MACROLIDE ANTIBIOTICS FOR CYSTIC FIBROSIS

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ABSTRACT

Background
The antibiotic treatment of chest infections which characterise cystic fibrosis (CF) has significantly improved prospects for people with CF. The nature of organisms causing these infections has restricted antibiotic choice. *Pseudomonas aeruginosa*, especially, is resistant to most oral antibiotics. There is evidence from the laboratory and from other disease processes that macrolide antibiotics, whilst not directly active against *Pseudomonas aeruginosa*, may have indirect actions against this organism.

Objectives
We aimed to test the hypotheses that macrolide antibiotics:
(1) improve clinical status compared to placebo or another antibiotic;
(2) have no unacceptable adverse effects.

If benefit was demonstrated, we aimed to assess the optimal type, dose and duration of macrolide therapy.

Search Strategy
We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group trials register comprising references identified from comprehensive electronic database searches, handsearching relevant journals and abstract books of conference proceedings.

We contacted principal investigators known to work in the field, previous authors and pharmaceutical companies who manufacture macrolide antibiotics for unpublished or follow-up data (December 2002).

Date of the most recent search of the Group's register: March 2003.

Selection Criteria
Published or unpublished randomised controlled trials of macrolide antibiotics compared to placebo, another class of antibiotic or another macrolide antibiotic. Studies comparing regimens of the same macrolide antibiotic at different doses will also be included.

Data collection and analysis
Two reviewers independently extracted data and assessed study quality. Two groups were contacted for missing data, but these were unavailable for the review.

Main Results
Searches identified eleven studies, two were included in this review (101 participants). One study enrolled adults and the other children (a significant number of whom were not colonised with *Pseudomonas aeruginosa*). Both studies report small but significant changes in respiratory function (% change in FEV1) in favour of azithromycin. Meta-analysis at the two-month time point demonstrated a significant benefit with respect to percentage change in FVC (weighted mean difference 5.42 (1.77 to 9.07)) from azithromycin, but no difference with respect to percentage change of FEV1. There were no significant adverse effects reported.

Reviewers' conclusions
The role of macrolides in the management of CF lung disease remains unclear and there are many unanswered questions. Two small randomised controlled trials have suggested short-term improvement

in respiratory function with azithromycin. Until the results of further studies are available the widespread use of azithromycin in CF cannot be advocated and should be restricted to well-designed randomised controlled trials.

This review should be cited as:
Southern KW, Barker PM, Solis A Macrolide antibiotics for cystic fibrosis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.

BACKGROUND

This review examines the use of macrolide antibiotics for the treatment of cystic fibrosis (CF) chest infection.

Cystic Fibrosis is the most common inherited disease in the Caucasian population. The disease is caused by mutation of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene (Riordan 1989). The protein that this gene codes for, has an important role in the transport of salt and water across the surface of epithelia (Boucher 1999). The sequelae of abnormal CFTR function are apparent in a number of organs in the body, however lung involvement is the most important cause of disability and death. The CF defect results in dehydrated airway secretions (Matsui 1998). Inability to clear these secretions and an abnormal inflammatory response accounts for the lung infection and damage that characterises the condition. Recurrent bacterial infection combined with an abnormal inflammatory process leads to a cycle of lung damage and further infection.

Characteristic organisms associated with CF chest infection are, most notably *Staphylococcus aureus* (*S. aureus*) in the early course of the disease and *Pseudomonas aeruginosa* (*P. aeruginosa*) at a later stage (Hutchison 1999). Production of a mucoid coat by *P. aeruginosa* is characteristic and appears to increase the pathogenicity of this organism in CF. In the laboratory *P. aeruginosa* is resistant to most antibiotics that can be taken orally. The only oral antibiotics that have direct killing activity against *P. aeruginosa* are quinolones such as ciprofloxacin. All other anti-pseudomonal antibiotics need to be given intravenously or aerosolised into the lungs. Another problem in the management of people with CF is the increasing resistance of *P. aeruginosa* following prolonged use of available antibiotics.

This review focuses on macrolide antibiotics with the aim of evaluating both their long- and short-term use in CF chest infection. The oldest and most widely used macrolide is erythromycin. Newer antibiotics in this class include clarithromycin, roxithromycin and azithromycin. Macrolides kill a wide range of bacteria which cause respiratory disease (including *S. aureus*), but are not directly active against *P. aeruginosa*, at least when assessed in the laboratory. In Japan, macrolides have been widely used since 1982 as a treatment for diffuse panbronchiolitis, a rare inflammatory lung condition, affecting older Japanese people, until recently virtually unrecognised outside of East Asia (Hoiby 1994). *P. aeruginosa* infection in these people is associated with a very poor outcome. Evidence has been presented (including one randomised controlled trial (RCT)) that, even at low doses, the long-term use of macrolides has a beneficial effect on outcome for these people (Kobayashi 1993). This has been attributed to a reduction in factors (called virulence factors) that increase the activity of *P.aeruginosa*. These virulence factors, such as the production of a mucoid biofilm which protects *P. aeruginosa* from the host defences, are important for the pathogenicity of *P.aeruginosa* in diffuse panbronchiolitis and CF. Of the newer macrolides, an azalide, azithromycin (Retsema 1987) is reported to show the most significant evidence in laboratory studies of activity against the virulence factors of *P.aeruginosa* (Molinari 1993; Mizukane 1994; Ichimiya 1996). In addition, macrolides have been cited as having direct anti-inflammatory properties (Labro 1998). Experiments in the laboratory suggest this relates to the effects on inflammatory cells (Anderson 1996; Yanagihara 1997).

The pharmacokinetics and bioavailability of azithromycin make it a potentially useful antibiotic for lower respiratory tract infection (Ball 1991). Macrolides, in particular azithromycin, may have a role in the long- or short-term treatment of CF chest infection, given their unique activity against the virulence factors of *P.aeruginosa*. As well as direct antibacterial properties the macrolides may prove to have an important role in the treatment of CF lung disease because of their additional anti-inflammatory properties (Ianaro 2000). The effect of this class of antibiotics on the natural history of CF lung disease will require careful evaluation.

OBJECTIVES

This review tested the hypotheses that macrolide antibiotics:
(1) improve clinical status compared to placebo, no placebo or another antibiotic;
(2) do not have unacceptable adverse effects.

If efficacy of macrolide antibiotics is demonstrated, we will examine the optimum dosing regimens and durations of therapy for CF.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

RCTs, published or unpublished. Quasi-randomised (e.g. alternate allocation and stratification) controlled trials were included if there was sufficient evidence that intervention and control groups were similar at baseline. Cross-over trials were considered for short-term outcomes only.

Types of participants

People included in the analysis fulfilled strict criteria for the diagnosis of CF. If two disease-causing genetic mutations were not recognised, participants should have a positive sweat test and clinical features consistent with CF.

Types of intervention

Short- or long-term (where long-term is 12 months or longer) use of a macrolide antibiotic compared to controls who receive placebo, another antibiotic class, another macrolide or the same macrolide at a different dose.

Types of outcome measures

Please note that the outcome measure "nutritional markers", which was previously listed under secondary outcomes, has been moved to primary outcomes. The reviewers felt that the close correlation between weight and mortality merited this outcome being moved to primary outcomes.

PRIMARY OUTCOMES

(1) Number of days as a hospital inpatient

(2) Lung function
(a) In adults or older children who can perform spirometry
(i) forced expiratory volume at one second (FEV1)
(ii) forced vital capacity (FVC)
(b) In infants non-routine tests such as
(i) thoracic gas volume (TGV)
(ii) airway conductance (Gaw)
(iii) maximum flow at functional residual capacity (Vmax FRC)
Other relevant lung function tests will also be considered.

(3) Age at which participant acquires long-term *P. aeruginosa* infection (as defined by more than two positive respiratory cultures/year) or acquisition of *P. aeruginosa* during the study period

(4) Number of additional courses of intravenous antibiotics

(5) Adverse effects of antibiotic treatment, for example, diarrhoea, skin rash and fungal infections

(6) Improvement in survival, as defined on a yearly basis starting at year one

SECONDARY OUTCOMES

(7) Number of additional courses of oral antibiotic required

(8) Number of courses of oral steroids

(9) Acquisition of other common pathogens such as *S.aureus* (including methicillin resistant S.aureus) and *Haemophilus influenzae*

(10) Nutritional markers such as Z scores for weight and height

(11) Development of allergic bronchopulmonary aspergillosis as defined by clinical symptoms (cough and wheeze), characteristic chest x-ray appearance, a rise in certain white blood cells (eosinophils) and positive antibodies against aspergillus

(12) Liver disease as defined by clinical measures (enlarged liver), radiographic measures (abnormal ultrasound or DISIDA scan) or biochemical measures (liver function tests abnormal on two or more occasions)

(13) Quality of life

(14) Changes in markers of inflammation, for example, cells or cytokines from samples of the lower respiratory tract

(15) Other outcomes (such as adverse events) that can not be anticipated will also be analysed

Outcomes were considered short-term if they were measured at the end of a treatment period, unless the treatment period was for 12 months or more. Outcomes were then considered long-term. Outcomes were also considered long-term if there was more than three months between the end of the treatment and the measure. Long-term outcome measures were not considered for cross-over studies.

We intended to group outcome data into those measured at one, three, six, twelve months and annually thereafter. Outcome data were recorded at other time periods and these were also considered in this review.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Cochrane Cystic Fibrosis and Genetic Disorders Group search strategy

Relevant studies were identified from the Group's cystic fibrosis trials register using the terms:
antibiotics;
erythromycin;
azithromycin;
clarithromycin;
roxithromycin.

The cystic fibrosis trials register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (updated each new issue), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of one journal - *Pediatric Pulmonology*. Unpublished work is identified by searching through the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

In addition, principal investigators, known to work in the field and previous authors were contacted for unpublished or follow-up data. Pharmaceutical companies, that manufacture macrolide antibiotics, were also approached (last contacted December 2002).

Date of the most recent search of the Group's trials register: March 2003.

METHODS OF THE REVIEW

Two reviewers (KWS and PMB) independently selected studies to be included in the review. Each reviewer assessed the methodological quality of each study, based on a method described by Schulz (Schulz 1995). In particular, reviewers examined the randomisation method, whether the study was blinded, whether intention-to-treat analyses were possible from the available data and if the number of participants lost to follow-up or subsequently excluded from the study was recorded. Data were extracted from included studies independently by two of the reviewers (KS and PMB), with the third reviewer (AS) arbitrating. There was no predetermined subgroup analysis.

For binary outcome measures, in order to allow an intention-to-treat analysis, data were sought on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up. For continuous outcomes, we recorded either mean change from baseline for each group or mean post-treatment/intervention values and standard deviation (SD) for each group (standard error will be converted to SD). For binary outcomes, we calculated a pooled estimate of the treatment effect for each outcome across studies, (the odds of an outcome among treatment allocated participants to the corresponding odds among controls). For continuous outcomes we calculated a pooled estimate of treatment effect by calculating the weighted mean difference. There were not enough studies included in this review to assess heterogeneity or to undertake a sensitivity analysis based on quality. Heterogeneity between study results will be tested in future updates if further studies are included using a standard chi squared test. A sensitivity analysis based on the methodological quality of the studies, including and excluding quasi-randomised studies, will also be performed.

It was difficult to combine data from the two included studies (Equi 2002; Wolter 2002) because of study design and because respiratory function was measured at different time points. However, data at two months was available from the Wolter study and could be extrapolated from the first treatment arm of Equi (by taking measurements from the figure in the paper reporting change in FEV1 and FVC and transforming the 95% CI to standard deviation). We have requested further data from the investigators of the Equi study, but these have not yet been obtained. If these data become available, they will be used for future updates.

DESCRIPTION OF STUDIES

Eleven studies were identified and reviewed. Two RCTs examining azithromycin versus placebo (101 participants) have been published (Equi 2002; Wolter 2002) and are included in this review. Wolter enrolled 60 adult participants (age range 18 to 44 years, receiving 250mg azithromycin once a day for three months). Mean (SD) FEV1(% predicted) for the placebo group was 62.3% (24.8), which was significantly greater than the azithromycin group (mean FEV1, 50.9 (18.3)). The placebo group contained more men (20 out of 30 versus 9 out of 30) who were on average taller and heavier. Fifty-seven participants provided a sputum sample at baseline; in 47 samples *P. aeruginosa* was isolated and in 24 samples *S. aureus* (Wolter 2002) was isolated. Equi enrolled 41 children (8 to 18 years, receiving 250mg azithromycin (or 500mg azithromycin if weight was greater than 40kg) once a day for six months) in a cross-over study (see next section). Baseline characteristics of the two treatment arms were similar (for placebo followed by azithromycin, FEV1, 61% (14) compared to azithromycin followed by placebo, FEV1, 59 (12)). Of the 41 children, 21 were chronically colonised with *P. aeruginosa* (as defined by three or more positive cultures in the preceding 12 months), although 38 of the 41 were receiving long-term anti-pseudomonal nebulised therapy. Twenty-five children were receiving long-term anti-staphylococcal prophylaxis and 12 had grown *S. aureus* on three or more occasions from respiratory cultures in the previous 12 months (Equi 2002).

Results from a recent RCT of 185 participants were presented at the North American CF Conference in New Orleans in 2002 (Saiman 2003). The treatment was 250mg azithromycin, or 500mg azithromycin if weight was greater than 40kg, given three times a week (Monday, Wednesday and Friday). However, data are not available for inclusion in this update. One RCT (Frederiksen 2001), examining placebo versus clarithromycin, has been reported in abstract form at the European CF Conference in Vienna in 2001, but the results have not been published and were not available for inclusion in this review. We are also awaiting details of a further study, presented to the American Thoracic Society in 2001 (Anstead 2001). Another study investigating different doses of azithromycin has not yet been completed, but the results will be included

when the data are available (McCormack 2003).

METHODOLOGICAL QUALITY

The first published study was of parallel design (Wolter 2002). Randomisation occurred in blocks but was not stratified. The baseline characteristics of the two treatment groups were different, with the placebo group having significantly more males with better respiratory function and nutritional status. The authors argue that this effect would bias against a positive result for the treatment arm, however a counter-argument could be that the treatment arm had more room for improvement. In the data analysis, appropriate adjustments were made for the differences between sex, body mass index (BMI) and FEV1. Quality of life was assessed using the validated Chronic Respiratory Disease Questionnaire (CRDQ). Some data points were missing, however the authors undertook an intention-to-treat analysis (Wolter 2002). The study was double-blind and allocation concealment was good since this was done by the hospital pharmacy independently of the trialists.

The second published study (Equi 2002) was a randomised, double-blind, placebo-controlled cross-over study with a two-month washout between two six-month treatment blocks. Allocation concealment was good since this was done independently of the trialists by the hospital pharmacy. This cross-over design was inappropriate for an intervention with potentially long-term consequences. However, results from the first arm of this study have been included in the meta-analysis (percentage change in FEV1 and FVC). All other outcomes in the Equi study are reported as a combination of data from both arms and were inappropriate for inclusion in MetaView. As stated under 'Methods of review', we are planning to include more data if these can be obtained from the investigators. Two participants withdrew from the study but their data were included in an intention-to-treat analysis.

RESULTS

PRIMARY OUTCOMES

(1) Number of days as a hospital inpatient
The Wolter study did not demonstrate a significant reduction in hospital inpatient days over three months (placebo mean 5.2 days (range 0 to 36 days), azithromycin mean 2.1 days (range 0 to 15 days), p = 0.056) (Wolter 2002). The Equi study did not report this outcome measure (Equi 2002).

(2) Lung function
(a) In adults or older children who can perform spirometry
(i) FEV1
The primary outcome measure for both studies was change in lung function from baseline (percentage change in FEV1). Wolter measured respiratory function at one, two and three months (Wolter 2002). Combining results from each of these time points (and adjusting the data for the different baseline characteristics of the two groups), the study demonstrated a mean excess effect of azithromycin over placebo of 3.62% (standard error 1.78). Equi measured respiratory function at two, four and six months (Equi 2002) and calculated a similar "mean excess effect" by dividing the average values for months four and six by the baseline values (two participants had a month four or month six value missing and a single value was used). By this method the median (data were non-parametric) relative difference between azithromycin and placebo was 5.4% (95% confidence interval (CI) 0.8 to 10.5) (Equi 2002). Combined data at the two-month time point are presented in MetaView (n = 82 for FEV1 and 76 for FVC) and give a weighted mean difference of 2.46% (95% CI, -1.45 to 6.38) for FEV1.

(ii) FVC
Combining the data at the two-month time point, the weighted mean difference for FVC was 5.42% (95% CI, 1.77 to 9.07) (n = 76) significantly in favour of azithromycin. The discrepancy in the number of participants was explained by incomplete data acquisition at all time points in the Wolter study (for example, data only available on 15 out of 30 participants in the placebo group for FVC at the two-month time point) (Wolter 2002).

(3) Age at which participant acquires long-term *P. aeruginosa* infection (as defined by more than two positive respiratory cultures/year) or acquisition of *P. aeruginosa* during the study period

It was also noted that a significant number of participants in the Equi study did not grow *P. aeruginosa* (17 out of 41 participants) during the study period (Equi 2002). The Wolter study did not report this outcome (Wolter 2002).

(4) Number of additional courses of intravenous antibiotics
The Wolter study reported significant reductions in the number of courses of intravenous (IV) treatment (mean number of courses with azithromycin 0.4 (range 0 to 2 courses) versus mean number of courses with placebo 1.1 (range 0 to 7 courses), $p<0.016$) and number of days of IV treatment (mean number of days with azithromycin 2.0 (range 0 to 14 days) versus mean number of days with placebo 7.1 (range 0 to 44 days)) (Wolter 2002). The Equi study did not detect any difference in IV treatment during the azithromycin phase compared to the placebo phase (Equi 2002).

(5) Adverse effects of antibiotic treatment; for example, diarrhoea, skin rash and fungal infections
In the Wolter study there were 16 adverse events reported in 15 participants (seven in the placebo group) (Wolter 2002). Of the three participants who discontinued treatment due to adverse events, urticarial reaction in a participant receiving azithromycin was reported "likely" to be related to the treatment drug, while neutropenia in a participant in the treatment group and "swelling" in a participant in the placebo group were reported as being "possibly" related to the study drug. A further two events were reported as "possibly" related to the study drug (rash in each of the treatment and placebo groups).

Equi did not report this outcome (Equi 2002).

(6) Improvement in survival, as defined on a yearly basis starting at year one
Neither study reported this outcome.

SECONDARY OUTCOMES

(7) Number of additional courses of oral antibiotic required
The Equi study reported a significant reduction in oral antibiotic usage whilst on azithromycin (18 out of 41 participants versus 27 out of 41 participants, $p = 0.005$) (Equi 2002). This outcome was not assessed by the Wolter study (Wolter 2002).

(8) Number of courses of oral steroids
Neither study reported this outcome.

(9) Acquisition of other common pathogens
There were no significant changes in organisms identified during the study period from respiratory culture. A relatively high prevalence of *S. aureus* was identified in the Wolter study (Wolter 2002).

(10) Nutritional markers such as Z scores for weight and height
The Wolter study reported no significant change in BMI (Wolter 2002). Equi did not report on this outcome (Equi 2002).

(11) Development of allergic bronchopulmonary aspergillosis as defined by clinical symptoms (cough and wheeze), characteristic chest x-ray appearance, a rise in certain white blood cells (eosinophils) and positive antibodies against aspergillus
Neither study reported this outcome.

(12) Liver disease as defined by clinical measures (enlarged liver), radiographic measures (abnormal ultrasound or DISIDA scan) or biochemical measures (liver function tests abnormal on two or more occasions)
An isolated case of transient raised serum liver enzymes is described by Equi, but full data are not available (Equi 2002). Wolter did not report on this outcome (Wolter 2002).

(13) Quality of life
Wolter employed a validated questionnaire to monitor quality of life (Wolter 2002). Both placebo and treatment groups were reported to have significant improvement in their overall scores over the course of the study ($p = 0.042$). Improvements in specific scores (dyspnoea, emotional, mastery and total) were higher for those receiving azithromycin. Improved fatigue scores were only seen in the azithromycin group.

Equi did not report on this outcome (Equi 2002).

(14) Changes in markers of inflammation, for example, cells or cytokines from samples of the lower respiratory tract
The Wolter study reported that treatment with azithromycin had a significant effect on the time trend of the inflammatory marker C-reactive protein (CRP) ($p<0.001$) (Wolter 2002). Equi did not report on this outcome (Equi 2002).

(15) Adverse events other than affecting liver
There were no serious adverse events reported in either study. Equi monitored hearing using pure tone audiometry before, during and on completion of each treatment period and detected no significant changes (Equi 2002).

DISCUSSION

Two RCTs have been published examining azithromycin versus placebo to treat CF chest disease (n = 101 participants). Another study examining clarithromycin versus placebo has been presented at an international CF Conference, but data from this study have not been published and were not available for this review (Frederiksen 2001). All trials have employed different dosage regimens and this reflects the lack of pharmacokinetic and toxicity data.

One of the two RCTs examining azithromycin enrolled adult participants, but the baseline characteristics of the two treatment groups were different (Wolter 2002). The primary outcome measure was percentage change in FEV1. Adjusting for the different baseline characteristics, the mean excess effect of azithromycin over placebo was 3.62% (standard error, 1.78). The second RCT enrolled 41 children, 17 of whom did not grow *P. aeruginosa* from their respiratory culture during the study (Equi 2002). This study employed a cross-over design, which may be problematic in assessing a therapy with potentially long-term effects. The study also demonstrated a statistically significant improvement in respiratory function in the azithromycin group (as defined by percentage change in FEV1), however, the clinical significance of this doubtful as the study was powered to detect a 7% difference in FEV1, but only a 5.4% difference was observed. Meta-analysis was only possible for respiratory function data at the two-month time point and demonstrated significant improvement in percentage change in FVC in the azithromycin group (76 participants), but no significant change in %FEV1 (82 participants). One study measured quality of life with evidence of significant improvement in the azithromycin group (Wolter 2002). There were no significant differences in adverse events reported in either study. Data from a larger RCT with 185 participants have been presented at the North American CF Conference in New Orleans 2002, but are not yet available for this review (Saiman 2003).

REVIEWER'S CONCLUSIONS

Implications for practice
The role of macrolide therapy in the treatment of CF lung disease remains unclear. Until the results of further studies are available the widespread use of azithromycin in CF cannot be advocated and should be restricted to well-designed randomised controlled trials.

Implications for research
A number of questions remain concerning the potential use of macrolide antibiotics for the treatment of CF lung disease.

(1) Should macrolide therapy be used long-term as an anti-pseudomonal therapy and is it safe?
(2) What is the correct dose to be administered to people with CF (both short and long-term)? Well-designed pharmacokinetic studies are urgently needed.
(3) Is improvement in lung function related to an anti-pseudomonal action or merely a reflection of other antibiotic properties?
(4) If efficacy is demonstrated, which macrolide has the greatest efficacy in CF?

(5) At which stage should macrolide therapy be initiated in CF? For example, is it more appropriate to commence this therapy at an early stage before the acquisition of *P. aeruginosa*?

ACKNOWLEDGEMENTS

The authors would like to thank the referees for their useful comments and suggestions. The help of the Cystic Fibrosis and Genetic Disorders Cochrane Group has been invaluable.

POTENTIAL CONFLICT OF INTEREST

None known

NOTES

Information on update completed in 2001

Most recent search of Group's Trials Register January 2001.

The descriptions of Ongoing studies were added to. New data from these ongoing studies will be incorporated when they become available and if they meet the inclusion criterion.

Two references by Baumann 2000 identified were excluded as they were not RCTs.

TABLES

Characteristics of included studies

Study	**Equi 2002**
Methods	Randomised placebo controlled cross-over trial.
Participants	Children (8 to 18 years). 41 participants.
Interventions	Azithromycin, 250 mg (500 mg if weight > 40 kg) once a day for six months versus placebo.
Outcomes	% change in FEV1 (FVC and MEF), hearing, sputum bacterial densities, inflammatory markers, exercise tolerance, subjective well-being.
Notes	Treatment arms not reported individually.
Allocation concealment	A
Study	**Wolter 2002**
Methods	Randomised placebo controlled trial.
Participants	Adults. 60 participants. The placebo group contained more men (20/30 versus 9/30), was taller, heavier and had better lung function (FEV1 mean (SD), 62.3 (24.8) versus 50.9 (18.3)).
Interventions	Azithromycin, 250 mg once a day for three months versus placebo.

Outcomes	% change in FEV1 (FVC), weight, quality of life, inflammatory markers, microbiology, respiratory exacerbations.
Notes	Baseline characteristics of two groups significantly different.
Allocation concealment	A

FEV1: forced expiratory volume at one second
FVC: forced vital capacity
MEF: maximum expiratory flow
SD: standard deviation

Characteristics of excluded studies

Study	Reason for exclusion
Anstead 1999	Open study.
Baumann 2000	Not a randomised controlled trial.
Jaffe 1998	Open study.
Ordonez 2001	Pilot study - not randomised controlled trial.
Pirzada 1999	Retrospective case control study, no randomisation.
Pukhalsky 2001	Not a randomised controlled trial.

Characteristics of ongoing studies

Study	**McCormack 2003**
Trial name or title	Azithromycin study.
Participants	Target 210 participants.
Interventions	Azithromycin 250 mg/d versus 1200 mg/wk.
Outcomes	
Starting date	
Contact information	Scott Bell BellS@health.qld.gov.au
Notes	
Study	**Saiman 2003**
Trial name or title	Azithromycin study.
Participants	87 in treatment group, 98 in placebo group. Age > 6 years, FEV1 > 30% predicted, chronic P. aeruginosa infection.
Interventions	Azithromycin (250 mg or 500mg if >40 kg) on Monday, Wednesday and Friday.
Outcomes	FEV1, exacerbation, quality of life, microbiology, adverse effects.
Starting date	Study completed, data analysis ongoing.
Contact information	Lisa Saiman LS5@columbia.edu
Notes	Saiman L Marshall B Campbell P USA multicentre

FEV1: forced expiratory volume at one second
P. aeruginosa: Pseudomonas aeruginosa

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Pukhalsky 2001

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Southern 2003

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** Indicates the major publication for the study*

GRAPHS

To view a graph or table, click on the outcome title of the summary table below.

To view graphs using MetaView, click on the "Show metaview" link at the top of the graph.

Azithromycin versus placebo				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Percentage change in FEV1			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
Percentage change in FVC			Weighted Mean Difference (Fixed) 95% CI	Subtotals only

COVER SHEET

Title	**Macrolide antibiotics for cystic fibrosis**
Reviewer(s)	**Southern KW, Barker PM, Solis A**
Contribution of reviewer(s)	**KWS conceived and drafted the review.** **AS contributed to the content of the review.** **PMB commented on the review.** **All reviewers examined and evaluated studies.** **KWS updated this review with comments from PMB and AS.** **KWS acts as guarantor of the review.**
Issue protocol first published	Information not available
Issue review first published	2000/3
Date of most recent amendment	27 May 2003
Date of most recent SUBSTANTIVE amendment	27 May 2003
Most recent changes	Date of most recent search of Group's trials register: March 2003. The following studies have been added to the section "Included studies": Equi 2002; Wolter 2003. Frederiksen 2001 has been added to the section "Studies awaiting assessment". We have requested data from the primary authors of this study in order to incorporate them into a later update. The following studies have been added to the section "Excluded studies": Ordonez 2001; Pukhalsky 2001. The following study has been added to the 'Ongoing studies' section: McCormack 2003.
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	27 March 2003
Date reviewers' conclusions section amended	Information not supplied by reviewer

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SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

SYNOPSIS

Two randomised controlled studies demonstrated small but significant short-term improvements in respiratory function comparing azithromycin to placebo for chest infection in people with cystic fibrosis

Cystic fibrosis is characterised by chest infection, particularly by the bacteria, *Pseudomonas aeruginosa*, which is resistant to nearly all antibiotics that can be taken by mouth. Macrolide antibiotics have no direct killing effect on *Pseudomonas aeruginosa*, however they may reduce the activity of this bacteria. Two randomised controlled trials in children and adults with cystic fibrosis demonstrated small but statistically significant improvements in respiratory function after treatment with azithromycin versus placebo. Further studies are required to define the role of azithromycin or other macrolide antibiotics for chest infection in people with cystic fibrosis.

Index Terms

Medical Subject Headings (MeSH)
Antibiotics, Macrolide [therapeutic use]; Bacterial Infections [drug therapy] [etiology]; Clinical Trials ; Cystic Fibrosis [complications] [drug therapy]; Outcome Assessment (Health Care)
Mesh check words: Human