Long-term clarithromycin in cystic fibrosis: effects on inflammatory markers in BAL and clinical status

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Macrolides have antiinflammatory effects that are potentially useful in cystic fibrosis (CF). In this placebo-controlled, randomized, double-blind crossover study, 18 CF patients were randomized to receive either clarithromycin (CM) (Group 1) or placebo (Group 2) for three months. After 15 days, the treatments were crossed over. Bronchoalveolar lavage (BAL) was obtained in the beginning and at the end of each treatment period. There was no significant difference in median cell counts and median cytokine levels at baseline, after CM use and after placebo use between the two groups. In Group 2, the median neutrophil elastase (NE) level decreased with CM. Patients had less acute pulmonary exacerbations and median clinical score decreased with CM in both groups. Median z-scores for weight increased with CM in Group 2. We could not demonstrate a fall in proinflammatory cytokines in BAL; however, some improvement in clinical status could be shown with three-month CM.

Key words: clarithromycin, cystic fibrosis, clinical status, inflammation.

One of the new aspects of treatment in cystic fibrosis (CF) is macrolide treatment for infection control and inflammation modulation[1]. Successful treatment strategies with macrolides in patients with diffuse panbronchiolitis (DPB), which shares many similarities with CF, has stimulated intense research to determine the potential role of macrolides in CF[2]. Although the exact mechanism is unknown, antiinflammatory rather than antimicrobial properties of macrolides seem to be responsible for the beneficial effects in DPB or CF. Data on the effects of long-term macrolide therapy on cytokine production in bronchoalveolar lavage (BAL) fluid in CF are still not available. Therefore, we aimed to evaluate in this study the effects of long-term clarithromycin (CM) treatment on BAL levels of interleukin (IL)-8, tumor necrosis factor (TNF)-α, neutrophil elastase (NE) levels, and cell count. In addition to effects on lung inflammation, we also aimed to show its effects on clinical improvement by evaluating z-score for weight, clinical status, acute pulmonary exacerbations, and pulmonary function tests in these patients.

Material and Methods

Diagnosis of CF was made with clinical findings suggestive of CF and at least two sweat chloride measurements greater than 60 mEq/L. Patients who were treated with antibiotics in the last two weeks, those who were clinically unstable, had an acute pulmonary exacerbation, macrolide allergy, or liver failure, and those on systemic or inhaled steroids were excluded.

A part of this study was presented as a poster at the 27th European Cystic Fibrosis Conference in Birmingham, 13-17 June 2004.

The study was designed as a randomized, double-blind and placebo-controlled crossover study of 6.5 months duration. Ethics approval for the trial was obtained and written informed consent was taken from the parents of every patient included in the study. CM tablets (250 mg) and suspension (250 mg) were labelled with red and the identical placebo was labelled with blue. Patients were randomized into two groups. They received either active drug (15 mg/kg/day in 2 divided doses) (Group 1) or placebo (Group 2) for three months. After 15 days of washout period, the treatments were crossed over and they received placebo or CM for an additional three months (Fig. 1). Patients continued to take their regular treatments like inhaled salbutamol, recombinant human DNAse, pancreatic enzymes, and chest physiotherapy throughout the study protocol.

Patients were seen in the outpatient clinic at the beginning of the study, at the third month of the study (first visit) and at the end of the second third month after the washout period (second visit). Patients were evaluated by a physician who was unaware of the treatment. In the beginning and at each visit, the complaints were questioned, systemic physical examination and anthropometric measurements were made, weight z-scores in kilograms by sex and age were calculated, and chest X-ray (CXR) and serum for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* antibodies were obtained. Pulmonary function tests (PFT) were performed in patients older than six years with spirometry (Vitalograph, Autospiro AS600 Minato). Every patient had tuberculin skin test (TST) with 5 TU PPD solution, and this test was considered to be positive if the reaction was greater than 15 mm in patients vaccinated with BCG.

The Modified National Institutes of Health (mNIH) scoring system was used for evaluation of complaints like hemoptysis, pneumothorax, pulmonary exacerbations, sputum production, activity, exercise tolerance, school/work, attitude, physical examination findings like clubbing, chest deformity, cyanosis, breath sounds, PFTs and CXR findings of patients[3]. This score was determined in the beginning and at each visit.

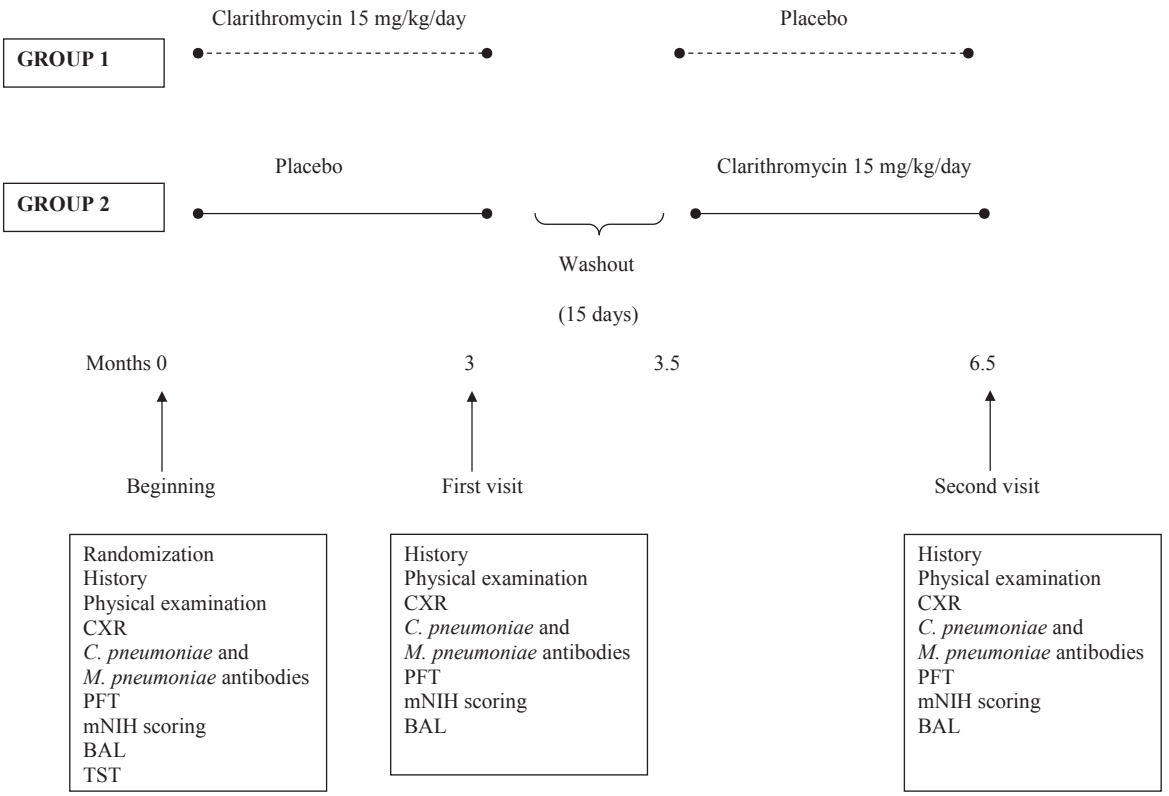

Fig. 1. The study protocol (CXR: Chest X-ray. PFT: Pulmonary function tests. mNIH: Modified National Institutes of Health. BAL: Bronchoalveolar lavage. TST: Tuberculin skin test).

As some patients could not perform PFTs, this scoring system was evaluated after excluding the PFT portion in all patients.

Acute pulmonary exacerbation was defined as increase in cough and sputum, decrease in exercise tolerance and appetite, fever, weight loss, dyspnea, tachypnea, retractions, new auscultation findings, new or increased infiltration in the CXR, worsening of the PFT, decrease in oxygen saturation, and leukocytosis, and was diagnosed by a physician blinded to the study. In these periods, patients were treated with oral or intravenous antibiotics at home or in the hospital depending on the severity of the symptoms, and they continued to take CM or placebo as well. The number of acute pulmonary exacerbations and their treatment were recorded during the study.

Side effects due to CM were also recorded. In order to be sure of the compliance, the tablets and suspensions were returned by the families and were counted at each visit.

Bronchoalveolar Lavage

Bronchoalveolar lavage fluid was obtained from every patient via flexible bronchoscopy with Olympus BF-3C40 and BF-P240 Evis Bronchovideoscope in the beginning and at each visit. If the patients had signs of acute pulmonary exacerbation in these visits, bronchoscopy was postponed to 15 days after the cessation of additional antibiotic treatment. For the standardization of the procedure, criteria of the European Respiratory Society were used[4]. The bronchoscope was wedged into the right middle lobe in patients who had widespread lesion and into the involved region in patients with localized lesions on CXR. All three BALs were done in the same lobe in the same patient. Sterile and warm (37°C) 0.9% saline (1 ml/kg) was instilled into the bronchus. The first recovered fluid was discarded in order to exclude upper airway contamination. Then, the same amount of saline was installed again and immediately recovered. This procedure was repeated 1-2 times more until 40-60% of the instilled saline was recovered.

Bronchoalveolar lavage sample was divided into two parts: one part was used for aerobic, *Mycobacterium tuberculosis* and fungi cultures as well as cytologic analysis. The second part was cleaned from the mucus by filtering through a sterile gauze and was used for cytokine level measurements of IL-8, TNF-α, NE, and total cell count after being centrifuged at 400xg for 10 minutes; its supernatant part was stored at -70°C.

Total cell count in BAL was measured with a Coulter STKS Hemoanalyzer. The differential cell count in BAL was performed after it was centrifuged at 3000 rpm for 10 minutes; 300 cells were counted and the percentage of cells were calculated.

Cytokine Analysis

Levels of IL-8, TNF-α and NE in BAL were measured with solid phase sandwich enzyme linked immunosorbent assay (ELISA) method. TNF-α assay was measured with Cytoscreen™, human TNF-α immunoassay kit (catalog # KHC3012/KHC3010-SB, BioSource International, Inc.; Camarillo, CA, USA). IL-8 level was measured with Cytoscreen™, human IL-8/NAP1 immunoassay kit (catalog # KHC0082/KHC0080-SB, BioSource International, Inc.; Camarillo, CA, USA). NE assay was performed by using Cytoscreen™, human NE immunoassay kit (catalog # KHC0011/KHC0012/KHC0011C BioSource International, Inc.; Camarillo, CA, USA).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows (SPSS Inc®) statistical program was used for statistical analysis. Median values were calculated for different variables. Wilcoxon test was used to compare median values in the same group and Mann-Whitney U test was used to compare median values between the two groups. A value of $p<0.05$ was considered to be significant.

Results

Eighteen CF patients were included in the study; however, 1 patient was excluded as he had rash due to CM in the first week of the study. Thus, the results of 17 patients were evaluated. Group 1 consisted of 9 and Group 2 of 8 patients. The youngest patient was 3 and the oldest was 14.8 years. Of all patients, 10 were males (58.8%) and 7 were females (41.2%). Two patients in Group 1 and 2 patients from Group 2 were delta F508

homozygous, and 2 patients in Group 1 and 5 patients in Group 2 were heterozygous for delta F508. No mutations could be detected in our hospital in the rest of our patients. Nine patients in Group 1 and 8 in Group 2 were on pancreatic enzymes, and 3 in Group 1 and 1 in Group 2 were on recombinant DNAse. The characteristics of patients are shown in Table I. There was no statistically significant difference between groups except in mNIH scores.

There was no statistically significant difference in median neutrophil, lymphocyte, macrophage and eosinophil count and median IL-8, TNF-α and NE levels between the two groups at the beginning of the study.

BAL Cell Count

There were no statistically significant differences between Groups 1 and 2 in median neutrophil, lymphocyte, macrophage and eosinophil counts at baseline, after CM use and after placebo use (Table II). Although not statisticially significant, at the end of CM use, there was a decrease in median neutrophil count and increase in median macrophage count in Group 1 when compared to baseline; however, in Group 2, there was decrease both in median neutrophil and macrophage counts with the use of CM. There was also no statistically significant difference in median cell counts both with CM and placebo use between Groups 1 and 2.

BAL Cytokine Levels

In Groups 1 and 2, there was no statistically significant difference in BAL median IL-8, TNF-α and NE levels at baseline, after CM use and after placebo use (Table III). In Group 1, although not statistically significant, the median NE level decreased with CM use when compared to baseline (Fig. 2). However, median IL-8 increased with CM use, and median TNF-α level was not affected after CM treatment. In Group 2, BAL median IL-8, TNF-α and NE levels were all decreased with placebo use, median NE levels were further decreased with CM use, but IL-8 and TNF-α levels were increased with CM use. The only statistically significant difference was the decrease in NE level between baseline and after CM use (Table III). There was no statistically significant difference in median IL-8, TNF-α and NE levels both with CM and placebo use between Groups 1 and 2.

Acute Pulmonary Exacerbations

Patients in Group 1 had 5 and 8 and patients in Group 2 had 2 and 10 acute pulmonary exacerbations while using CM and placebo, respectively (p: 0.1 and p: 0.03, respectively). Patients in both groups needed oral antibiotics only while on CM; however, they needed intravenous antibiotics while on placebo.

Z-score for Weight

The median z-score for weight was -0.67 at baseline, -0.5 at the end of CM use and -0.44 at the end of placebo use in Group 1, which was not statistically significant. In Group 2, it was -0.41 at baseline and -0.28 at the end of placebo use and it increased to 0.13 at the end of CM use; the increase between the end of placebo and CM use was statistically significant (p: 0.01). There was no statistically significant difference between median z-scores of Group 1 and 2 at baseline, after CM use and after placebo use.

mNIH Score

Median mNIH score was 31 at the beginning of the study, whereas it decreased to 24 with use of CM (p: 0.01), and then did not change

Table I. Characteristics of Patients at the Beginning of the Study

		Group 1 (n=9)	Group 2 (n=8)	p
Age (years)*		10.6 (5.3-14.8)	8.4 (3-14.5)	0.1
Sex	Female	3	4	0.4
	Male	6	4	
Z-score for weight*		-0.67 (-1.27-1.00)	-0.41 (-1.69 – 2.46)	1
mNIH score*		31 (19-35)	20.5 (15-33)	0.03
FEV_1 (%)*		77.5 (62-101)	98 (60-117)	0.3

mNIH: Modified National Institutes of Health. FEV_1: Forced expiratory volume in 1 second.
*Median values (minimum-maximum).

Table II. Median (Minimum-Maximum) Bronchoalveolar Lavage Cell Counts

Group 1	Baseline	CM	Placebo
Neutrophil (/mm³)	194 (48-609)	82 (30-323)	78 (18-444)
p	0.3	0.4	
	0.3		
Lymphocyte (/mm³)	4 (2-42)	8 (1-513)	12 (8-24)
p	0.7	0.4	
	0.1		
Macrophage (/mm³)	24 (4-54)	35.5 (2-494)	42 (6-144)
p	0.2	0.6	
	0.1		
Eosinophil (/mm³)	0 (0-21)	0 (0-3)	6 (0-8)
p	0.1	0.06	
	1		
Group 2	**Baseline**	**Placebo**	**CM**
Neutrophil (/mm³)	133 (40-828)	75 (4-1230)	56 (6-1456)
p	0.4	0.8	
	0.7		
Lymphocyte (/mm³)	9.5 (2-18)	18 (0-128)	4 (1-196)
p	0.1	0.8	
	0.2		
Macrophage (/mm³)	22 (4-72)	92 (2-225)	43 (20-1120)
p	0.1	0.5	
	0.7		
Eosinophil (/mm³)	2 (0-18)	0 (0-8)	0 (0-25)
p	0.1	0.6	
	0.3		

Table III. Bronchoalveolar Lavage Median (Minimum - Maximum) IL-8, TNF-α and NE Levels

Group 1	Baseline	CM	Placebo
IL-8 (pg/ml)	768.3 (395.5-1252.6)	844.9 (413.3-1210.9)	974 (389.6-1268.9)
P	0.9	0.7	
	0.5		
TNF-α (pg/ml)	37.6 (7.6-127.3)	37.6 (9.8-275.1)	17 (5.8-120.9)
P	0.9	0.3	
	0.2		
NE (u/ml)	31 (8.3-96.5)	26.1 (7.8-39)	25.2 (9.4-83.3)
p	0.3	0.3	
	0.4		
Group 2	**Baseline**	**Placebo**	**CM**
IL-8 (pg/ml)	908.8 (117.8-1316.5)	775.1 (34.7-1499.9)	833.5 (104.2-1644.3)
p	0.4	0.1	
	1		
TNF-α (pg/ml)	37.6 (9.8-275.1)	16.7 (3.5-363.1)	33.3 (11.6-145.4)
P	0.5	0.4	
	0.6		
NE (u/ml)	49.2 (19.5-125.1)	38.1 (9.7-78.6)	28.5 (12.4-65.9)
p	0.1	0.2	
	0.02		

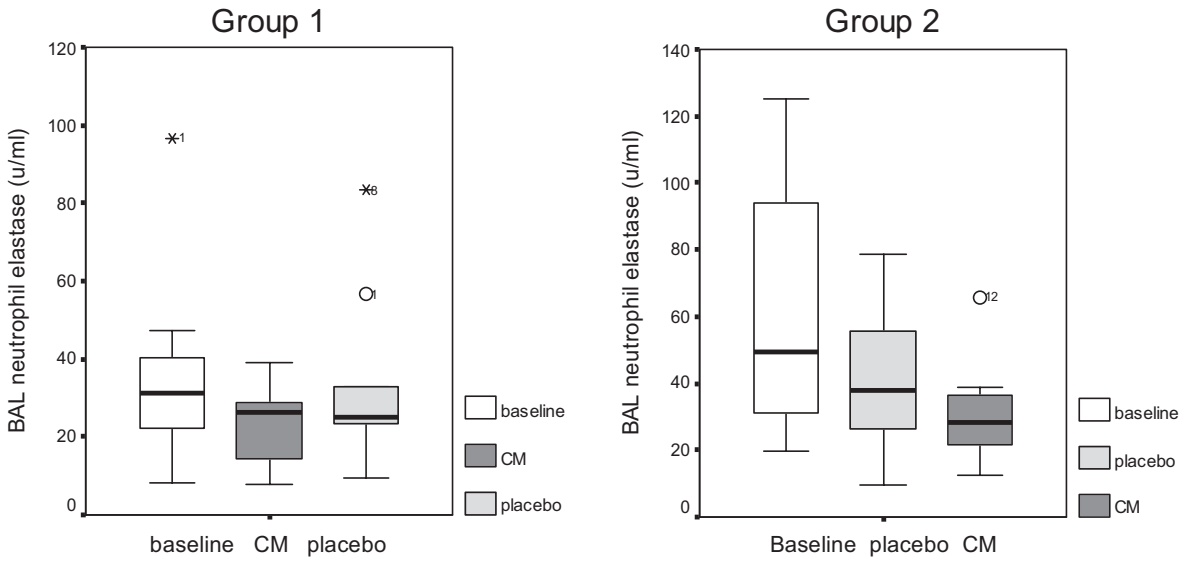

Fig. 2. Bronchoalveolar lavage (BAL) neutrophil elastase levels in both groups.

at the end of placebo use in Group 1. In Group 2, the basal score was 20.5, which increased to 23 at the end of placebo use and then decreased to 20 with CM use, which was statistically significant (p: 0.04). There was no statistically significant difference between median mNIH score of Group 1 and 2 at baseline, after CM use and after placebo use.

Pulmonary Function Tests

In Group 1, the median forced expiratory volume in 1 second (FEV1%) value was 77.5% in the beginning, whereas it was 75% with CM use and then was 83% at the end of placebo use, although not statistically significant. In Group 2, it was 98% in the beginning and then decreased to 89% with placebo and to 87.5% with CM use, all without statistical significance (Fig. 3). There was no statistically significant difference between median FEV1% values of Group 1 and 2 at baseline, after CM use and after placebo use.

Microorganisms in the BAL

No microorganisms grew in the BAL of 2 patients in Group 1 and 4 patients in Group 2 at the beginning of the study. After CM use, new

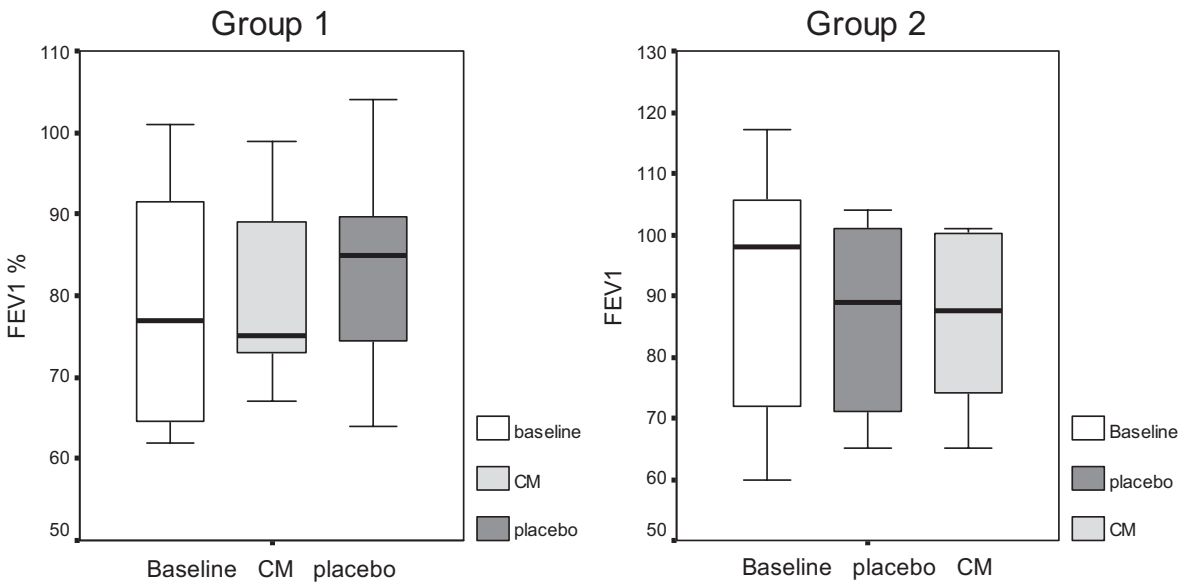

Fig. 3. Forced expiratory volume in 1 second (FEV_1)% values in both groups.

growth of *Pseudomonas aeruginosa* in 2 patients and *Stenotrophomonas maltophilia* in another patient in Group 1 and *Burkholderia cepacia* in 1 patient in Group 2 were noticed. No cultures grew fungi or *M. tuberculosis*. Prophylaxis with isoniazid was given to 3 patients whose TST was found to be positive. The families of those patients had no tuberculosis disease.

No side effects of CM were seen in our patients except in one patient who was excluded from the study because of rash in the first month that was attributed to CM. All patients were compliant with treatment.

Discussion

In this study, we found that three-month use of CM at a dose of 15 mg/kg/day did not cause a significant fall in inflammatory cytokines in the BAL of CF patients; however, it led to a decrease in acute pulmonary exacerbations and improvement in clinical status in all and an increase in weight in some patients.

Until now, several investigators have tried to determine the efficacy of macrolides in CF patients[5-9]. In studies by Ordonez et al.[6] and Equi et al.[7], induced sputum was used to measure cytokines. However, it is known that ELISA results in sputum samples are frequently poorly reproducible and there is marked inter-individual variability and often the need for extensive dilution of the sample[10]. The difficulty of expectorating sputum even with induction in young children, the effects of chest physiotherapy and rhDNAse, and the inability to know from which portion of the lung the sputum originates are some other disadvantages of using sputum in airway inflammation studies in children with CF. On the other hand, flexible bronchoscopy is known to be a safe procedure in children with minimal major side effects. Therefore, we preferred to use BAL to measure levels of cytokines and cell counts, which would more accurately reflect airway inflammation. Until now, there have been no data regarding BAL before and after macrolide therapy in CF, and our study is thus the first such study. Performing three BALs in a patient over a six-month period is a difficult task, and therefore, we believe that our data is valuable.

Previous studies of BAL and sputum of CF patients showed increased concentrations of inflammatory markers of IL-8, TNF-α and NE[11-14]. Macrolides have been shown to suppress those inflammatory cytokines[6,15,16]. In our study, with a three-month CM therapy, BAL IL-8 and TNF-α concentrations were not decreased, and there was only a decrease in NE in both groups. The failure to see an effect of macrolides on IL-8 and TNF-α in contrast with in vitro sudies in the literature might have been because of the oral or intravenous antibiotics used during acute pulmonary exacerbations. In addition, bacterial load in the lungs of our patients might have influenced the cytokine levels; some reports conclude that bacterial load is important in determining IL-8 levels in CF airways[17]. Another possible explanation for the different response of cytokines to macrolides can be the genetic factors of patients, which may be responsible for different pharmacokinetics and drug clearance.

Macrolides have also been shown in previous studies to reduce the number of acute pulmonary exacerbations and the need for intravenous antibiotics[2,8] and to increase body weight and body mass index (BMI)[18,19] in CF patients. As the population involved children in our study, we preferred to present z-scores and used z-scores for weight in this short period for comparison. Our results showed that the use of CM was associated with increase in weight in some of our CF patients. It has been speculated that increase in body weight and BMI with macrolide treatment might have reflected enhanced intestinal motility and improved nutrient absorption, or that the improved pulmonary status of the patients caused reduced calorie demand, which resulted in improved BMI[19]. The decreased number of acute pulmonary exacerbations and hospitalizations might also have caused the weight gain in these patients.

We found in this study that there was a statistically significant improvement in clinical scores in both groups at the end of CM use when compared to placebo, which we believe is one of the most important conclusions of this study. The mechanism of improvement in clinical status seems to be independent of the airway inflammation but may be related to the decreased number of acute pulmonary exacerbations while on CM.

The emergence of problem pathogens like *P. aeruginosa, S. maltophilia* and *B. cepacia* while on CM therapy seems to be a limitation for

using macrolides in children for a long period; however, there is no data or evidence available to attribute these new growths to CM use. Further research should be undertaken to clarify this isuue.

The clinical improvement with CM in our patients might have been attributed to coinfection with atypical bacteria such as Mycoplasma or *C. pneumoniae* or atypical mycobacteria, but these conditions were excluded as serology for *M. pneumoniae* and *C. pneumoniae* in the beginning and at each visit were negative and BAL cultures for *M. tuberculosis* were all negative.

The most important side effects of macrolides are diarrhea, nausea, vomiting, abdominal pain, increase in liver enzymes, and rash[20]. The only side effect in our study was rash in one patient whom we had to exclude from the study; the rest of the patients tolerated the drug very well.

In conclusion, we could not demonstrate a fall in the levels of proinflammatory cytokines in our study except in NE levels; however, some increase in weight, improvement in clinical status and decrease in acute pulmonary exacerbations could be shown with the use of three-month CM in CF. The small number of patients included in the study, the lack of serum or BAL levels of CM, the difference in severity of pulmonary status and in ages of our patients, and the different antibiotics used in the acute pulmonary exacerbation periods are some limitations of our study. The power of this study is not high and therefore the statistical analyses of comparisons may not reflect the exact numbers; however, it is obvious that our individual findings are valuable as they were obtained by BAL, which is an invasive method, and they can provide input for metaanalyses in the future. As there is a very complex cytokine response in CF and as the genotype of CF patients can vary widely, further and multicenter studies with larger numbers of patients are needed to clearly demonstrate the effects of long-term macrolide treatment in CF.

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