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REVIEW

Azithromycin for cystic fibrosis

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ABSTRACT: During what is a relatively barren time for new therapies for cystic fibrosis (CF), azithromycin has received a lot of attention as a potential treatment for CF lung disease. Laboratory studies suggest that azithromycin may have indirect actions, including anti-inflammatory, in addition to the standard antibacterial properties. The unique pharmacokinetics of azithromycin sets it aside from other macrolide antibiotics, but may result in increased resistance patterns.

Three well-designed randomised controlled trials have demonstrated a small but significant improvement in respiratory function (forced expiratory volume in one second) with azithromycin compared with placebo. These trial results are confirmed by a recent meta-analysis. Mild adverse events (wheeze, diarrhoea and nausea) were significantly increased in one trial. There is no clear consensus regarding the correct dose and length of treatment with azithromycin.

The present review discusses the role of azithromycin in the management of cystic fibrosis and the need for close monitoring of patients started on this drug. In addition, clinics should liaise closely with their microbiology departments and monitor resistance patterns.

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Active treatment of lung infection is a cornerstone of cystic fibrosis (CF) management [1]. Together with attention to nutritional well-being, this strategy has led to considerable improvement in median survival for people with CF over the past 50 yrs [2]. However, over the past decade, little in the way of therapeutic advance has been available for the CF team. Recombinant DNAse, and purer formulations of tobramycin have improved the range of aerosolised therapies available [3, 4], but there have been no new anti-pseudomonal antibiotics, and more fundamental therapies, such as ion transport modulation or gene replacement, are yet to prove themselves at clinical trial [5, 6]. In this climate, azithromycin has been enthusiastically embraced by many centres across the world as a potentially important and relatively inexpensive treatment for CF lung disease. The present study will critically review evidence from randomised controlled trials (RCTs) and reflect on the role of azithromycin in the management of CF lung disease. Meta-analysis in the current review is from a recent update of a systematic review published on the Cochrane database [7, 8]. Investigators gave original data to the present review and are acknowledged for their contribution.

Background

Azithromycin is an azalide antibiotic, which is a subclass of the macrolide family [9]. It has no direct killing effect against the Gram-negative bacteria, *Pseudomonas aeruginosa*, but it is active against other Gram-negative bacteria, such as *Haemophilus influenzae* and *Moraxella catarrhalis*. It has a similar, though less potent, spectrum of activity as erythromycin against Gram-positive bacteria, such as *Streptococci* and *Staphylococcus aureus*. The structure of azithromycin results in a distinct pharmacokinetic profile to other macrolides, such as erythromycin and clarithromycin. Although plasma concentrations are low, azithromycin has good tissue penetration and high concentrations in airway secretions can be achieved. Consequently, a short course of once a day treatment has been advocated for soft tissue and respiratory tract infection. These advantages may be offset by development of resistance in target pathogens because of the widespread use and long tissue half-life of azithromycin [10]. A recent report described high nasal carriage rates of *S. aureus* from students in the USA; a quarter of these isolates were resistant to azithromycin [11]. Similar to other macrolides, azithromycin also has a role in treating atypical infections such as *Mycoplasma pneumoniae*, Lyme disease and *Chlamydia pneumoniae*.

Early reports of macrolides for cystic fibrosis

In 1994, HOIBY [12] highlighted similarities between CF and diffuse panbronchiolitis, a condition associated with chronic *P. aeruginosa* lung infection, found principally in the East Asian population. He commented on the improvement that many of these patients had experienced in their respiratory condition following treatment with the macrolide antibiotic, erythromycin, and suggested that macrolide antibiotics might have a role in CF through indirect anti-pseudomonal properties.

The variety of nonantibiotic effects attributed to azithromycin has been extensively reviewed by BUSH and RUBIN [13]. There is good evidence that macrolides modulate inflammatory pathways by suppressing pro-inflammatory cytokines [14]. In addition, macrolides may have more wide ranging effects on the innate immune system, modulating neutrophil function, reducing the presentation of adhesion molecules and altering expression of nitric oxide synthases [15–17]. Finally, macrolides may have more mechanistic effects, reducing airway mucus production and altering the biofilm phenotype of *P. aeruginosa* [18, 19].

Does azithromycin work in cystic fibrosis?

Three well-designed RCTs have examined azithromycin *versus* placebo for CF lung disease [20–22]. All employed appropriate treatment allocation and concealment. In total, 286 adults and children (>8 yrs) with CF were included in these trials (table 1). Change in forced expiratory volume in one second (FEV1) over the course of the study period was the primary outcome measure in each trial, though different methods were used to analyse these data (table 1). Although the three trials examined different time points, and a trial by EQUI *et al*. [20] employed a cross-over design, meta-analysis of relative change in FEV1 was possible with data at five time points (data from the first arm of the cross-over study were included as the two groups had similar baseline characteristics). Relative change in FEV1 is calculated as follows:

$$\frac{(\text{FEV1\% pred at end of study} - \text{FEV1\% pred at beginning} \times 100)}{\text{FEV1\% pred at beginning}} \quad (1)$$

At both 1 and 6 months, the weighted mean difference in relative change of FEV1 is significantly in favour of azithromycin (table 2; fig. 1). At 6 months, this value was 5.8% (95% confidence interval: 2.4–9.2%). This meta-analysis is consistent with the reported improvements in FEV1 in each of the trials and provides reassurance of a small but true improvement in FEV1 with azithromycin. Similar improvements are seen with forced vital capacity (significant at time points 2 months and 6 months). These data suggest a consistent, but small improvement in respiratory function following treatment with azithromycin for a period of 6 months.

Regarding secondary outcomes that are more relevant to patients, WOLTER *et al*. [20] demonstrated a significant reduction in hospital inpatient days and number of additional courses of *i.v.* antibiotics in the azithromycin group. These findings were not reproduced in the studies by EQUI *et al*. [21] or SAIMAN *et al*. [22]. However, SAIMAN *et al*. [22] did demonstrate a significant reduction in the number of patients admitted in the azithromycin group (14 out of 97 *versus* 29 out of 98; p=0.05).

WOLTER *et al*. [20] and SAIMAN *et al*. [22] employed validated "Quality of Life" (QoL) questionnaires to monitor for improvement over the trial period. WOLTER *et al*. [20] demonstrated improvement in both groups (RCTs improve your QoL!), although more pronounced in the azithromycin group. SAIMAN *et al*. [22] demonstrated a significant improvement in the "physical functioning" component of their questionnaire in the azithromycin group. EQUI *et al*. [21] demonstrated no difference with a visual analogue score (appropriate for children). Overall, the changes in these secondary outcomes were not impressive, and inconsistencies between the studies were found.

Table 1. – Details of three randomised controlled trials included in the Cochrane review [8]

Study [Ref]	Study design	Subjects n	Age range yrs	Concerns	Primary outcome measure	Adverse events
WOLTER *et al*. 2002 [19]	RPCT, 250 mg OD for 3 months	60	18–44	More males overall and improved respiratory function in the placebo group	Change in FEV1 % pred[#], mean±SE excess effect of AZM was 3.62±1.78%	One urticarial reaction, likely related to AZM
EQUI *et al*. 2002 [20]	RPCT cross-over, 250 mg OD for 6 months[¶], 500 mg if weight >40 kg	41	8–18	Potential for hangover effect into the second arm of the study. A significant number of participants did not grow *P. aeruginosa*	Relative change in FEV1 between AZM and placebo treatment periods, taking the average of months 4 and 6 and dividing by the baseline FEV1 and multiplying by 100. Median relative difference was 5.4% in favour of AZM (95% CI: 0.8–10.5)	Transient rise in liver enzymes in one participant
SAIMAN *et al*. 2003 [21]	RPCT, multi-centre, 500 mg (250 if <40 kg) three times a week for 6 months	185	6–adult age (19 subjects aged <13 yrs)	Randomisation stratified to prevent centre bias	Relative change in FEV1. Mean±SD increase in the AZM group was 0.097±0.26 L compared with 0.003±0.23 L in the placebo group. Mean difference between groups 6.2% (95% CI: 2.6–9.8)	Significant increased reporting of nausea, diarrhoea and wheezing with AZM

RPCT: randomised placebo-controlled trial; OD: once a day; *P. aeruginosa*: *Pseudomonas aeruginosa*; FEV1 % pred: forced expiratory volume in one second expressed as percentage predicted; AZM: azithromycin; 95% CI: 95% confidence interval. [#]: combining data at each time point; [¶]: each arm.

Table 2. – Data at five time points for the relative changes in forced expiratory volume in one second (FEV_1) from the three randomised controlled trials included in the Cochrane review [8, 20–22]

Study or sub-category	Subjects n	Azithromycin mean±SD	Subjects n	Placebo mean±SD	Weight %	WMD fixed (95% CI)
At 1 month						
WOLTER *et al.* [20]	22	2.92±7.72	23	-1.32±5.51	41.05	4.24 (0.31–8.17)
SAIMAN *et al.* [22]	87	4.01±13.03	97	0.20±9.10	58.95	3.81 (0.53–7.09)
Subtotal 95% CI	109		120		100.00	3.99 (1.47–6.51)
Test for heterogeneity: Chi^2=0.03, df=1 (p=0.87), I^2=0%						
Test for overall effect: Z=3.10 (p=0.002)						
At 2 months						
EQUI *et al.* [21]	20	5.29±9.69	21	3.25±13.86	27.57	2.04 (-5.25–9.33)
WOLTER *et al.* [20]	24	1.51±8.84	17	-1.17±5.85	72.43	2.68 (-1.82–7.18)
Subtotal 95% CI	44		38		100.00	2.50 (-1.33–6.33)
Test for heterogeneity: Chi^2=0.02, df=1 (p=0.88), I^2=0%						
Test for overall effect: Z=1.28 (p=0.20)						
At 3 months						
WOLTER *et al.* [20]	22	2.95±9.22	21	-0.91±5.99	37.20	3.86 (-0.77–8.49)
SAIMAN *et al.* [22]	87	2.33±12.47	95	0.32±11.99	62.80	2.01 (-1.55–5.57)
Subtotal 95% CI	109		116		100.00	2.70 (-0.12–5.52)
Test for heterogeneity: Chi^2=0.39, df=1 (p=0.53), I^2=0%						
Test for overall effect: Z=1.87 (p=0.06)						
At 4 months						
EQUI *et al.* [21]	20	8.07±14.58	21	2.73±15.37	100.00	5.34 (-3.83–14.51)
Subtotal 95% CI	20		21		100.00	5.34 (-3.83–14.51)
Test for heterogeneity: NA						
Test for overall effect: Z=1.14 (p=0.25)						
At 6 months						
EQUI *et al.* [21]	20	6.74±13.74	21	3.45±16.56	13.21	3.29 (-6.01–12.59)
SAIMAN *et al.* [22]	84	4.44±13.60	93	-1.77±10.66	86.79	6.21 (2.58–9.84)
Subtotal 95% CI	104		114		100.00	5.82 (2.45–9.20)
Test for heterogeneity: Chi^2=0.33, df=1 (p=0.57), I^2=0%						
Test for overall effect: Z=3.38 (p=0.0007)						

The relative change in FEV1 is presented for each trial at each available time point. Combined data are available at four time points (1, 2, 3 and 6 months). The weighted mean difference (WMD) is presented for individual and combined trial data (positive value (fig. 1) favours treatment with azithromycin). Chi^2: Chi-squared test is a test for heterogeneity; I^2: a measure of inconsistency across studies due to heterogeneity rather than chance; df: degrees of freedom (although these values suggest consistency, the number of studies is too small for this to be a valid assumption); Z value: this is a test for overall effect of the combined data (significant at 1 and 6 months); 95% CI: 95% confidence interval; NA: not applicable.

Why does it work?

Having noted the significant improvement in respiratory function, it is useful to reflect on the mechanism of action. Does it relate to an indirect anti-pseudomonal or anti-inflammatory effect, or is it simply the result of standard antibiotic properties of azithromycin? WOLTER *et al.* [20] reported a significant effect on the "time trend" of C-reactive protein over the course of the study with a fall in the azithromycin group. However, this systemic measure of inflammation is not a valid predictor of the local inflammatory process in the airways [23]. SAIMAN *et al.* [22] measured interleukin-8 and neutrophil elastase (both markers of inflammation in CF) in sputum and demonstrated no clinically significant difference between the groups at the end of the study period.

There was no evidence of decreased acquisition of *P. aeruginosa* in patients treated with azithromycin. In the study by SAIMAN *et al.* [22], eight patients had a new acquisition of *P. aeruginosa* (five in placebo group). There was no significant change in pathogens isolated from respiratory culture in the studies by either WOLTER *et al.* [20] or EQUI *et al.* [21]. However, in the study by SAIMAN *et al.* [22], 12 patients in the placebo group had recently detected *S. aureus* compared to two in the azithromycin group (p=0.01). All the trials had relatively high levels of *S. aureus* isolated in the patients involved. Even if the mechanism of action for azithromycin is anti-pseudomonal, a significant reduction in positive respiratory cultures may not occur, particularly if the action is indirect. However, these data, overall, are not supportive of an anti-inflammatory hypothesis, and data from the study by SAIMAN *et al.* [22] suggest that the improvement in respiratory function may relate to the anti-staphylococcal properties of azithromycin.

Azithromycin has received the most attention for CF, although other macrolide antibiotics have been examined in clinical trials. A total of four underpowered trials have examined clarithromycin and have not reported a difference in outcomes (data presented at conferences but not published) [8].

Is azithromycin safe?

There have been no reports of serious adverse events related to azithromycin in any of the trials reported to date; however, the RCT is not the ideal tool for detecting serious, but uncommon, adverse events, and the longest duration of treatment was 6 months. The study by SAIMAN *et al.* [22] reported a significant increase in mild adverse effects (wheeze, diarrhoea and nausea) in patients receiving azithromycin. Whilst diarrhoea and nausea are recognised sequelae of macrolide therapy, it is more difficult to explain the increased

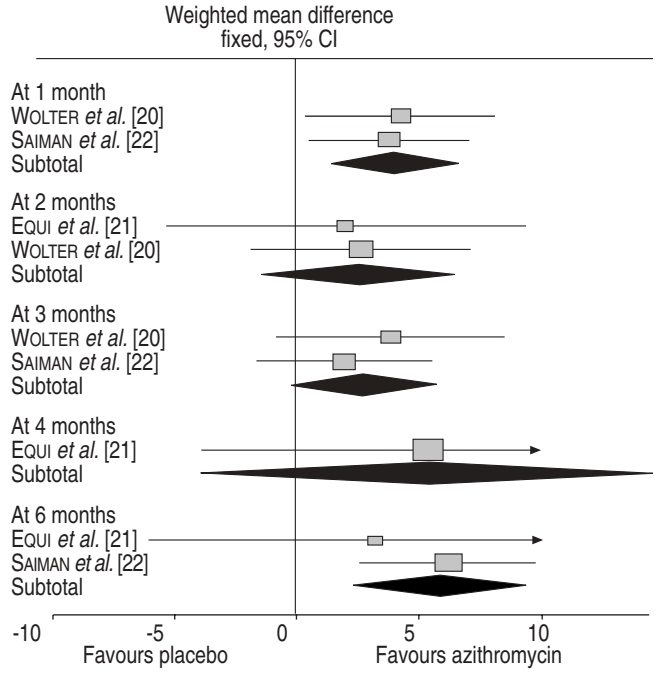

Fig. 1. – A "forest" plot demonstrating the combined data for relative change in forced expiratory volume in one second from the three randomised controlled trials included in the Cochrane review, "macrolide antibiotics for cystic fibrosis" [8, 20–22]. Data are available for five times points (1, 2, 3, 4 and 6 months). The plots show results from individual trials: mean (■) and 95% confidence interval (95% CI; —) and combined data (◆). The weighted mean difference consistently favours treatment with azithromycin and is statistically significant at 1 and 6 months. Refer to table 2 for specific data in relation to this figure.

relative risk (RR) of wheeze in these patients (RR=4.2; 95% confidence interval: 1.46–12.25)) [8]. There are no data from the trial by SAIMAN *et al*. [22] to suggest an increased incidence of allergic bronchopulmonary aspergillosis, but some attention to this finding is required in future studies. These adverse events are mild and may be self-limiting. However, this increased RR may result in reduced concordance with azithromycin treatment.

Given the unique pharmacology of azithromycin, it is important that careful monitoring and reporting of adverse events is undertaken on patients started on the drug. In a small randomised study assessing different doses of azithromycin, a significant rise in liver enzymes occurred in one patient on 1,000 mg of azithromycin, once a day for 5 days (and smaller rises in two other patients) [24]. All returned to normal levels, and ultrasound scans were normal 2 weeks after the dosing period. An isolated rise in liver enzymes in one patient was reported by EQUI *et al*. [21].

What is the correct dose?

There are limited data available as to the correct dosage of azithromycin in CF. The largest of the three RCTs employed a dose of 500 mg given once on a Monday, Wednesday and Friday (dose reduced to 250 mg in patients weighing <40 kg). The studies by WOLTER *et al*. [20] and EQUI *et al*. [21] employed daily dosage regimes with no obvious improvement in outcome compared to the study by SAIMAN *et al*. [22]. The pharmacokinetic study by CIPOLLI *et al*. [24] demonstrated high levels of azithromycin in bronchial secretions 6 days after a 5-day course (either 500 or 1,000 mg), supporting the SAIMAN *et al*. [22] study regime of intermittent dosing and raising the possibility that even less frequent administration (*i.e.* weekly) may be a possible strategy.

When should we prescribe azithromycin for cystic fibrosis?

There is consistent evidence from three well-designed placebo-controlled RCTs of a significant, although small, improvement in respiratory function in CF patients receiving azithromycin for periods of 3–6 months. Should the CF team now prescribe azithromycin for all their patients? The current authors suggest that there are still questions to be answered before adopting this policy, not least regarding dosage. There is probably a good argument for reserving azithromycin for patients with chronic *P. aeruginosa* infection, in whom maintaining respiratory condition has been difficult. Of concern in this cohort of patients (many of whom will be on DNAse) is the reported inhibitory effect of macrolides on DNAse activity [25]. DNA hydrolysis was significantly reduced *in vitro* by all macrolides, but most noticeably by azithromycin. The subgroup analysis in the trial by EQUI *et al*. [21] demonstrated an apparent lack of efficacy when participants were on DNAse. The possibility of azithromycin inhibiting DNAse *in vivo* requires further investigation.

Some participants in the three RCTs (table 1) were not infected with *P. aeruginosa*. However, at present, it is not clear whether azithromycin improves respiratory condition in such cases. A further study is planned in the USA examining the question of the use of azithromycin for children with CF without chronic *P. aeruginosa* infection (personal communication, L. Saiman, Columbia University, New York, NY, USA). In CF centres that advocate anti-staphylococcal prophylaxis (generally in Europe), azithromycin may replace the standard regime (often flucloxacillin or cefradine), as well as offering potential anti-pseudomonal effects. The role of azithromycin as a prophylactic agent in newly diagnosed infants, for example those identified through newborn screening programmes, requires a rigorous multi-centre RCT with clearly defined and relevant outcomes. There is an urgent need for such a study, which must assess increasing resistance patterns to azithromycin, as well as efficacy outcomes.

All patients prescribed azithromycin for medium to long-term periods need to be monitored carefully for adverse effects. In view of the transient derangement in liver function experienced in the study by CIPOLLI *et al*. [24], it would appear prudent to monitor this with an annual liver ultrasound scan and twice yearly analysis of serum enzymes. Any adverse effects noted should be reported to the national drug monitoring agency and to the national CF database.

In a barren time for new therapies, azithromycin increases the cystic fibrosis physician′s armamentarium and offers a potentially useful therapy to arrest respiratory decline. However, questions remain as to its precise role in the clinic and continued vigilance is required for adverse outcomes.

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