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[Intervention Review]

Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis

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ABSTRACT

Background

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic reaction to colonisation of the lungs with the fungus *Aspergillus fumigatus,* and affects around 10% of people with cystic fibrosis. ABPA is associated with an accelerated decline in lung function. High doses of corticosteroids are the main treatment for ABPA; although the long-term benefits are not clear, and their many side effects are well-documented. A group of compounds, the azoles, have activity against *A fumigatus*, and have been proposed as an alternative treatment for ABPA. Of this group, itraconazole is the most active. A separate antifungal compound, amphotericin B, has been used in aerosolised form to treat invasive infection with *A fumigatus*, and may have potential for the treatment of ABPA. Antifungal therapy for ABPA in cystic fibrosis needs to be evaluated. This is an update of a previously published review.

Objectives

The review aimed to test the hypotheses that antifungal interventions for the treatment of ABPA in cystic fibrosis:
1. improve clinical status compared to placebo or standard therapy (no placebo); and
2. do not have unacceptable adverse effects.

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

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register, which comprises references identified from comprehensive electronic database searches, handsearches of relevant journals, and abstract books of conference proceedings. Date of the most recent search of the Group's Trials Register was 28 September 2021.

We searched ongoing trials registries, most recently on 11 March 2022.

Earlier, we also approached pharmaceutical companies regarding possible unpublished trials.

Selection criteria

Published or unpublished randomised controlled trials, in which antifungal treatments were compared to either placebo or no treatment, or where different doses of the same treatment were used in the treatment of ABPA in people with cystic fibrosis.

Data collection and analysis

The searches identified six trials; none of which met the inclusion criteria for the review.

Main results

We included no completed randomised controlled trials. There is currently one ongoing trial, which we may find eligible for a future update.

Authors' conclusions

At present, there are no randomised controlled trials that evaluate the use of antifungal therapies for the treatment of ABPA in people with cystic fibrosis, although one trial is currently ongoing.

Trials with clear outcome measures are needed to properly evaluate the use of corticosteroids in people with ABPA and cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Treatments to fight fungal infections that cause allergic bronchopulmonary aspergillosis in people with cystic fibrosis

Review question

We planned to review the evidence about the effect of treatments to fight fungal infections that cause allergic bronchopulmonary aspergillosis (ABPA) in people with cystic fibrosis.

Background

ABPA is an allergic lung reaction to a type of fungus (usually *Aspergillus fumigatus*) in some people with cystic fibrosis. It causes a cough and wheezing, and sometimes fever. If left untreated, ABPA can lead to long-term lung damage. It is usually treated with a high dose of corticosteroids (also known as steroids). However, it has not been proven that corticosteroids can prevent lung function from deteriorating in the long term. Also, long-term use of corticosteroids is linked to some serious side effects. Treating the fungus that causes ABPA may be an alternative to using high doses of corticosteroids to combat the allergic reaction. This is an update of a previously published review.

Search date

The evidence is current to 28 September 2021.

Study characteristics

We did not find any trials that we could include in the review.

Key results

There is currently no evidence to recommend the use of antifungal treatment in people with cystic fibrosis and ABPA.

We need trials to assess the effects of corticosteroids in this population in the long and the short term.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder affecting people of Northern European descent (CF Foundation 2000; Farrell 2018). Chronic, progressive lung disease is the major cause of morbidity and shortened survival. This lung disease is characterised by a cycle of bacterial infection and lung damage (Hutchinson 1999). With increasing age, *Pseudomonas aeruginosa* is the major cause of chronic infection. However, a proportion of people with CF are also affected by allergic bronchopulmonary aspergillosis (ABPA). This is an allergic reaction to colonisation of the lungs with the fungus *Aspergillus fumigatus*. ABPA is associated with an accelerated decline in lung function in people with CF (Simmonds 1990). ABPA is diagnosed by a collection of clinical and laboratory criteria, including a consistent history; pulmonary infiltrates, which show as shadows on a chest X-ray (CXR); raised total serum immunoglobulin E (IgE) levels; skin test reaction to *A fumigatus* antigen; and antibodies to *A fumigatus* (Geller 1999). As these criteria are not specific, and vary with the course of disease, a diagnosis of ABPA can be difficult to make.

The reported prevalence of ABPA in people with CF is around 10%, much higher than the non-CF population (Laufer 1984; Mroueh 1994; Simmonds 1990). Many of the findings of ABPA overlap with common manifestations of the lung disease in CF.

Description of the intervention

Currently, high doses of corticosteroids are the main treatment for ABPA. However, an alternative strategy in the treatment of ABPA is to reduce or clear the lung of *A fumigatus* colonisation by using antifungal agents. A group of compounds, azoles, that can be taken orally, have activity against *A fumigatus*.

How the intervention might work

Corticosteroids are thought to treat the inflammatory and allergic aspects of the condition. Whilst there is anecdotal evidence of impressive clinical and radiographic response to this therapy, there is little support from randomised controlled trials (Capewell 1989). There is evidence from uncontrolled trials for the use of corticosteroids in ABPA in the non-CF population for acute treatment of exacerbations (Rosenberg 1978; Varkey 1998); doses of prednisone of 7.5 mg/day seem to inhibit the development of infiltrates (Safirstein 1973). The long-term benefits of steroids on the course of the disease, particularly in people with CF, are not clear, and their many side effects are well documented (Lai 2000).

Itraconazole is the most active of the group of compounds known as azoles (Denning 1992). A separate compound with good activity against *A fumigatus* is amphotericin B. However, this is not absorbed orally, and when given intravenously is frequently associated with toxicity (Meunier 1991). Amphotericin has been used in a nebulised form to treat invasive infection with *A fumigatus*, but remains very expensive (Purcell 1995).

Why it is important to do this review

Data from uncontrolled trials suggest itraconazole may be an effective additional therapy to steroids (Denning 1991; Nepomuceno 1999). The use of itraconazole for ABPA in people without CF was evaluated in a separate Cochrane Review (Wark 2004). A randomised, double-blind trial of the use of itraconazole in ABPA in people without CF (28 treated; 27 placebo) showed that those taking itraconazole responded better than those taking a placebo. This was defined by a reduction of at least 50% in corticosteroid dose and 25% in serum IgE level, along with evidence of clinical improvement, with no increase in adverse events (Stevens 2000). A second randomised controlled trial of itraconazole in stable ABPA in people without CF showed a reduction in eosinophilic inflammation, serum IgE levels, and exacerbations, implying that itraconazole is a useful adjunctive treatment for ABPA (Wark 2003). Whilst encouraging, these data need to be reproduced in larger trials, and the specific effects of itraconazole for ABPA in CF need to be evaluated. It cannot be assumed that therapies that have demonstrated efficacy in the non-CF population will be equally efficacious and safe to use in people with CF.

This is an updated version of previously published reviews (Elphick 2000; Elphick 2012; Elphick 2014; Elphick 2016).

OBJECTIVES

The review aimed to test the hypotheses that antifungal interventions for the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis:

1. improve clinical status compared to placebo or standard therapy (no placebo); and
2. do not have unacceptable adverse effects.

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), published or unpublished. We would have included quasi-RCTs, e.g. using alternate allocation and stratification, if there was sufficient evidence that intervention and control groups were similar. We planned to include both short- and long-term trials, when short-term trials evaluated treatment for up to six months, and long-term trials, treatment over six months.

Types of participants

Children and adults with defined cystic fibrosis (CF), diagnosed clinically, and by sweat or genetic testing, including all ages and all degrees of severity, who also had allergic bronchopulmonary aspergillosis (ABPA), diagnosed by clearly defined clinical and laboratory criteria.

For trials including participants with ABPA both with and without CF, we planned to attempt a separate analysis for those with CF and ABPA. If this was not possible, we would have excluded the results from the meta-analysis, but described them for participants with CF.

Types of interventions

Antifungal treatments compared to either placebo or no treatment, or trials in which different doses of the same treatment were used for treating ABPA in people with CF. We would have included

these trials if the only difference between the groups was use of antifungal treatment, or a comparison of different antifungal regimens.

The major interventions were:

1. oral azoles;
2. nebulised amphotericin.

Had we identified trials studying other antifungal interventions, we would have also considered these.

Types of outcome measures

We planned to assess the following outcome measures at one, three, six, 12 months, and annually thereafter.

Primary outcomes

1. Rate of reduction of steroid dosage
2. Clinical improvement
   a. Improvement in symptoms, e.g. wheeze
   b. Improvement in chest x-ray (CXR) scores
   c. Improvement in spirometric lung function, e.g. forced expiratory volume at one second (FEV1) and forced vital capacity (FVC)
   d. Nutritional status, e.g. weight gain, body mass index (this outcome measure may be complicated by the confounding influence of steroid reduction on weight)
3. Time to next exacerbation, or acute ABPA episode

Secondary outcomes

1. Laboratory evidence of improvement in ABPA
   a. Reduction in total serum immunoglobulin E (IgE) and IgG to *A fumigatus*
   b. Reduction in peripheral eosinophil count
   c. Reduction in total serum IgE
   d. Reduction in the frequency of isolation of *A fumigatus* in respiratory culture
2. Quality of life assessments
3. Adverse events, in particular: liver function abnormalities; peripheral neuropathy (azoles); nephrotoxicity; and arrhythmias (amphotericin)

We considered outcomes to be short-term if they were measured at the end of the treatment period, unless the treatment period was for six months or longer, in which case, we considered outcomes to be long-term. We also considered outcomes to be long-term if it was more than three months between the end of the treatment and the measure.

Search methods for identification of studies

We searched for all relevant published and unpublished trials, without restrictions on language, year, or publication status

Electronic searches

The Cystic Fibrosis and Genetic Disorders Group's Information Specialist identified relevant trials from the Group's Cystic Fibrosis Trials Register, using the terms: allergic bronchopulmonary aspergillosis OR aspergillus fumigatus.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; updated following each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995, and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching 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 section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 28 September 2021.

We also searched the following trial registers:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 11 March 2022);
- World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int/; searched 11 March 2022).

For details of the search strategies, please see Appendix 1

Searching other resources

We checked the bibliographies of included studies and any relevant systematic reviews identified, for further references to relevant trials.

We contacted principal investigators known to work in the field, and previous authors for unpublished or follow-up data. We also approached pharmaceutical companies that manufacture antifungal agents.

Data collection and analysis

Selection of studies

The two review authors (originally HEE and KWS; for the 2022 update, NF and KWS) planned to independently select the trials to be included in the review.

Data extraction and management

Each review author planned to independently extract data using standard data acquisition forms. If disagreement arose on the suitability of a trial for inclusion in the review or on its quality, we planned to reach a consensus by discussion.

We planned to group outcome data into those measured at one, three, six, 12 months, and annually thereafter. We also planned to consider examining any outcome data reported at other time periods.

Assessment of risk of bias in included studies

Each review author planned to independently assess the risk of bias for each trial using the Cochrane RoB 1 tool, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). In particular, we planned to assess the following, leading to a high, unclear, or low risk of bias:

- allocation (both generation of sequence and its concealment);
- blinding (of clinicians, participants, and outcome assessors);

- incomplete outcome data;
- selective reporting;
- any other potential sources of bias.

If there was any disagreement on these judgements, we planned to reach a consensus by discussion.

Measures of treatment effect

For continuous outcomes, we planned to record either the mean change from baseline for each group, or mean post-treatment or intervention values and the standard deviation, or standard error for each group.

For binary outcome measures, we planned to calculate a pooled estimate of the treatment effect for each outcome across trials (the odds of an outcome among treatment allocated participants to the corresponding odds among controls).

For any time-to-event outcomes included in the review, we planned to obtain a mixture of logrank and Cox model estimates from the trials. We planned to combine all results using the generic inverse variance method, since we would be able to convert the logrank estimates into log hazard ratios and standard errors, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022).

Unit of analysis issues

We planned to acknowledge the level at which randomisation occurred in each trial. Trials with non-standard designs, such as cross-over trials, and cluster-randomised trials, should be analysed using methods appropriate to the design, because naive analysis may underestimate or overestimate the precision of the trial (Higgins 2022).

Dealing with missing data

In order to allow an intention-to-treat analysis, we planned to seek data on the number of participants by allocated treatment group, irrespective of compliance and whether the participant was later thought to be ineligible, or otherwise excluded from treatment or follow-up.

Assessment of heterogeneity

We planned to test for heterogeneity between trial results using a standard Chi^2 test and the I^2 statistic, for which the following ranges and judgements would apply:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity; and
4. 75% to 100%: considerable heterogeneity.

We recognise that the importance of the observed value of I^2 depends on:

1. the magnitude and direction of effects; and
2. strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for I^2).

Assessment of reporting biases

We planned to consider reporting bias (the favourable selection of reported results).

We would have initally assessed such bias by ensuring that all outcomes listed in the Methods section of the trial report were addressed in the results section. Additionally, we would have constructed a funnel plot and assessed the symmetry therein, had we been able to include more than 10 trials in a meta-analysis. We would have plotted the number of participants in the trial against a measure of treatment effect; if the funnel plot was asymmetrical, we would consider whether this was due to reporting bias (Page 2022).

Data synthesis

Before embarking on data synthesis, we planned to ensure that we were confident that the findings from the individual trials were collated correctly. We planned to compare the magnitude and direction of effects reported by trials to how we would present the data in the review.

Then we planned to decide upon the meta-analysis method (either a fixed-effect or a random-effects model). If we decided not to undertake meta-analyses (e.g. if we considered there to be at least substantial heterogeneity, as defined above), we planned to systematically synthesize the findings of multiple trials and report them narratively.

If we were not able to analyse any data quantitatively (e.g. skewed data using medians and interquartile ranges), we also planned to use a narrative synthesis. We planned to do this according to the SWiM guidelines, which provide nine reporting items to promote transparent reporting of how trials are grouped, the standardised metric used for the synthesis, the synthesis method, how data are presented, a summary of the synthesis findings, and limitations of the synthesis (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

Had we identified at least moderate heterogeneity (as defined above), we planned to analyse different antifungal treatments separately, e.g. oral azoles separately from nebulised amphotericin B.

Sensitivity analysis

We planned to undertake an overall analysis, both with and without quasi-RCTs, to ensure that they did not bias the final result. We also planned to undertake a sensitivity analysis based on the risk of bias of the trials for randomisation and allocation concealment.

We planned to use sensitivty analysis to assess the impact of any trials including ABPA participants with and without CF (see Types of participants). People with non-CF ABPA are the subject of another Cochrane Review, in which the results were dealt with similarly (Wark 2004).

Summary of findings and assessment of the certainty of the evidence

We planned to prepare summary of findings tables for each comparison included in the review, listing population, setting, intervention, and comparison, and report an illustrative risk for the experimental and control intervention (Schünemann 2021). Using

GRADE methodology, we planned to grade the overall certainty of the body of evidence as high, moderate, low, or very low, basing our judgements on the risk of bias within the trials, their relevance to the population of interest (indirectness), unexplained heterogeneity or inconsistency, imprecision of the results, and high risk of publication bias (Schünemann 2006). We planned to downgrade the certainty of the evidence once if the risk was serious, and twice if the risk was very serious; and to describe the rationale for each judgement in footnotes to each table.

For each comparison, we planned to report the following outcomes.

1. Rate of reduction of steroid dosage at three months
2. Rate of improvement in FEV1 at three months
3. Time to next exacerbation
4. Reduction of both total and *Aspergillus* specific IgE from laboratory test results at three months
5. Quality of life at three months
6. Adverse events at three months

RESULTS

Description of studies

Results of the search

Searches identified 11 references to six trials. We excluded five trials (Aaron 2012; Cohen-Cymberknoh 2008; Gangneux 2018; NCT00787917; Proesmans 2010). The sixth trial is a randomised controlled trial (RCT) of posaconazole to determine dosage in children and adolescents, which is still recruiting participants. Therefore, the results are not available for review yet, and we listed it as ongoing (NCT04966234).

Included studies

We did not identify any trials that met the inclusion criteria for this review.

Excluded studies

We excluded five trials in total. Two excluded trials considered the treatment of sputum colonised with *Aspergillus fumigatus*, not allergic bronchopulmonary aspergillosis (ABPA (Aaron 2012; Gangneux 2018)). A third trial investigated different types of steroids and not antifungal therapies (Cohen-Cymberknoh 2008). The intervention in the Novartis trial was not relevant (anti-total immunoglobulin E (IgE) therapy (NCT00787917)). The fifth trial was not randomised (Proesmans 2010).

Ongoing studies

One trial is ongoing (NCT04966234). See Ongoing studies for details.

This is an open-label, multicentre (31 sites across Europe), parallel RCT with a 12-week intervention, and follow-up to 12 months post-randomisation.

Planned sample size is 135 children. Inclusion criteria are: aged between eight and 18 years of age, a diagnosis of CF and the presence of *Aspergillus* infection, weighing over 20 kg, and be in a clinically stable condition. The children must be able to perform lung function tests, and to produce a sputum sample.

The intervention group (N = 90) will receive posaconazole, either as gastro-resistant tablets, Noxafil® 100 mg, or 105 mL Noxafil® 40 mg/mL oral suspension, for 12 weeks. The control group (N = 45) will not receive any active intervention.

The primary outcomes are pharmacokinetic, and the number of children with negative sputum sample for *Aspergillus*, three months after randomisation. Secondary outcomes include pharmacokinetic outcomes at days 21 to 35, and day 84 of treatment; the number of children with a favourable clinical response, and no signs of *Aspergillus* infection (defined by pulmonary exacerbations, days on antibiotics and corticosteroids, hospital admissions, change in lung function and weight, computer tomography (CT)-chest abnormalities, quality of life) at three, six, and 12 months after randomisation; the number of children with no signs of *Aspergillus* infection (defined by negative sputum cultures and negative serology) at three, six, and 12 months after randomisation; and adverse events and serious adverse events (up to one year after randomisation).

Risk of bias in included studies

We did not include any trials in this review.

Allocation

We did not include any trials in this review.

Blinding

We did not include any trials in this review.

Incomplete outcome data

We did not include any trials in this review.

Selective reporting

We did not include any trials in this review.

Other potential sources of bias

We did not include any trials in this review.

Effects of interventions

We did not include any trials in this review.

DISCUSSION

Allergic bronchopulmonary aspergillosis (ABPA) is an important complication of cystic fibrosis (CF), contributing to worsened morbidity, and leading to progressive deterioration in lung function. Most of the diagnostic criteria for ABPA overlap with common manifestations of lung disease in CF, which makes the diagnosis complicated.

Trials with clear outcome measures are needed to properly evaluate this potentially useful treatment for CF.

Summary of main results

At present, there are no randomised controlled trials (RCTs) that evaluate the use of antifungal therapies for the treatment of ABPA in people with CF. We identified one ongoing trial, which may provide evidence for this review question in the future (NCT04966234).

Overall completeness and applicability of evidence

We did not include any trials in this review.

Quality of the evidence

We did not include any trials in this review.

Potential biases in the review process

The search strategies were comprehensive, and unlikely to have missed any relevant trials. Also, two review authors independently assessed the search results.

Agreements and disagreements with other studies or reviews

Whilst there is anecdotal evidence of a response to corticosteroid therapy, there is no support for this from RCTs in CF. The long-term benefits of steroids on the course of the disease, particularly in people with CF, are not clear, but their many side effects are well documented. Consequently, treatment with antifungal agents may be advantageous over treatment with corticosteroids alone, and may lead to safely reduced doses of steroid therapy. Two RCTs of itraconazole in ABPA in people without CF, showed a reduction in corticosteroid dose and eosinophilic inflammation, along with clinical and serological evidence of improvement, with no increase in adverse events. A number of uncontrolled trials and case reports have also documented that the use of itraconazole in ABPA is advantageous. However, a recent report of suppression of adrenal glucocorticoid synthesis reported a potential adverse effect in 11 out of 25 people with CF who were treated with both itraconazole and budesonide. The likely pathogenesis is that an itraconazole caused an increase in systemic budesonide concentration due to inhibited metabolism, leading to suppressed adrenocorticotrophic hormone secretion (Skov 2002). The presence of adrenal insufficiency would be an important adverse effect to identify as an outcome measure in future trials. Caution also needs to be taken with prescribing azole antifungal treatment to individuals who are taking cystic fibrosis transmembrane (CFTR) modulators, because there is a potential for drug interactions. The CFTR modulators ivacaftor, tezacaftor, and elexacaftor are all primarily metabolised via CYP3A-mediated oxidation, and triazole drugs are all CYP3A inhibitors. Therefore, dose adjustments have to be made if prescribing both drugs.

AUTHORS' CONCLUSIONS

Implications for practice

There are no published data available to recommend the use of antifungal therapies for allergic bronchopulmonary aspergillosis (ABPA) in people with cystic fibrosis (CF). Use of these drugs in people with CF remains experimental. We await the outcomes of the ongoing trial.

Implications for research

This Cochrane Review identified the need for a well designed, adequately powered, multicentre, randomised controlled trial to assess the efficacy and possible adverse effects of antifungal therapies for ABPA in people with CF. Outcome measures, such as pulmonary function, should be clearly stated, and multicentre trials should be co-ordinated, so that maximum power is available to achieve a clear result. Trials should look at the effects on both acute exacerbations and chronic outcome measures, and therefore, cross-over trials would not be suitable. The adjuvant role of antifungals with corticosteroids should be investigated, including the effects on reduction of corticosteroid dose and the potential for serious adverse effects, including adrenal suppression. It cannot be assumed that therapies that have demonstrated efficacy in the non-CF population will be equally efficacious and safe to use in people with CF, and therefore, these two groups should be studied separately.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aaron 2012	Treatment of sputum colonised with *A fumigatus*, not ABPA
Cohen-Cymberknoh 2008	Comparison of different types of steroids, not antifungals
Gangneux 2018	Treatment for *Aspergillus fumigatus* colonisation; not ABPA
NCT00787917	Not a relevant intervention, anti IgE therapy for ABPA
Proesmans 2010	Non-randomised study

A fumigatus: *Aspergillus fumigatus*
ABPA: allergic bronchopulmonary aspergillosis

Characteristics of ongoing studies *[ordered by study ID]*

NCT04966234

Study name	A new posaconazole dosing regimen for paediatric patients with cystic fibrosis and *Aspergillus* infection (cASPerCF)
Methods	RCT (2:1 randomisation ratio intervention: control). Participants in the posaconazole arm will be stratified for body weight and positive sputum cultures for *Aspergillus species*. Parallel design Open-label Multi-centre (31 locations across Europe) Duration: 12 week intervention; follow-up to 12 months post-randomisation
Participants	Estimated enrolment: 135 participants

NCT04966234 *(Continued)*

Inclusion criteria

1. Diagnosed with CF (genetic diagnosis, abnormal sweat test, or both, and clinical phenotype of lung disease)
2. Age ≥ 8 years and < 18 years
3. Body weight ≥ 20 kg
4. Presence of *Aspergillus* infection, as defined for this study
5. Clinically stable condition without a significant change in lung function (FEV1 ± 10%) or significant worsening of respiratory symptoms over the previous month
6. Able to perform lung function test (FEV1%)
7. Able to produce a sputum sample (spontaneous or induced sputum)
8. Informed consent given
9. If female and of childbearing age, must be using highly effective contraception (and must agree to continue for 7 days after the last dose of investigational medicinal product)

Exclusion criteria

1. Non-CF lung disorder
2. Age < 8 yrs or ≥ 18 yrs
3. Body weight < 20 kg
4. Not able to perform lung function test (FEV1%)
5. Unable to produce a sputum sample (spontaneous or induced sputum)
6. Clinically unstable condition with significant change in lung function or significant worsening of respiratory symptoms
7. Unable to tolerate oral medication
8. Known hypersensitivity to itraconazole or posaconazole, or their excipients
9. On active transplant list or transplant recipient
10. Azole-resistant *Aspergillus species* cultured
11. Receiving terfenadine, ergot alkaloids, astemizole, cisapride, pimozide, halofantrine, quinidine, or HMG-CoA reductase inhibitors metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin)
12. Receiving omalizumab
13. Received systemic mould-active antifungals in the last month
14. Shortened or elongated QT interval
15. Cardiac failure
16. ALT ≥ 200 U/L
17. AST ≥ 225 U/L
18. Alkaline phosphatase ≥ 460 U/L
19. Bilirubin ≥ 50 umol/L
20. eGFR < 20 ml/min/1.73 m^2 (calculated with the Schwartz formula)
21. Known glucose-galactose malabsorption problems
22. Pregnancy or breastfeeding
23. Females of childbearing age who do not intend to use contraception measures
24. Informed consent not given

Interventions	**Intervention** (N = 90): will receive posaconazole (gastro-resistant tablets Noxafil® 100 mg, or 105 mL Noxafil® 40 mg/mL oral suspension) for 12 weeks **Control** (N = 45): no active intervention
Outcomes	**Primary outcomes** 1. Pharmacokinetic parameters of posaconazole Cmax (at steady state, days 5 to 10 of treatment) 2. Pharmacokinetic parameters of posaconazole Cmin (at steady state, days 5 to 10 of treatment) 3. Pharmacokinetic parameters of posaconazole Tmax (at steady state, days 5 to 10 of treatment)

NCT04966234 *(Continued)*

4. Pharmacokinetic parameters of posaconazole area under the curve during 1 dosing interval, and over 24 hours (at steady state, days 5 to 10 of treatment)
5. Pharmacokinetic parameters of posaconazole clearance (at steady state, days 5 to 10 of treatment)
6. Pharmacokinetic parameters of posaconazole distribution volume (at steady state, days 5 to 10 of treatment)
7. Pharmacokinetic parameters of posaconazole half-life (at steady state, days 5 to 10 of treatment)
8. Number of children with negative sputum sample for *Aspergillus* 3 months after randomisation

Secondary outcome measures

1. Pharmacokinetic parameters of posaconazole Cmax (days 21 to 35, and day 84 of treatment)
2. Pharmacokinetic parameters of posaconazole Cmin (days 21 to 35, and day 84 of treatment)
3. Pharmacokinetic parameters of posaconazole Tmax (days 21 to 35, and day 84 of treatment)
4. Pharmacokinetic parameters of posaconazole area under the curve (days 21 to 35, and day 84 of treatment)
5. Pharmacokinetic parameters of posaconazole clearance (days 21 to 35, and day 84 of treatment)
6. Pharmacokinetic parameters of posaconazole distribution volume (days 21 to 35, and day 84 of treatment)
7. Pharmacokinetic parameters of posaconazole half-life (days 21 to 35, and day 84 of treatment)
8. Participants with a favourable clinical response and no signs of *Aspergillus* infection (defined by pulmonary exacerbation rate, days on antibiotics and corticosteroids, hospital admissions, change in FEV1, change in BMI, CT-chest abnormalities, QoL; at 3, 6, and 12 months after randomisation)
9. Participants with no signs of *Aspergillus* infection (defined by negative sputum cultures and negative serology; at 3, 6, and 12 months after randomisation)
10. Proportion of participants experiencing AEs and SAEs (up to 1 year after randomisation)

Starting date	22 April 2021
Contact information	Study Director: Prof Adilia Warris, University of Exeter, UK (a.warris@exeter.ac.uk)
Notes	Estimated primary completion date: April 2023 Estimated study completion date: November 2023

AE: adverse event
ALT: alanine transaminase
AST: aspartate aminotransferase
BMI: body mass index
CF: cystic fibrosis
Cmax: maximum serum concentration
Cmin: minimum serum concentration
CT: computer tomography
eGFR: estimated glomerular filtration rate
FEV1: forced expiratory volume in 1 second
QoL: quality of life
RCT: randomised controlled trial
SAE: serious adverse event
Tmax: time taken to reach Cmax

APPENDICES

Appendix 1. Trials registers search strategies

Database	Search terms	Date last searched
clinicaltrials.gov	**Basic Search** Condition or disease: cystic fibrosis Other terms: aspergillus fumigatus OR allergic bronchopulmonary aspergillosis OR itraconazole OR voriconazole OR pozaconaleOR amphoteracin B	11 March 2022
WHO International Clinical Trials Registry Platform (ICTRP) trialsearch.who.int/	**Basic Search** cystic fibrosis AND (aspergillus fumigatus OR allergic bronchopulmonary aspergillosis OR itraconazole OR voriconazole OR pozaconaleOR amphoteracin B)	11 March 2022

WHAT'S NEW

Date	Event	Description
27 June 2022	New citation required but conclusions have not changed	The previous lead author stepped down from the team, and a new lead author joined the review team (NF). No new data were included, so our conclusions remain the same.
27 June 2022	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new, potentially eligible references for the review. We identified one ongoing randomised control trial that should be considered at the next review update (NCT04966234). Plans for the format of a summary of findings table were added to the Methods section.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 4, 2000

Date	Event	Description
19 November 2018	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Register identified six new references potentially eligible for inclusion in this review. Three were additional references to three already excluded studies (Aaron 2012; Cohen-Cymberknoh 2008; NCT00787917). Three references, for two studies, were pending classification.
29 September 2016	New citation required but conclusions have not changed	Since no new data were added to this review, our conclusions remain the same.
29 September 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in the review.

Date	Event	Description
20 November 2014	New citation required but conclusions have not changed	As no new studies were included in this update of the review, our conclusions remain the same.
20 November 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Trials Register identified two new references, both of which we excluded (Aaron 2012; NCT00787917). The Plain Language Summary was redrafted in line with new Group guidance.
9 May 2012	New citation required but conclusions have not changed	This review has been updated.
9 May 2012	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in this review. The Proesmans study has now been moved from awaiting classification to excluded studies, following contact with the author of the study (Proesmans 2010).
30 March 2010	New search has been performed	Two studies were newly identified; one is listed as awaiting classification (Proesmans 2009), and the other has been excluded (Cohen-Cymberknoh 2008). Itraconazole and voriconazole were added as therapeutic agents to be included in future searches and updates.
31 March 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register found no new trials eligible for inclusion in this review.
20 March 2008	Amended	Converted to new review format.
20 August 2007	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register found no new trials eligible for inclusion in this review. The plain language summary was re-drafted in light of the current guidance from The Cochrane Collaboration.
17 August 2006	New search has been performed	New search, no new studies found
14 August 2005	New search has been performed	New search, no new studies found
28 June 2004	New search has been performed	New search, no new studies found
30 June 2003	New search has been performed	New search, no new studies found
30 July 2002	New search has been performed	New search, no new studies found
30 June 2001	New search has been performed	New search, no new studies found
18 August 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dr Southern conceived the review and contributed towards the writing of the protocol and review.

Dr Elphick drafted the protocol and review. Dr Elphick completed the updates of the review up to 2016.

For the 2022 update, Dr Francis led the update of the review and acts as guarantor of the review.

DECLARATIONS OF INTEREST

Dr Natalie Francis declares no known potential conflict of interest.

Dr Kevin Southern declares no known potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- none to declare, Other

  none

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the protocol was published, we have updated the methods with the latest Cochrane guidance, most recently adding plans for summary of findings tables.

NOTES

Please see related review:

Wark PAB, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD001108. DOI: 10.1002/14651858.CD001108.pub2.

INDEX TERMS

Medical Subject Headings (MeSH)

Antifungal Agents [therapeutic use]; *Aspergillosis, Allergic Bronchopulmonary [complications] [drug therapy]; Aspergillus fumigatus; *Cystic Fibrosis [complications] [drug therapy]; Itraconazole [therapeutic use]

MeSH check words

Humans