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Azoles for allergic bronchopulmonary aspergillosis associated with asthma (Review)

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[Intervention Review]

Azoles for allergic bronchopulmonary aspergillosis associated with asthma

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ABSTRACT

Background

Allergic bronchopulmonary aspergillosis is hypersensitivity to the fungus Aspergillus fumigatus that complicates patients with asthma and cystic fibrosis. The mainstay of treatment for allergic bronchopulmonary aspergillosis remains oral corticosteroids, though this does not completely prevent exacerbations and may not prevent the decline in lung function.

Objectives

The purpose of this review was to determine the efficacy of azoles in the treatment of allergic bronchopulmonary aspergillosis.

Search methods

We searched the Cochrane Airways Group Asthma trials register, CENTRAL, MEDLINE and EMBASE. Searches are current as of May 2008.

Selection criteria

All controlled trials that assessed the effect of azole antifungal agents compared to placebo or other standard therapy for allergic bronchopulmonary aspergillosis were reviewed. Patients with cystic fibrosis were not included.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information. Adverse effects information was collected from the trials.

Main results

Twelve trials were identified, but only three were prospective, randomised and controlled. A total of 94 participants were included. One demonstrated a reduction in immunological markers of disease activity and symptom scores using ketoconazole 400 mg daily for 12 months. There was no significant improvement in lung function. The other two examined the use of itraconazole for 16 weeks. In one there was a reduction in sputum eosinophils by 35% compared to 19% with placebo ($p < 0.01$). In the same trial, the number of exacerbations requiring oral corticosteroids was 0.4 per patient with itraconazole compared with 1.3 per patient with placebo ($p < 0.03$). Meta-analysis of data from both trials showed that itraconazole treated patients were more likely to have decline in serum IgE over 25% or more (Peto OR 3.30; 95% confidence intervals 1.30 to 8.15).

Authors' conclusions

Itraconazole modifies the immunologic activation associated with allergic bronchopulmonary aspergillosis and improves clinical outcome, at least over the period of 16 weeks. Adrenal suppression with inhaled corticosteroids and itraconazole is a potential concern.

PLAIN LANGUAGE SUMMARY

Antifungal drugs (azoles) for allergic bronchopulmonary aspergillosis associated with asthma

Allergic bronchopulmonary aspergillosis is a condition that complicates some people with chronic asthma. Standard treatment for this condition is high doses of oral steroids. The azole antifungal drugs attack the fungus that causes this condition and short term studies suggest that they may have some benefit when added to standard therapy.

BACKGROUND

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex condition resulting from hypersensitivity to the fungus Aspergillus fumigatus (Af). Individuals with ABPA are colonised with Aspergillus fumigatus, this leads to persistent exposure and generates a chronic inflammatory reaction in the airways. Corticosteroids are used to suppress this response. ABPA was first described in the United Kingdom in 1952 (Hinson 1952) and since then has become recognised as an important complication in patients with cystic fibrosis and chronic asthma. It's prevalence probably varies around the world and has been estimated to occur in 1 to 2% of chronic asthmatics (Greenberger 1988) and up to 10% of patients with cystic fibrosis (Laufer 1984). In cystic fibrosis there is some evidence to suggest that those with allergic bronchopulmonary aspergillosis (ABPA) have a faster decline in lung function (Laufer 1984). In chronic asthma, ABPA follows a more variable course with recurrent exacerbations and at least in a proportion this leads to bronchiectasis and irreversible fibrotic lung disease (Patterson 1982).

The cornerstone of treatment of ABPA has been systemic ingested corticosteroid therapy, used for treatment of acute exacerbations, to prevent relapse and to preserve lung function. This requires prolonged treatment with high steroid doses and patients are at significant risk from the side effects of corticosteroids. Aspergillus is believed to cause persistent colonization, but not invasive disease in ABPA. The role of antifungal therapy in ABPA is unclear.

The only antifungal agents of known efficacy against Aspergillus fumigatus are amphotericin B and the azoles (ketoconazole and itraconazole, though not fluconazole). The use of amphotericin B is limited by its toxicity and cost. Azole antifungal agents (of which ketoconazole and itraconazole are members) work by inhibiting ergosterol synthesis in the fungal cell membrane and thereby inhibit fungal growth. Itraconazole has fewer side effects and a wider spectrum of activity than ketoconazole. Itraconazole has also been shown to be an effective treatment for invasive aspergillosis, especially if the site of infection is in the lungs. Treatment of ABPA with specific antifungal agents has the advantage of not just modifying the immune response to the organism but of removing or reducing the antigenic stimulus to the destructive airway inflammation in these patients.

OBJECTIVES

The purpose of this review is to determine the efficacy of azoles in the treatment of ABPA.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and prospective controlled trials (CCTs) that studied the efficacy of azole antifungal agents in ABPA.

Types of participants

Participants of studies had to have a diagnosis of ABPA, based upon the criteria as defined by Rosenberg 1977and Greenberger 1988; these criteria are:

(1) Diagnosis of asthma or cystic fibrosis
(2) Immediate cutaneous reactivity to Aspergillus fumigatus
(3) Elevated total serum IgE
(4) Elevated serum specific IgE or IgG antibodies to Aspergillus fumigatus
(5) Peripheral blood eosinophilia
(6) Radiographic changes (not always present)
i) History pulmonary infiltrates (transient and fixed)
ii) Proximal bronchiectasis
patients who were immunosuppressed or had evidence of invasive aspergillus infection or who had aspergilloma without evidence of allergic airways disease were not included. Patients with Cystic Fibrosis were not included in this review and are the subject of a separate review Elphick 2000.

Types of interventions

Studies were included that examined the effect of the azole antifungals in ABPA. We included studies of efficacy for itraconazole and ketoconazole as these are the two currently available triazoles with activity against Aspergillus fumigatus.

Types of outcome measures

(1) Lung function (absolute change and change in % predicted):
Forced Expiratory Volume at one second (FEV1)
Forced Vital Capacity (FVC)
Lung Volume (Residual Volume (RV) and Total Lung Capacity (TLC))
Forced Expiratory Flow 25-75% (FEF 25-75)
(2) Immunological parameters:
Serum eosinophils
Serum total IgE
Precipitating antibodies to Aspergillus antigen
(3) Symptom improvement:
Improvement of quality of life scores or other forms of measures
Improvement of exercise tolerance
(4) Radiographic change:
Impact on pulmonary infiltrates on Chest X Ray (CXR)
Impact on bronchiectasis on CT scan
(5) Medication use:
Impact on corticosteroid use, frequency, dose and route of administration
Impact on frequency and use of bronchodilators
Impact on frequency and use of antibiotics for exacerbations of their lung
disease
(6) Frequency of Exacerbations of ABPA where a clear definition is described:
demonstrating a worsening in airway obstruction, symptoms and an
increase in serum eosinophils or total serum IgE or new infiltrates on CXR
(a) Admission rates to hospital
(b) Outpatient treatments (hospital in the home)
(unscheduled visits to the doctor)
(7) Adverse events

Search methods for identification of studies

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory

journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:

(Aspergill* or "bronchopulmonary aspergillosis") and (azole* or triazole* or itraconazole or ketoconazole or vorconazole or voriconazole)

Additonal searches of CENTRAL, MEDLINE and EMBASE were conducted. See Appendix 1 & Appendix 2 for the full strategies used in these databases. All databases have been searched from their inception up to May 2008. There were no language restrictions.

Following the database searches, we obtained the full text of identified articles and we contacted trial authors for additional information if necessary.

Data collection and analysis

One reviewer identified all trials that appeared to fit the criteria for inclusion for full review. Two reviewers independently selected trials for inclusion in the review and also assessed the methodological quality of the included trials, with particular emphasis on the allocation concealment, which was ranked using the Cochrane approach:
Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment

Where there was uncertainty authors were contacted to clarify the randomisation method used.

Two independent reviewers extracted data using specially designed extraction forms. Inter-rater reliability was assessed by simple agreement, Kappa and weighted Kappa statistics. These comparisons were performed for each outcome.

We entered outcome data into RevMan for statistical analysis. Categorical outcomes were assessed as odds ratios and 95% confidence intervals. Continuous outcomes were analysed as effect sizes. A fixed effect model was used to obtain summary statistics for overall efficacy of the use of azoles in Allergic Bronchopulmonary Aspergillosis.

RESULTS

Description of studies

The following information was collected about each of the included studies:
(1) Demographics: age and gender
(2) Type of study; whether it was cross-over or parallel, controlled or a randomised control trial
(3) Type of intervention: which azole antifungal agent, dose, frequency and length of treatment
(4) Severity of lung disease: based on FEV1 and FVC
(5) Diagnostic criteria: Criteria used to diagnose ABPA, asthma and Cystic Fibrosis
(6) Concurrent conditions: any concurrent conditions that warranted exclusion from the study.

A request was sent to authors to obtain any missing data.

Shale 1987 was a randomised control trial, 10 participants were allocated to receive ketoconazole 400 mg daily for 12 months (six in the intervention arm and four in the control arm). Participants were excluded if they had a significant exacerbation of their disease in the preceding six months. Diagnostic criteria were the presence of asthma, serum eosinophilia, a history of pulmonary infiltrates, immediate skin test positivity to Aspergillus fumigatus and specific IgE and IgG to Aspergillus. However they also included three participants who did fulfil these criteria with evidence of an Aspergillus mycetoma, making this a heterogeneous group. Given the small numbers it is difficult to apply these results to participants with ABPA alone. Participants had mild to moderate airflow limitation with a mean FEV1 % predicted of 83.3% (SEM 9.6).

Stevens 2000 was a parallel, randomised double blind placebo controlled trial of Itraconazole 200 mg BD for 16 weeks with 55 participants. The trial was then unblinded and all participants received 200 mg daily for a further 16 weeks. Inclusion criteria were an FEV1/FVC ratio of < 0.7, immediate skin test positive to Aspergillus, an elevated total serum IgE, IgG antibodies to Aspergillus, a history of pulmonary infiltrates and dependence on oral corticosteroids. Participants with cystic fibrosis were not excluded, though none were recruited. Exclusion criteria were: recent use of antifungal agents, pregnancy or lactation, abnormal liver function tests, use of medications that affect the metabolism of itraconazole, age less than 13 years or weight less than 40 kg. Participants in both groups were matched in terms of age, lung function, exercise tolerance, history of pulmonary infiltrates and the proportion with bronchiectasis. The placebo arm had more males.

Wark 2003 was a parallel randomised double blind placebo controlled trial of Itraconazole 400 mg daily for 16 weeks with 29 participants. Inclusion criteria were: asthma with evidence of variable airflow obstruction, immediate skin sensitivity to Aspergillus fumigatus, positive serum IgE and IgG antibodies to Aspergillus fumigatus, a serum total IgE of > 1000 IU/ml. Participants were stratified according to the presence of proximal bronchiectasis on CT scan. Exclusion criteria were: cystic fibrosis, pregnancy or lactation the recent use of anti-fungal agents. Participants in both groups were matched in terms of age, sex, severity of disease on lung function, systemic immune activation to Aspergillus fumigatus and parameters of airway inflammation in induced sputum.

Risk of bias in included studies

Two reviewers independently assessed the full text versions of the included trials for their methodological quality with particular emphasis on the allocation concealment that was ranked using the Cochrane approach:
(1) Concealment of allocation
i) Grade A: Adequate concealment, if there was true randomisation that was described in adequate detail.
ii) Grade B: Uncertain
iii) Grade C: Clearly inadequate, if the process was not randomly allocated, such as alternative allocation or an open study.
(2) Blinding of Interventions
The studies were described as blinded, using a double dummy approach.
(3) Withdrawals
All patients were clearly accounted for.
(4) Blinding of outcome assessment

Shale 1987 gave a clear description of inclusion and exclusion criteria. The study was described as randomised, but the method of randomisation was not described. The trial was adequately double blinded with a clear description. An adequate description of the statistical analysis was provided. There was no mention of adverse events nor the method used to assess for them. The overall quality score was five out of a maximum of eight.

Stevens 2000 gave a clear description of inclusion criteria. The quality score was eight out of eight. The trial was randomised and double blinded. There was clear documentation of withdrawals and all adverse events.

Wark 2003 gave a clear description of inclusion criteria. The quality score was eight out of eight. The trial was randomised and double blinded. There was clear documentation of withdrawals and all adverse events.

Effects of interventions

Ketoconazole

Shale 1987 randomly assigned 10 participants with ABPA (who had not had an exacerbation in the previous six months) to receive ketoconazole 400 mg daily or placebo. All were on inhaled corticosteroids and one on prednisone. The trial was conducted in a double blind fashion. Treatment led to a 40% reduction in specific IgG antibody to Aspergillus fumigatus ($p < 0.05$). The placebo group remained stable. Total IgE and specific IgE were significantly reduced after 12 months ($p < 0.05$) but tended to rise in the placebo arm. There was a significant improvement in symptom scores in the treatment arm and this correlated with the change in the IgG levels. There were no significant changes in spirometry in either group over the twelve months. Though this study had small numbers, it demonstrated an improvement in immunological markers and symptoms. This was a group who were selected because they had mild and stable disease (only one required oral corticosteroids) and it may be argued that additional treatment would be less likely to have a large impact in a short period of time. An earlier uncontrolled study (Fournier 1984) had failed to show a benefit from ketoconazole 400 mg daily in nine patients, all of whom were also on 10 to 15 mg of prednisone daily.

Itraconazole

The study by Stevens 2000 was a multi centre trial involving 13 centres. They recruited 55 participants with ABPA on at least 10 mg of prednisone daily and randomised them to itraconazole or placebo. The itraconazole arm received 200 mg BD initially for 16 weeks. Steroid reduction was attempted. The study was then unblinded and all received 200 mg daily for a further 16 weeks. In the treatment group 46% of participants achieved an improvement in one of the following outcome parameters: a 50% or more reduction in oral corticosteroid dose, a 25% or greater fall in IgE, or a 25% increase in pulmonary function tests (FEV1, FVC, Diffusion of carbon dioxide across the lung (DLCO), FEF and peak flow) or exercise tolerance. Only 19% of the placebo group met one of these criteria for improvement (Fisher exact $p = 0.04$). While the difference between the groups was significant in terms of overall response, it failed to reach statistical significance for each of these outcomes when examined separately. Adverse events were similar in both groups. Quality of life scores were not significantly different. This study demonstrated that itraconazole is safe in this setting and is potentially efficacious in ABPA as an adjunct to corticosteroids.

Wark 2003 was a single centre study in which the primary outcomes were markers of airway inflammation measured using induced sputum. Participants who received itraconazole had a 35% reduction (95%CI 20 to 48% reduction) in sputum eosinophils that was sustained throughout the trial, while the placebo arm showed no change (the 95%CI included a 19% fall and a 12% increase). There was a similar fall in sputum eosinophil cationic protein, a marker of eosinophil degranulation and airway inflammation. The itraconazole group showed a 42% fall (95%CI 19, 58 % reduction), the placebo group had a 23% fall (the 95%CI included a 66% fall and a 30% increase). There was a similar fall in systemic immune activation. Participants on itraconazole had a median fall in serum IgE of 310 IU/ml compared to a rise in the placebo group of 18 IU/ml ($p < 0.001$). These data could be pooled with the results from Stevens 2000. This meta-analysis demonstrated that participants who received itraconazole were more likely to have a decline in serum IgE of 25% or more, Odds Ratio 3.26 (1.30 to 8.15) compared to placebo.

Wark 2003 also demonstrated that participants on itraconazole had fewer exacerbations of their chest disease requiring the use of oral corticosteroids during the period of the trial, with a mean number of exacerbations per participants of 0.4 (SD 0.5) compared to placebo 1.3 (SD 1.2) $p = 0.03$. They did not demonstrate any statistically significant change in lung function, though the itraconazole arm recorded an increase in FEV1 of 7.9% and the placebo arm a fall of 1.9% ($p = 0.5$). The proportion who had an increase in FEV1 of 25% or more were pooled with data from Stevens 2000 for participants who had an improvement in lung function parameters (FEV1, FVC, DLCO, FEF and peak flow). Those on itraconazole had increased odds of demonstrating an increase in lung function, but this did not reach statistical significance, OR 2.15 (0.85 to 5.46).
Wark 2003 had one participant withdraw from the trial with nausea related to itraconazole use, but there were no other serious adverse events. While not included in this review Skov 2002 reported a subject with Cystic Fibrosis who developed Cushings syndrome while using inhaled corticosteroids and Itraconazole. They then went on to demonstrate in participants with Cystic Fibrosis that co-existent use of inhaled Budesonide and Itraconazole led to suppression of adrenal glucocorticoid synthesis in 11 of 25 participants.

There were no other prospective controlled trials. The study by Nepomuceno 1999 retrospectively reviewed 172 patients with cystic fibrosis and found 16 to have ABPA. All but two patients had been treated with prednisone previously. Itraconazole was added to prednisone in 12 cases along with inhaled corticosteroids, one case was treated with itraconazole and inhaled steroids alone. Patients with pre-existing liver dysfunction were excluded. Their course was compared to the three excluded patients and historical data on the five cases who had attended the hospital with known ABPA prior to commencing itraconazole. Taking into account the limitations of using such a control group, they demonstrated a reduction in the number of episodes of acute exacerbations of ABPA by 55% and a 47% greater reduction in oral corticosteroid dose.

The other studies were all uncontrolled case series or case reports (see "Table of excluded studies"). Doses of itraconazole ranged from 50 to 400 mg per day and only two patients had side effects that were mild and did not necessitate a change in treatment. In

all studies immunological parameters showed improvement, there was a substantial reduction in corticosteroid dose, with prednisone being ceased in 7/14 participants. Improvements in symptoms were more variable and did not appear to be as impressive for those with cystic fibrosis. Denning 1991 were the only ones to measure the effect on lung function and they demonstrated a significant improvement with treatment. Two studies Matsuzaki 1997 and Nikaido 1998 reported the use of itraconazole without concomitant prednisone in acute ABPA. Both demonstrated an improvement in immunology and radiographic measures of disease.
None of these studies continued treatment or reported on follow up beyond 12 months.

DISCUSSION

Allergic bronchopulmonary aspergillosis remains an important complication of asthma, contributing to worsened morbidity and leading to progressive deterioration in lung function. We still do not adequately understand the pathogenesis and the implications for prognosis of this disease. While corticosteroids do appear to induce remission acutely, recurrent exacerbations continue to occur despite maintenance treatment with corticosteroids and the effect of corticosteroids on preservation of lung function is not known.

Evidence from in-vitro work clearly shows that Aspergillus fumigatus is well adapted to survive in the human airway. Persistence of the organism is a constant source of antigenic stimulus, but there is also evidence that it can modify the nature of the resulting inflammatory response by release of virulence factors and proteases. This suggests a need to extend therapy beyond corticosteroids. Consequently treatment with specific antifungal agents may be advantageous over treatment with corticosteroids alone.

There are now three prospective randomised trials using azoles in ABPA. Shale 1987 used Ketoconazole and demonstrated a reduction in immune activation and symptoms but no change in lung function. Stevens 2000 and Wark 2003 both used itraconazole for 16 weeks and found a significant fall in markers of systemic immune activation. Wark 2003 also demonstrated a reduction in markers of airway inflammation in induced sputum and patients on itraconazole had fewer severe exacerbations of disease that required the use of prednisone. The capacity of Itraconazole, in combination with inhaled corticosteroids, to induce adrenal suppression is an important potential adverse effect and its clinical ramifications will warrant monitoring in future studies. In addition if Itraconazole potentiates the adrenal suppressing effects of corticosteroids it may also enhance their other known side effects such as osteoporosis or cataract formation and this too will need to be monitored.

Neither Wark 2003 nor Stevens 2000 showed a significant change in lung function, however the majority of included patients had long standing disease with bronchiectasis, so it is likely that they had an element of irreversible lung disease. Under these circumstances much larger numbers of patients and longer follow-up may be required to detect a difference in lung function.

AUTHORS' CONCLUSIONS

Implications for practice

Two trials demonstrate that itraconazole reduced the inflammation associated with ABPA and improves clinical outcomes over 16 weeks. As both the intensity of the inflammatory response and acute exacerbations of the disease are felt to lead to progressive lung disease, the ability of itraconazole to modify both of these factors in the short term may have important implications for the chronic management of the disease. However, longer term trials are required before a firm recommendation can be made for the use of itraconazole as adjunctive treatment for patients with ABPA.

Implications for research

As ABPA is a disease that is characterised by frequent exacerbations and may lead to progressive and irreversible lung disease there remains an important need to determine whether itraconazole modifies the long-term progress of the disease. Any such studies should measure clinical outcomes such as corticosteroid dose, frequency of exacerbations, quality of life scores, as well as with serological tests for total IgE, Aspergillus precipitins and eosinophilia. Pulmonary function tests and radiographic changes on thoracic CT would also be relevant but to detect a change in these parameters follow up would need to exceed 12 months. To detect any effect on progressive changes in lung function, trials over three years such as those in chronic obstructive pulmonary disease may be needed. In addition the adjuvant role of itraconazole with both inhaled and oral corticosteroids should be addressed, especially its ability to reduce overall corticosteroid dose. In the light of the recent findings of adrenal suppression after using inhaled corticosteroids and itraconazole, future studies will need to address this as a potential adverse effect. In addition they should consider looking for evidence for an increase in other side effects associated with corticosteroid use where both agents are used together.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Shale 1987

Methods	Randomised placebo controlled double blind trial.
Participants	no. = 10; 6 in intervention arm and 4 in control arm. Mean age 47.8 years, range 23 to 76 years.
Interventions	Ketoconazole 400mg daily for 12 months.
Outcomes	FEV1 % predicted, FVC % predicted, Specific IgE to Aspergillus, Total serum IgE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

Stevens 2000

Methods	Randomised placebo controlled double blind trial.
Participants	no. = 55.

Stevens 2000 *(Continued)*

Interventions	Itraconazole 200mg BD for 16 weeks.
Outcomes	Steroid reduction, total serum IgE, pulmonary function and exercise tolerance.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Dynamic randomization permitted balanced distribution of patients in the two groups at each center according to various prognostic factors, including the stage of disease. Study drugs were randomly assigned numbers in blocks and arbitrarily distributed among sites... The patients were scheduled to be stratified according to the presence or absence of cystic fibrosis, but no patients with cystic fibrosis enrolled. Treatment assignments were not available either to investigators or to patients during or after the trials.'
Allocation concealment (selection bias)	Low risk	'Randomization was performed at a central location, according to site, and each patient was assigned a medication number on entry.

Wark 2003

Methods	Randomised placebo controlled double blind trial.
Participants	no. = 29.
Interventions	Itraconazole 400 mg daily for 16 weeks.
Outcomes	Sputum eosinophils, serum total IgE, IgG to Af, frequency of exacerbations and FEV1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers chart. Stratified on the basis of diagnosis of ABPA-CB or ABPA without CB but with serologic criteria.
Allocation concealment (selection bias)	Low risk	Assigned by the pharmacy department.

no.: number
FEV1: Forced Expiratory Volume in 1 second
FVC: Forced Vital Capacity
IgE: Immunoglobulin E
IgG: Immunoglobulin G
Af: Aspergillus Fumigatus

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

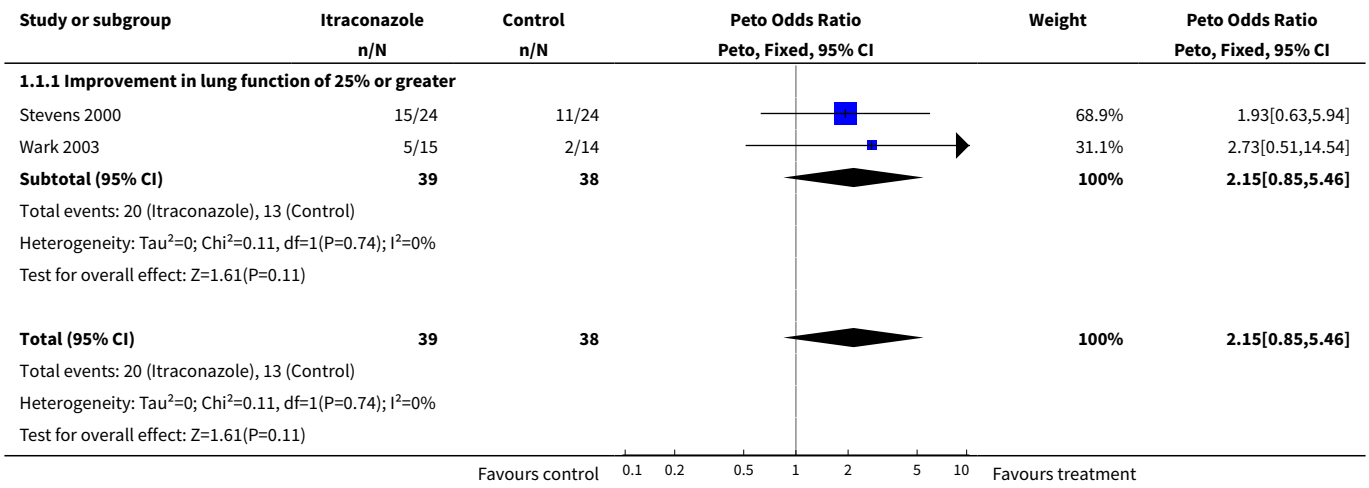
Study	Reason for exclusion
De Beule 1988	No control group. The outcome criteria were unclear.
Denning 1991	No control group.
Fournier 1984	No control group.
Germaud 1992	No control group.
Greenberger 2002	Not a randomised controlled trial.
Kumar 2003	Case series
Lebeau 1994	No control group.
Matsuzaki 1997	Case report only no control group.
Moss 2002	Not a randomised controlled trial.
Nepomuceno 1999	A retrospective case control trial. The control group was a mixture of subjects who had previously been treated at the institution and subjects used as cases prior to the use of itraconazole. As this was not a prospective control trial and the controls were so heterogenous it was not included.
Nikaido 1998	Case report only, no controls.
Pacheco 1993	Case report only, no controls.
Skov 2002	Not a randomised control trial. All subjects had cystic fibrosis.
Stevens 2003	Review article not RCT
Vlahakis 2002	Not a randomised controlled trial.

DATA AND ANALYSES

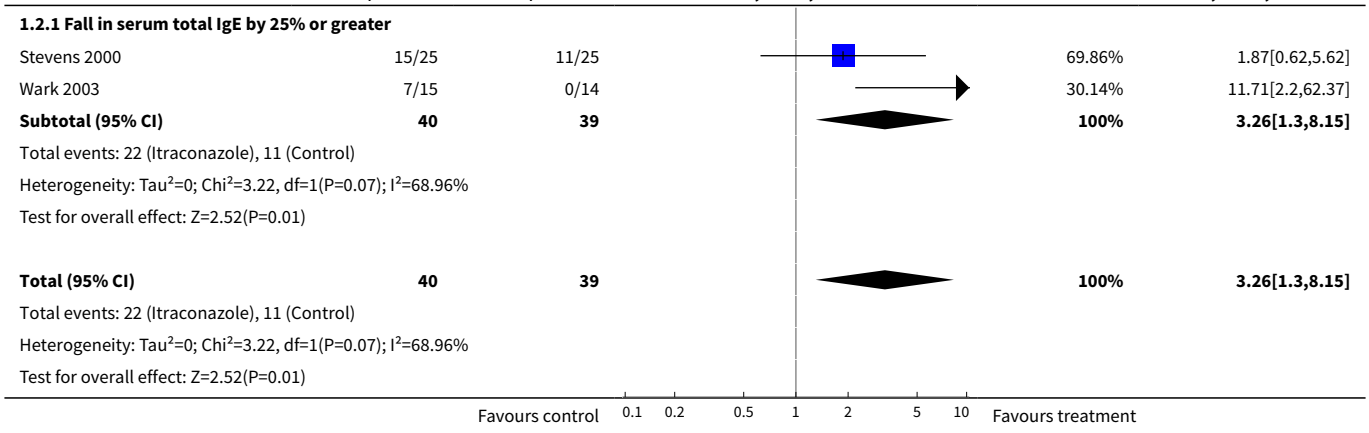
Comparison 1. Itraconazole 400 g daily versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in lung function	2	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.15 [0.85, 5.46]
1.1 Improvement in lung function of 25% or greater	2	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.15 [0.85, 5.46]
2 Serum Total IgE	2	79	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [1.30, 8.15]
2.1 Fall in serum total IgE by 25% or greater	2	79	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [1.30, 8.15]

Analysis 1.1. Comparison 1 Itraconazole 400 g daily versus Placebo, Outcome 1 Improvement in lung function.



Analysis 1.2. Comparison 1 Itraconazole 400 g daily versus Placebo, Outcome 2 Serum Total IgE.



APPENDICES

Appendix 1. Topic search strategies

CENTRAL search	MEDLINE search	EMBASE search
1.exp ASPERGILLOSIS, ALLERGIC BRONCHOPULMONARY/ or exp ASPERGILLOSIS/	1.exp ASPERGILLOSIS, ALLERGIC BRONCHOPULMONARY/ or exp ASPERGILLOSIS/	1. exp LUNG ASPERGILLOSIS/ or exp ASPERGILLOSIS/
2. aspergillosis.mp.	2. aspergillosis.mp.	2. exp bronchopulmonary aspergilloma/ 3. aspergillosis.mp. 4. 1 or 2 or 3

(Continued)

3. 1 or 2	3. 1 or 2	5. (azole$ or triazole$ or itraconazole or ketoconazole or vorconazole or voriconazole).mp.
4. exp Azoles/	4. exp Azoles/	6. pyrrole/ or exp triazole derivative/
5. (azole$ or triazole$ or itraconazole or ketoconazole or vorconazole or voriconazole).mp.	5. (azole$ or triazole$ or itraconazole or ketoconazole or vorconazole or voriconazole).mp.	7. 5 or 6
6. 4 or 5	6. 4 or 5	8. 4 and 7
7. 3 and 7	7. 3 and 7	

Appendix 2. RCT search filters

MEDLINE	EMBASE
1. exp "clinical trial [publication type]"/	1. Randomized Controlled Trial/
2. (randomized or randomised).ab,ti.	2. Controlled Study/
3. placebo.ab,ti.	3. randomization/
4. dt.fs.	4. Double Blind Procedure/
5. randomly.ab,ti.	5. Single Blind Procedure/
6. trial.ab,ti.	6. Clinical Trial/
7. groups.ab,ti.	7. Crossover Procedure/
8. or/1-7	8. follow up/
9. Animals/	9. exp prospective study/
10. Humans/	10. or/1-9
11. 9 not (9 and 10)	11. (clinica$ adj3 trial$).mp.
12. 8 not 11	12. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (mask$ or blind$ or method$)).mp.
	13. exp Placebo/
	14. placebo$.mp.
	15. random$.mp.
	16. (latin adj3 square$).mp.
	17. exp Comparative Study/
	18. ((control$ or prospectiv$ or volunteer$) adj3 (trial$ or method$ or stud$)).mp.
	19. (crossover$ or cross-over$).mp.
	20. or/11-19
	21. 10 or 20
	22. exp ANIMAL/
	23. Nonhuman/

(Continued)

	24. Human/
	25. 22 or 23
	26. 25 not 24
	27. 21 not 26

WHAT'S NEW

Date	Event	Description
4 September 2017	Amended	New literature search run to assess the need to update this review. One potentially eligible study identified and added to Studies awaiting classification.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 2, 2000

Date	Event	Description
4 June 2014	Amended	PLS title amended
27 June 2008	New search has been performed	New search run to June 2008. No new studies were identified.
27 June 2008	Amended	Converted to new review format.
4 March 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PW and AW devised the protocol with editorial support from PG. PW and AW assessed manuscripts for inclusion in the review. PG offered editorial support during development of the review and the analysis.

DECLARATIONS OF INTEREST

Two reviewers(PABW, PGG) were associated with the trial by Wark 2003.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Asthma Foundation of New South Wales, Australia.
- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Antifungal Agents [adverse effects] [*therapeutic use]; Aspergillosis, Allergic Bronchopulmonary [*drug therapy]; Asthma [*complications]; Itraconazole [adverse effects] [therapeutic use]; Ketoconazole [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans