

Macrolide therapy in cystic fibrosis: new developments in clinical use

Clin. Invest. (2013) 3(12), 1179–1186

Macrolide therapy, in particular azithromycin, has been shown to improve aspects of lung health in patients with cystic fibrosis (CF), in particular those with chronic *Pseudomonas aeruginosa* colonization. It is postulated that macrolide antibiotics exert their clinical effects through direct anti-inflammatory mechanisms that are separate from their antibacterial properties. A number of clinical trials have explored the clinical effects of macrolide therapy in CF. Those in recent years have focused on different population groups, including patients without *P. aeruginosa* airway colonization and those with relatively preserved pulmonary function; and different dosing regimens, including different macrolides and treatment durations. This article presents a review of the clinical trials of macrolide therapy in CF published over the past 5 years.

Keywords: anti-inflammatory therapy • azithromycin • clarithromycin
• cystic fibrosis • lung disease • macrolid • microbiological profile

K Frayman & P Robinson*

Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Melbourne, Australia 3052

*Author for correspondence:

E-mail: phil.robinson@rch.org.au

Cystic Fibrosis (CF) remains the most common lethal inherited condition of the Western world. While major advances in therapy of this condition have occurred in recent years, including the very promising development of so called mutational-specific therapies, such as Ivacaftor, progressive suppurative lung disease secondary to bacterial infection remains the major cause of morbidity and mortality of this condition [1]. While improvements in antibiotic therapy including different dose formulations (such as dry powder tobramycin for inhalation) and delivery devices, and approaches to specific infections have been developed in recent years, these improvements have been complemented by other investigations examining the benefits of anti-inflammatory therapies in controlling the progression of lung disease in CF. Early trials have involved a range of such agents including oral steroids, inhaled steroids and ibuprofen [2,3]. Macrolide therapy, in particular with azithromycin, has been shown to have beneficial effects in improving aspects of lung health in patients with CF, particularly those with airway colonization from *Pseudomonas aeruginosa* in the absence of any direct antibacterial effect. The postulated mechanism of this beneficial action is through an antiinflammatory action – the nonantibiotic role being emphasized by the somewhat unusual dosing often employed, such as alternate days or Monday, Wednesday, Friday dosing. In the 2007 CF pulmonary guidelines from the US Cystic Fibrosis Foundation committee concluded that “there was a substantial benefit in the studies supporting the use of azithromycin to improve lung function and to reduce the risk of exacerbations on patients colonized with *P. aeruginosa*” [4]. More recently, in a review of current treatment options for CF lung disease, Flume and Van Devanter noted, “Macrolide antibiotics are currently recommended as a chronic therapy for patients with CF to improve lung function and to reduce exacerbations despite some degree of uncertainty as to the exact mechanism by which macrolides exert their clinical effect” [5]. Between the release of these two

**FUTURE
SCIENCE** part of **fsg**

publications several studies have been conducted examining different aspects of macrolide therapy in treating CF lung disease. Studies have utilized different patient populations including patients without *P. aeruginosa* airway colonization, different doses and even different macrolides, apart from azithromycin. This review examines in detail these studies and considers whether azithromycin therapy should still be limited to patients with CF and *P. aeruginosa* airway colonization.

Methods

An initial search for relevant articles was conducted using Medline. Search terms of 'cystic fibrosis', 'azithromycin', 'clarithromycin', 'azithromycin', 'roxithromycin' and 'macrolides' were used. To provide an up-to-date review, the search was limited to publications released after the original Cystic Fibrosis Foundation document was published in 2007. The search was further limited to articles published prior to December 2012. In the initial search, a total of 55 publications were identified. This was then further limited to papers that described clinical trials of macrolide therapy in controlling lung disease in CF and that were published in English. Review articles that did not describe original research were not included.

The final selection identified seven clinical trials that had been published in peer-reviewed journals in the 5-year period from January 2008 to December 2012. All had examined the use of macrolide antibiotics in the management of patients with CF. Five of the studies focused on the use of azithromycin, covering aspects such as its role as an anti-inflammatory agent following intravenous therapy in patients colonized with *P. aeruginosa* [6], long-term use in the *P. aeruginosa* negative paediatric population [7,8], and the efficacy and tolerability of low versus high-dose azithromycin [9]. The final azithromycin-related study was a retrospective cohort study describing changes in the microbiological profile associated with long-term low dose azithromycin use in patients with established Gram-negative infection in a single CF center [10]. Two further studies were randomized, double-blind, placebo-controlled cross-over trials of clarithromycin, together involving 81 pediatric and adult participants from four CF centers [11,12].

Clinical trials of azithromycin

The five clinical studies of azithromycin involved 415 participants across 53 international CF centers (Table 1). Steinkamp *et al.* conducted a randomized, double-blind, placebo-controlled trial of weekly azithromycin in 38 participants at 11 CF centers in Germany and Switzerland [6]. Study participants were at least 8 years of age and 20 kg or over, had a forced expiratory volume in 1 s (FEV₁) of 30–80%, were chronically colonized with *P. aeruginosa* and had completed a course of intravenous

antipseudomonal therapy for treatment of an acute pulmonary exacerbation, with documented improvement, immediately prior to commencement of the trial. Patients receiving any systemic antibiotics other than the study drug and those receiving regular elective intravenous antipseudomonal therapy were excluded, as were patients with pre-existing non-CF related gastrointestinal disease, renal, cardiac or significant hepatic dysfunction. The trial was 8 weeks in duration and compared once-weekly azithromycin with placebo. Doses were determined by body weight. Participants weighing 20–29 kg, 30–39 kg, 40–49 kg and 50 kg or above received 500, 750, 1000 and 1250 mg weekly, respectively. The mean azithromycin dose was 21.2mg/kg/week. The primary end point was the absolute change in FEV₁ (% predicted). Secondary end points were changes in clinical signs and symptoms, spirometry, oxygen saturation, microbiological results, quality of life, serum inflammatory markers (CRP, total IgG and IL-8) and sputum parameters (alginate production of *P. aeruginosa*, sputum viscoelasticity, chloride secretion and DNA concentration). Safety profile, adverse events, and sputum and serum azithromycin concentrations were also examined [6].

In total, 29 participants, of mean age 24.8 years, completed the study. There were no significant differences in the pulmonary function tests of participants in the treatment and placebo groups at the commencement of the study. Both groups demonstrated a mean decline in FEV₁ over the 8-week study period of 3.7% and 5% respectively, with this difference not meeting statistical significance. The study demonstrated significant differences between the two groups in a number of its secondary end points. Azithromycin treatment was associated with improved serum inflammatory markers, microbiological profile, sputum alginate concentration, clinical signs and symptoms, and quality of life when compared with placebo. Specifically, CRP increased by 0.9 mg/l (SD: 6.6 mg/l) and 21.6 mg/l (SD: 60.4 mg/l), respectively ($p = 0.019$); IL-8 decreased by -3.1 pg/ml in the treatment group whilst increasing by +2.9 pg/ml in the placebo group ($p = 0.015$); and lipopolysaccharide binding protein increased by 0.9 and 7.0 µg/ml, respectively ($p = 0.015$). The proportion of participants with *P. aeruginosa* cultured from their respiratory secretions decreased from 81 to 75% in the treatment group whilst increasing from 63 to 100% in the placebo group. The proportion of patients with *Staphylococcus aureus* in their respiratory secretions changed similarly, decreasing from 19 to 17% in the treatment group and increasing from 19 to 50% of participants in the placebo group. The treatment group had significantly lower sputum alginate concentration than the placebo group (85 and 353 µg, respectively; $p = 0.048$), lower mean cough and sputum scores and significantly higher ratings in quality of

life scores related to weight, respiratory symptoms and disordered eating. Weekly azithromycin was well tolerated during this trial. Treatment-related adverse events occurred with similar frequency in the treatment and placebo groups (19 and 17.6%, respectively), none of which were severe. In summary, weekly azithromycin treatment did not show any significant effect on the primary efficacy variable of pulmonary function. Azithromycin treatment did, however, show significant effects on a number of the study's secondary variables [6].

Two trials by Saiman *et al.* examined the use of long-term azithromycin in the *P. aeruginosa*-negative pediatric population [7,8]. The initial study was a randomized, double-blind, placebo-controlled trial involving 260 children aged 6–18 years with a FEV₁ of at least 50% predicted in 40 CF centers in the USA and Canada. Patients were excluded if they had received antibiotics within 14 days of screening. Participants received either azithromycin, at doses of 250 or 500 mg (body weight below or above 36 kg) 3 days per week or placebo for 24 weeks. The primary end point was absolute change in FEV₁ (l). Additional end points were other pulmonary function test parameters, pulmonary exacerbations, initiation of antibiotic treatment, hospitalization, changes in weight, height and BMI and adverse events, including symptoms, changes in key laboratory indices (liver function enzymes, creatinine and neutrophil count) and microbiological profile [7].

In total, 252 participants completed the study. They had mild lung disease at baseline, with a FEV₁ of 97.7 and 99.6% predicted in the active and placebo groups, respectively. No significant differences in FEV₁ or other pulmonary function parameters were observed during the study. There was a 50% reduction in pulmonary exacerbations in the azithromycin treatment group ($p = 0.03$). Overall, 21% of the treatment group and 39% of the placebo group experienced acute pulmonary exacerbations (-18% treatment effect; $p = 0.03$). There was a -27% difference in the commencement of oral antibiotics in favor of the treatment group ($p < 0.001$), but no differences in the requirement for intravenous or inhaled antibiotics. Participants treated with azithromycin had significant increases in weight and BMI and a significant decrease in the prevalence of cough in comparison with those treated with placebo. Treatment was not associated with an increased risk of adverse safety events; however, an increase in treatment-emergent pathogens was seen in the azithromycin group, where macrolide-resistant *S. aureus* and *Haemophilus influenzae* occurred 27 and 7% more frequently, respectively, than in the treatment group. In summary, azithromycin treatment did not show any significant effect on the primary efficacy variable of pulmonary function. Azithromycin treatment did

Table 1. Azithromycin studies.

Study (year)	Characteristics	Epidemiology	<i>P. aeruginosa</i>	Treatment duration	Dose	Primary end point	Statistical significance	Ref.
Steinkamp (2008)	Randomized, double-blind, placebo-controlled	n = 38 Age ≥ 8 years (mean 24.8 years) FEV ₁ = 30–80%	Positive	8 wk	20–29 kg: 500 mg/wk 30–39 kg: 750 mg/wk 40–49 kg: 1000 mg/wk ≥ 50 kg: 1250 mg/wk	FEV ₁ (% predicted)	p = 0.708	[6]
Saiman (2010)	Randomized, double-blind, placebo-controlled	n = 260 Age: 6–18 years FEV ₁ ≥ 50%	Negative	24 wk	<36 kg: 250 mg x 3 days/wk ≥ 36 kg: 500 mg x 3 days/wk	FEV ₁ (l)	p = 0.61	[7]
Saiman (2012)	Open label follow-on	n = 146 Age: 6–18 years FEV ₁ ≥ 50%	Negative	24 wk	<36 kg: 250 mg x 3 days/wk	Multiple, including pulmonary function tests; exacerbations; weight	No statistically significant changes	[8]
Kabra (2010)	Randomized-controlled	n = 56 Age: 5–18 years FEV ₁ < 80%	46% positive	6 months	5 mg/kg/day or 15 mg/kg/day	FEV ₁ (% predicted)	p = 0.6923	[9]
Hansen (2009)	Descriptive retrospective	n = 70 Median age: 29.1 years (1.5–53.2)	Chronic Gram-negative infection	Median: 4 years (0.7–5.1)	<40 kg: 250 mg alternate days >40 kg: 250 mg daily	Colonization with and macrolide resistance of <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>M. catarrhalis</i>	Statistically significant decreased colonization but increased macrolide resistance (<i>Staphylococcus</i>)	[10]

FEV₁: Forced expiratory volume in 1 s; *M. catarrhalis*: *Moraxella catarrhalis*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Staphylococcus pneumoniae*; wk: Week.

however show significant effects on a number of the study's secondary variables [7].

An open-label study was subsequently conducted in order to compare clinical efficacy and safety end points with the placebo-controlled trial. It involved 146 participants (84%) from the initial study, at 32 North American CF centers, for a further 24 weeks. All participants received azithromycin 3 days per week at doses of 250 or 500 mg. Analysis was based on initial randomization – the group that received azithromycin followed by azithromycin and the group that received placebo followed by azithromycin. The efficacy end points of the study were changes in pulmonary function parameters, acute pulmonary exacerbations and changes in body weight. The safety and tolerability end points reported included adverse events, abnormalities in key laboratory parameters and changes in microbiological profile [8].

There was no significant improvement in pulmonary function in either participant group, although a trend toward improvement was noted in the placebo–azithromycin group, which had an increase in mean FEV₁ of 0.1 l (95% CI: -0.02–0.23) and 4.48% predicted (95% CI: -1.04–9.99). The odds of pulmonary exacerbation, hospitalization and commencement of intravenous and inhaled antibiotics in the open-label and placebo-controlled trials were similar in both participant groups. Oral antibiotics were commenced more frequently in the azithromycin–azithromycin group in the open-label phase of the study as compared with the placebo–controlled phase (odds ratio: 1.9; 95% CI: 1.0–3.5). There were no significant changes in oral antibiotic use in the placebo–azithromycin group. The study reported a trend towards increased weight gain in the open-label phase in the placebo–azithromycin group. Azithromycin was well tolerated and adverse event rates were comparable in both groups in both phases of the study. The prevalence of macrolide-resistant *S. aureus* increased from 10 to 28% in the placebo–azithromycin group ($p = 0.044$) while there were no significant changes in microbiology in the azithromycin–azithromycin group from the placebo-controlled to the open-label phase of the trial. In summary, azithromycin treatment did not show any significant effects on the study's efficacy end points [8].

Low and high-dose azithromycin were compared in a study by Kabra of 56 children with CF aged 5–18 years with FEV₁ < 80% predicted in New Delhi, India. Participants were randomized to receive either 5 mg/kg/day or 15 mg/kg/day of azithromycin for a period of 6 months, with follow up for at least 12 months. The primary end point was change in FEV₁. The study's secondary end points were pulmonary exacerbations, antibiotic use, *P. aeruginosa* culture on deep throat swab, clinical scores, weight and sputum IL-8 concentrations [9].

In total, 47 participants completed the study. They had moderate lung disease at baseline, with FEV₁ of 51 and 66% in the low- and high-dose groups, respectively, and 46% of participants had respiratory secretions positive for *P. aeruginosa*. There was no significant difference in mean FEV₁ between the two groups at any point, although both groups demonstrated a decline in pulmonary function over time, beginning at 12 months after commencement of the trial in the low-dose group and at 9 months in the high-dose group. The study also demonstrated clinical decline after cessation of azithromycin. Whilst the number of pulmonary exacerbations was comparable between the two groups, those treated with high-dose azithromycin had a significant increase in exacerbations in the second 6 months of follow up, from 0.05 to 0.34 per child per month ($p < 0.05$). Clinical scores were also comparable between the groups at baseline and at 6 months but the low-dose group demonstrated a significant decline between 6 and 12 months ($p < 0.05$). In summary, treatment with low- versus high-dose azithromycin showed no significant difference in the primary efficacy variable of pulmonary function.

Hansen *et al.* examined the impact of long-term azithromycin treatment on sputum microbiological profile in a group of patients with CF [10]. The descriptive, retrospective study involved 70 patients at the Copenhagen (Denmark) CF centre who had been treated continuously with low dose azithromycin for a period of at least three months. Participants had established Gram-negative infection or recurrent *P. aeruginosa* colonization, a median age of 29.1 years (range 1.5–53.2 years) at the commencement of azithromycin and had been treated for a median duration of 4 years (range 0.7–5.1 years). They received azithromycin 250 mg daily if their weight was above 40 kg and 250 mg alternate days if they were below 40 kg. The study compared all respiratory cultures in the 2 years preceding commencement of azithromycin with those obtained during treatment. Its end points were changes in incidence of colonization with *S. aureus*, *H. influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* and the development of macrolide resistance in the same organisms [10].

There was a decrease in *S. aureus* associated with azithromycin use. The proportion of patients with at least one culture positive for *S. aureus* decreased from 63 to 36% ($p < 0.01$) and the prevalence of *S. aureus* decreased from a mean of 12.1 to 6.1% of sample results ($p < 0.0006$). In contrast, the number of patients with macrolide-resistant isolates of *S. aureus* increased from three to 11 ($p < 0.03$), although one patient was described as having lost their macrolide-resistant strain during treatment. The proportion of *S. aureus* isolates with macrolide-resistance increased from 7 to 52.5% during treatment with azithromycin ($p < 0.0001$), with the

development of macrolide-resistance occurring a median of 1.5 years after commencement of azithromycin. No *S. aureus* isolates developed methicillin-resistance during treatment with azithromycin.

The prevalence of both *H. influenzae* and *S. pneumoniae* decreased significantly with azithromycin treatment, from 1.5 to 0.2% ($p < 0.003$) and from 1 to 0.3% ($p < 0.05$), respectively. There were no changes in the number of patients with at least one positive culture for either organism. No macrolide-resistant strains of either organism were isolated. There was no change in the prevalence of *M. catarrhalis* after the commencement of azithromycin, although one macrolide-resistant isolate developed. In summary, long-term azithromycin treatment was associated with a significant decrease in the prevalence of *S. aureus*, *H. influenzae* and *S. pneumoniae* and with a significant increase in the proportion of macrolide-resistance *S. aureus* isolates.

Clinical trials of clarithromycin

Randomized placebo-controlled, double-blind, cross-over trials of clarithromycin have involved 81 pediatric and adult participants at four international CF centers (Table 2). The earlier trial of 18 participants in Turkey aged 3–14.8 years was of 6.5 months duration. Participants received 15 mg/kg of clarithromycin daily, in two divided doses, for 3 months followed by placebo, with a 15-day washout period, or placebo followed by clarithromycin. Participants were not receiving antibiotics at baseline. The mean FEV₁ was 77.5% in group 1 and 98% in group 2. The study's primary end point was effect of clarithromycin on markers of lung inflammation obtained on bronchoscopic alveolar lavage (BAL). The secondary end point was clinical improvement, specifically weight, clinical status, acute pulmonary exacerbations and changes in pulmonary function tests [11].

In total, 17 participants completed the trial. There were no significant differences in BAL markers of lung inflammation. Clarithromycin treatment was associated with significant decreases in the modified NIH clinical scores and in the number and severity of pulmonary exacerbations, as well as a significant increase in weight in one group. There were no significant changes in pulmonary function in either group. One patient was excluded due to a rash attributed to clarithromycin. No other adverse events were observed although four patients grew new pathogens in their sputum (*P. aeruginosa* × 2, *Stenotrophomonas maltophilia* × 2, *Burkholderia cepacia* × 1) during the trial. In summary, clarithromycin treatment did not show any significant effect on the primary efficacy variable of markers of lung inflammation. Clarithromycin treatment did show significant effect on a number of the study's secondary variables, but not on pulmonary function [11].

The second study of clarithromycin, conducted by Robinson *et al.*, was a double-blind, randomized-controlled cross-over trial involving 63 adults and children, of mean age 16.7 ± 11.0 years, in three CF centers in Winston-Salem (NC, USA), and Perth and Melbourne (Australia) for a period of 11 months. Participants had a mean FEV₁ of 75.3% at baseline and 60% were positive for *P. aeruginosa*. They were randomized to receive clarithromycin, 500 mg slow-release daily for 5 months followed by placebo for 5 months, with a 1-month wash-out period, or placebo followed by clarithromycin. The study's primary end point was change in pulmonary function parameters. The secondary end points were quality of life, number of pulmonary exacerbations, height and weight, sputum inflammatory mediator content, sputum transportability and surface properties, bacterial flora, nasal potential difference, breath condensate and safety of clarithromycin treatment [12].

No significant differences were observed in any of the study's primary or secondary end points, including no difference in change in pulmonary function during the 5 months of clarithromycin treatment when compared with the 5 months of placebo treatment. Side effects were more common during placebo therapy, with only sinusitis occurring more frequently with clarithromycin treatment (17.2%) than with placebo (13.1%). In summary, clarithromycin treatment did not show any significant effect on the study's primary or secondary variables [12].

Discussion

Studies conducted over the 5 year period of this review have documented that while some improvements in secondary clinical end points, such as exacerbation rates and laboratory measures, including inflammatory markers and microbiological characteristics of sputum, were found in association with azithromycin therapy, no study examining the use of either azithromycin or clarithromycin was associated with any significant improvement in lung function. While it is tempting to pool the results of all the trials to perform a meta-analysis, the diverse and significant differences of the trials preclude this form of assessment. Steinkamp's study, for example, examined the effects of a weekly dose (of between 500 and 1250 mg) of azithromycin administered for 8 weeks to patients over 8 years of age whose sputum grew *P. aeruginosa* and who had completed a period of intravenous antibiotic therapy immediately prior to trial enrolment [6]. In contrast, Saiman's studies examined the effects of a three-times a week dose (of between 750 and 1500 mg per week) of azithromycin administered for 24 weeks to patients whose sputum did not grow *P. aeruginosa*. Despite these differences both trials failed to show a benefit of azithromycin in improving lung function while both did show improvements in clinical and laboratory secondary end points.

Table 2. Clarithromycin studies.

Study (year)	Characteristics	Epidemiology	<i>P. aeruginosa</i>	Treatment duration (months)	Dose	Primary end point	Statistical significance	Ref.
Dogru (2009)	Randomized, double-blind, placebo-controlled crossover	n = 18 Age: 3–14.8 years FEV ₁ (%): 60–117	Not described	3	15 mg/kg/day in two divided doses	Inflammatory markers in BAL	No significant decrease in inflammatory markers	[11]
Robinson (2012)	Randomized, double-blind, placebo-controlled crossover	n = 63 Age: 16.7 ± 11.0 years (mean ± SD) FEV ₁ : 75.3% ± 22.8% (mean ± SD)	60% positive	5	500 mg slow-release daily	Pulmonary function FEV ₁ and FVC	No statistically significant changes with treatment	[12]

BAL: Bronchoalveolar lavage; FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity; *P. aeruginosa*: *Pseudomonas aeruginosa*.

How then can we interpret the results of these five inherently different studies? Several studies published before the time frame of this current review have confirmed the benefit of azithromycin on both lung function, as a primary end point, and secondary end points, including clinical, such as exacerbation rates and quality of life, and laboratory parameters (inflammatory markers and changes in bacterial load), for patients with CF who are chronically colonized with *P. aeruginosa*. While some trials in this group have failed to identify such improvements, for example, Steinkamp *et al.*'s failure to show improvement in their study's primary efficacy end point of change in FEV₁ [6], expert advisory groups have considered that azithromycin anti-inflammatory therapy should be considered a therapeutic option for patients over the age of 6 years with chronic airway colonization with *P. aeruginosa* [4].

Saiman's studies stand as the sole investigations from this review period to examine the use of azithromycin anti-inflammatory therapy on patients with CF who did not have airway colonization with *P. aeruginosa*. A significant benefit seen in lung function in those patients treated with azithromycin was in neither the original placebo-controlled 24-week trial or the open-label extension trial. It is interesting to speculate on the reason for this finding. While it may simply relate to the degree or even type of airway inflammation caused by airway colonization with *P. aeruginosa* compared with other bacterial organisms, it is also worth noting that lung function, as assessed by the primary efficacy variable FEV₁, was well preserved in Saiman's study group. In the original study group mean FEV₁ at enrolment was predicted to be between 97–99% in the two treatment groups, placebo and active treatment. This contrasts with both Steinkamp's and Kabra's study of *P. aeruginosa* positive patients where FEV₁ at enrolment was lower (30–80% in Steinkamp and <80% in Kabra) [6,9]. Thus it is possible that azithromycin is

only effective when airway inflammation has reached a degree sufficient to result in lower airway damage as assessed by changes in lung function. Certainly the findings from Saiman's studies do not provide hard evidence that *P. aeruginosa*-negative CF patients with preserved lung function should be started on azithromycin. It will be interesting to review the results of the trial currently being conducted in Australian CF pediatric centers [10] where the primary efficacy end point is the incidence of bronchiectasis on CT scan at 3 years of age.

It is expected that the anti-inflammatory effect of azithromycin occurs at different systemic exposure levels to that required for its antibiotic role. In the studies examined in this review, therapy was given either daily, three-times weekly or weekly without any dosing regime being associated with a significant improvement in lung function. Furthermore, study periods from 8 to 26 weeks all failed to be associated with improvements in lung function. While it is possible that the 8-week trial length employed by Steinkamp *et al.* was too short to detect any difference between treatment groups, the findings of significant differences in inflammatory markers such as IL-8 in azithromycin-treated patients compared with placebo-treated patients argues against this. Furthermore, while the trials reviewed did not show any significant effect of azithromycin on primary efficacy end points of lung function most trials did show an improvement in secondary parameters in particular the incidence of exacerbations. These findings mirror findings from the recent major adult trials of azithromycin use in non-CF bronchiectasis [13–15].

It is possible that any beneficial effect of macrolide therapy occurs not as a result of an anti-inflammatory action but rather a direct interference with *P. aeruginosa*. Ichimiya reported that azithromycin was able to inhibit biofilm formation by *P. aeruginosa* at concentrations well below the minimum inhibitory concentration. This may

further explain why the beneficial effect of macrolide therapy appears to be limited to those patients with CF and airway colonization with *P. aeruginosa* [16].

Recently new Cystic Fibrosis Pulmonary Guidelines have been published by the Cystic Fibrosis Foundation, updating recommendations from their 2007 publication and taking into account results of trials published in the intervening period. The committee, in considering the use of azithromycin in treating CF lung disease differentiated their recommendations based on whether patients had *P. aeruginosa* or not in their airways. The committee concluded, "The committee rated the certainty of net benefit supporting the use of chronic azithromycin as high for individuals infected with *P. aeruginosa*, and the estimate of benefit was rated as moderate. The certainty of benefit was judged to be moderate for individuals without *P. aeruginosa* infection, and the estimate of net benefit was small" [17].

No new safety issues were identified in the trials examined. In particular, unlike the recent description of worrying cardiac side effects in adult studies of azithromycin use in non-CF bronchiectasis no cardiac side effects were identified in these trials.

Although being used as an anti-inflammatory agent the underlying antibiotic properties of macrolides have been shown to have clinical effects on airway colonization characteristics. Most worrying perhaps is the increase of *Mycobacterium abscessus* colonization, which parallels the increased use of azithromycin in one CF clinic as reported by Renna *et al.* [18]. While no increase in *M. abscessus* isolation was reported in any of the reviewed trials there was clear indication from the azithromycin trials of an increase in macrolide resistant *S. aureus* in three trials and macrolide resistant *H. influenzae* in the trials by Saiman *et al.* [7,8].

Two studies were published during the review period examining the use of clarithromycin as an anti-inflammatory therapy to control CF lung disease. Clarithromycin is an appealing macrolide for anti-inflammatory therapy as it has a good safety profile and, as is the case in azithromycin, has been shown to have an excellent uptake into both inflammatory cells and respiratory tissues [19]. Unlike the trials conducted with azithromycin, neither study of clarithromycin was able to show changes in inflammatory markers obtained either from BALs or sputum of patients with CF. Both trials were conducted over at least 3 months and included patients with mild-moderate lung disease. In the largest study, Robinson *et al.* studied patients both with and without *P. aeruginosa* airway colonization [12]. While subgroup analysis of the results was conducted using the presence of *P. aeruginosa* as a variable, no beneficial effect on clinical end points such as spirometry, quality of life or inflammatory markers was seen in the *P. aeruginosa*-positive

clarithromycin treated group. While this may be the result of a Type II error due to small group numbers the possible beneficial effect of clarithromycin as an anti-inflammatory agent to treat CF lung disease will require a larger study examining *P. aeruginosa*-positive patients in detail.

Future perspective

This review has examined seven studies of macrolide usage in the treatment of CF lung disease using a variety of doses, schedules and study length and two different macrolides published over a recent 5-year period. In no study was a beneficial effect of macrolide therapy found on lung function parameters. In particular, in a study of patients who did not have *P. aeruginosa* colonization of their airways and who had well preserved lung function, macrolide therapy did not improve lung function. Several studies using azithromycin did show significant improvements in clinical end points such as exacerbation rate and changes in inflammatory markers. Several of these effects were evident even in a short-term 8-week study. Two additional studies examined the use of clarithromycin in treating lung disease in CF. While no improvements in lung function were noted in the largest study with the use of clarithromycin there was a suggestion of an improvement in inflammatory markers obtained on bronchial lavage in a smaller study. Such changes were not replicated in the larger study where sputum was used to assess inflammation. This may be related to the use in this study of both *P. aeruginosa*-positive and -negative patients.

The examined trials from this review period have, while failing to show significant improvements in lung function in both *P. aeruginosa*-positive and -negative treated patients, shown a possible benefit in reducing the number of pulmonary exacerbations. The use of azithromycin in patients negative for *P. aeruginosa* still needs to be confirmed, although one study has shown improvements in end points such as exacerbations rates. Similarly the possible role for clarithromycin in treating lung disease in patients with CF who are *P. aeruginosa*-positive remains to be confirmed.

Financial & competing interests disclosure

P Robinson was his sites principal investigator for the clarithromycin trial mentioned in the text. This study was part funded by Abbott Pharmaceuticals with financial aid being provided to the site, not to P Robinson directly. P Robinson was not involved with protocol development but was the principal author of the relevant quoted manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Background

- Macrolide therapy, in particular azithromycin, has been shown to improve aspects of lung health in patients with cystic fibrosis, especially those with chronic *Pseudomonas aeruginosa* colonization. Its effect is thought to be due to an anti inflammatory action.
- The clinical trials of macrolide therapy in CF published over the five-year period from January 2008–December 2012 demonstrated no significant improvement in lung function with the use of either azithromycin or clarithromycin.

Studies of azithromycin

- Studies of azithromycin demonstrated improvements in their secondary end points, in particular, decreased incidence of pulmonary exacerbations and improvements in laboratory measures of inflammation.
- Azithromycin therapy did not improve lung function parameters in patients with well-preserved lung function and without *P. aeruginosa* airway colonization.

Studies of clarithromycin

- The studies of clarithromycin demonstrated no significant improvements in pulmonary function or in measures of lung inflammation.

Safety & adverse effects

- No new safety issues were identified in the clinical trials included in this review. In particular, no adverse cardiovascular effects were encountered.
- Concerns regarding changes in sputum microbiological profile associated with macrolide therapy have been raised. These studies illustrate an increase in the prevalence of macrolide-resistance *Staphylococcus aureus* and *Haemophilus influenzae* with long term azithromycin use.

Future perspective

- The role for azithromycin therapy in patients without *P. aeruginosa* colonization requires further exploration.

References

- Ramsey BW, Davies J, McElvaney NG *et al.* A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N. Engl. J. Med.* 365(18), 1663–1672 (2011).
- Konstan MW, Schluchter MD, Xue W, Davis PB. Clinical use of ibuprofen is associated with slower FEV1 decline in children with cystic fibrosis. *Am. J. Resp. Crit. Care Med.* 176(11), 1084–1089 (2007).
- Balfour-Lynn IM, Klein NJ, Dinwiddie R. Randomised control trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis. *Arch. Dis. Child* 77(2), 124–130 (1997).
- Flume PA, O'Sullivan BP, Robinson KA *et al.* Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am. J. Resp. Crit. Care Med.* 176(10), 957–969 (2007).
- Flume PA, Van Devanter DR. State of progress in treating cystic fibrosis respiratory disease. *BMC Med.* 10, 88 (2012).
- Steinkamp G, Schmitt-Grohe S, Doring G *et al.* Once-weekly azithromycin in cystic fibrosis with chronic *Pseudomonas* infection. *Respir. Med.* 102(11), 1643–1653 (2008).
- Saiman L, Anstead M, Mayer-Hamblett N *et al.* Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with *Pseudomonas aeruginosa*: a randomised control trial. *JAMA* 303(17), 1707–1715 (2010).
- Saiman L, Mayer-Hamblett N, Anstead M *et al.* Open-label, follow-on study of azithromycin in pediatric patients with CF uninfected with *Pseudomonas aeruginosa*. *Pediatr. Pulmonol.* 47(7), 641–648 (2012).
- Kabra SK, Pawalya R, Lodha R *et al.* Long-term daily high and low doses of azithromycin in children with cystic fibrosis: a randomized control trial. *J. Cyst. Fibros.* 9(1), 17–23 (2010).
- Hansen CR, Pressler T, Holby N, Johansen HK. Long-term, low-dose azithromycin reduces the incidence but increases macrolide resistance in *Staphylococcus aureus* in Danish CF patients. *J. Cyst. Fibros.* 8(1), 58–62 (2009).
- Dogru D, Dalgic F, Kiper N *et al.* Long-term clarithromycin in cystic fibrosis: effects on inflammatory markers in BAL and clinical status. *Turk. J. Pediatr.* 51(5), 416–423 (2009).
- Robinson P, Schecter MS, Sly PD *et al.* Clarithromycin therapy for patients with cystic fibrosis: a randomized control trial. *Pediatr. Pulmonol.* 47(6), 551–557 (2012).
- Altenburg J, De Graaff CS, Stienstra Y *et al.* Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: The BAT randomised control trial. *JAMA* 309(12), 1251–1259 (2013).
- Serisier DJ, Martin ML, McGuckin MA *et al.* Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: The BLESS randomized controlled trial. *JAMA* 309(12), 1260–1267 (2013).
- Wong C, Jayaram L, Karalus N *et al.* Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomized, double-blind, placebo-controlled trial. *Lancet* 380(9842), 660–667 (2012).
- Ichimiya T, Takeoka K, Hiramatsu K, Hirai K, Yamasaki T, Nasu M. The influence of azithromycin on the biofilm formation of *Pseudomonas aeruginosa* *in vitro*. *Chemotherapy* 42(3), 186–191 (1996).
- Mogayzel PJJ, Naureckas ET, Robinson KA *et al.* Cystic Fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am. J. Resp. Crit. Care Med.* 187(7), 680–689 (2013).
- Renna M, Schaffner C, Brown K *et al.* Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. *J. Clin. Invest.* 121(9), 3554–3563 (2011).
- Shinkai M, Rubin BK. Macrolides and airway inflammation in children. *Paediatr. Respir. Rev.* 6(3), 227–235 (2005).

■ Website

- Australian New Zealand Clinical Trials Registry
www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12610001072000