continuous variables and numbers (%) for categorical variables. Multiple imputation was used for missing pulmonary function data. Analysis of variance for repeated data was performed to compare the pulmonary function data/arterial gases before and after the beginning of the azithromycin treatment and the paired Wilcoxon rank sum test to compare the number of exacerbations and antibiotic cures. The differences were considered significant for P-values less than 0.05.

3. Results

3.1. Patients

The demographic data for the patients included are described in Table 1. Briefly, 68 CF patients (33 girls and 35 boys) were included. Of these, 41 (60.3%) were homozygotes for the CFTR F508del mutation, and 66 (97%) were pancreatic insufficient. At T0, the median age was 9.95 ± 3.61 yrs, and the median BMI z-score was −0.3 ± 1.8. Among the 68 patients who took azithromycin for more than 12 months, 50 were observed for 2 full years after the initiation of the

Table 1
Baseline characteristics of the patients.

Total (n)	68
Age (yrs), mean (SD)	9.95 (3.61)
Sex (male/female)	35/33
CFTR genotype	
F508del/F508del	41
F508del/others	20
Others	7
BMI z score (SD)	−0.3 (1.8)
Pancreatic insufficiency (n, %)	66 (97%)
Colonized by *P. aeruginosa*	13 (19%)
Colonized by MSSA	29 (43%)
Colonized by MRSA	13 (19%)
NTM infection	1 (1%)

Abbreviations: *CFTR*: cystic fibrosis transmembrane regulator; BMI: body mass index, *P. aeruginosa*: *Pseudomonas aeruginosa*; MSSA: methicillin-sensitive *Staphyloccocus aureus*; MRSA: methicillin-resistant *Staphyloccocus aureus*; NTM: nontuberculous mycobacteria.
The data are the means (SD) or numbers (%) unless otherwise indicated.