Endpoints for antifungal clinical trials for fungal asthma

David W. Denning
The University of Manchester
Global Action Fund for Fungal Infections
'Fungal asthma'
ABPA versus SAFS

SAFS = severe asthma with fungal sensitisation

Denning et al, Med Mycol 2013:51:361
Fungal asthma endpoints

**Primary endpoint options:**
- Measures of lung function - walking distance, step tests, FEV1
- Patient reported outcomes (respiratory) - AQLQ, ACQ, SGRQ
- Patient reported outcomes (general) - WHO QoL/EuroQol 5D
- Exacerbations
- Corticosteroid usage/reduction
Fungal asthma endpoints

**Primary endpoint options:**
Measures of lung function – walking distance, step tests, FEV1,
Patient reported outcomes (respiratory)- AQLQ, ACQ, SGRQ
Patient reported outcomes (general) - WHO QoL/EuroQol 5D
Exacerbations
Corticosteroid usage/reduction

**Supportive endpoints:**
Radiology
Sputum markers: eosinophils, culture, qPCR, mycobiome
IgE and fungal-specific IgE
Breath biopsy (exhaled breath condensate)
Fungal asthma endpoints

**Primary endpoint options:**
- Measures of lung function - walking distance, step tests, FEV1
- Patient reported outcomes (respiratory) - AQLQ, ACQ, SGRQ
- Patient reported outcomes (general) - WHO QoL/EuroQol 5D
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**Supportive endpoints:**
- Radiology
- Sputum markers: eosinophils, culture, qPCR, mycobiome
- IgE and fungal-specific IgE
- Breath biopsy (exhaled breath condensate)

**Composite endpoint - examples**
Randomised studies of antifungals for fungal asthma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antifungal, duration</th>
<th>Benefit?</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPA</td>
<td>Natamycin inh, 52 wks</td>
<td>No</td>
<td>Currie, 1990</td>
</tr>
<tr>
<td>ABPA</td>
<td>Itraconazole, 32 wks</td>
<td>Yes</td>
<td>Stevens, 2000</td>
</tr>
<tr>
<td>ABPA</td>
<td>Itraconazole, 16 wks</td>
<td>Yes</td>
<td>Wark, 2003</td>
</tr>
<tr>
<td>“Trichophyton” asthma</td>
<td>Fluconazole, 20 wks</td>
<td>Yes</td>
<td>Ward, 1999</td>
</tr>
<tr>
<td>SAFS</td>
<td>Itraconazole, 32 wks</td>
<td>Yes</td>
<td>Denning, 2009</td>
</tr>
<tr>
<td><em>A. fumigatus</em>-associated asthma</td>
<td>Voriconazole, 12 wks</td>
<td>No</td>
<td>Agbetile, 2014</td>
</tr>
<tr>
<td>Acute stage ABPA</td>
<td>Itraconazole, 16 wks</td>
<td>Yes</td>
<td>Agarwal, 2016</td>
</tr>
<tr>
<td>Acute stage ABPA</td>
<td>Voriconazole, 16 wks</td>
<td>Yes</td>
<td>Agarwal, 2018</td>
</tr>
<tr>
<td>Steroid resistant, severe asthma</td>
<td>Itraconazole, 16 weeks</td>
<td>Yes</td>
<td>Mirmadraee, 2019</td>
</tr>
</tbody>
</table>
TABLE 3. DEFINITION OF A RESPONSE IN THE DOUBLE-BLIND TRIAL.*

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in the dose of corticosteroid by 50 percent or more</td>
</tr>
<tr>
<td>Decrease in the total IgE concentration by 25 percent or more</td>
</tr>
<tr>
<td>At least one of the following</td>
</tr>
<tr>
<td>Increase in exercise tolerance by at least 25 percent</td>
</tr>
<tr>
<td>Improvement by 25 percent in results of at least one of five pulmonary-function tests†</td>
</tr>
<tr>
<td>Resolution of infiltrates present at enrollment and attributable to allergic bronchopulmonary aspergillosis and no subsequent development of infiltrates, or absence of development of any infiltrates during the study if no infiltrates were present at enrollment‡</td>
</tr>
</tbody>
</table>

* Patients were considered to have had a response if they met the first two criteria and at least one of the conditions of the third. Responses were assessed by comparing values at week 0 with those at week 16.

† The following were assessed: forced expiratory volume in one second, forced vital capacity, forced expiratory flow in the midexpiratory phase, peak flow rate, and carbon monoxide diffusing capacity.
Randomised trial of itraconazole in ABPA

Corticosteroid dependant ABPA with asthma
  Phase 1 - 200mg BID v placebo, 16 weeks
  Phase II - 200mg daily in all patients, 16 weeks

Randomised trial of itraconazole in ABPA

Corticosteroid dependant ABPA with asthma
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<table>
<thead>
<tr>
<th></th>
<th>Itra</th>
<th>Placebo then Itra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>13/28 (46%)</td>
<td>5/27 (19%) p = 0.04</td>
</tr>
<tr>
<td>Overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior response</td>
<td>4/13 (31%)</td>
<td>8/20 (40%) NS</td>
</tr>
<tr>
<td>(n=33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Randomised trial of itraconazole in ABPA

Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

Overall response

Itra        Placebo then Itra

Overall 17/28 (61%) response rate

No prior response

(n=33)

Randomised trial of itraconazole in ABPA

Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

Overall response

Itra

Placebo then Itra

Overall 17/28 (61%) response rate

No prior response

(n=33)

Number needed to treat = 3.58

Randomised trial of itraconazole in ABPA

ABPA with asthma, n = 29
Phase 1 - 200mg BID v placebo, 16 weeks
Primary outcome measure - Sputum eosinophil count

P < 0.01

Reduced exacerbation rate
No change in FEV1 or PEF

Wark et al, J Clin All Immunol 2003; 111:952
Antifungal treatment of severe asthma with fungal sensitisation (SAFS)

11 patients with Trichophyton skin test allergy, skin dermatophyte infection and moderate/severe asthma,

Rx with fluconazole or placebo for 5 months, then all received fluconazole.

Fluconazole v. placebo at 5 months

- Bronchial hypersensitivity reduced \( p = 0.012 \)
- Steroid requirements reduced \( p = 0.01 \)

Peak flow increased in 9/11 at 10 months

Ward et al, J Allergy Clin Immunol 1999;104:541;
A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

Ritesh Agarwal, MD, DM; Sahajal Dhooria, MD, DM; Inderpal Singh Sehgal, MD, DM; Ashutosh N. Aggarwal, MD, DM; Mandeep Garg, MD; Biman Saikia, MD; Digambar Behera, MD; and Arunaloke Chakrabarti, MD

4 months treatment in both arms

Prednisolone 0.5mg/Kg for 4 wks then tapered over 3 mths

Itraconazole 200mg BID
Endpoints

Clinical improvement in cough and dyspnea - 4 point scale

Composite response of:
1. Improvement in cough and dyspnea (≥75%) AND
2. Partial clearance of CXR abnormalities (≥50%) AND
3. Serum IgE fall by ≥25%

ABPA exacerbation =
Clinical and/or radiological worsening + serum IgE ≥2x prior level

Asthma exacerbation =
Clinical exacerbation without CXR or IgE 2x prior level

Exacerbations investigations:
CXR
Total IgE
Sputum for AFB and bacterial culture

Agarwal et al, Chest 2018;153:656
# Primary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prednisolone Group (n = 63)</th>
<th>Itraconazole Group (n = 68)</th>
<th>Estimated Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with response following 6 wk of treatment</td>
<td>63 (100%)</td>
<td>60 (88.2%)</td>
<td>−11.8 (−21.5 to −3.7)</td>
<td>.007</td>
</tr>
<tr>
<td>Subjects with response following 3 mo of treatment</td>
<td>63 (100%)</td>
<td>60 (100%)</td>
<td>0 (−0.06 to 0.06)</td>
<td>...</td>
</tr>
<tr>
<td>Percentage decline in IgE following 6 wk of treatment (n = 123)</td>
<td>54.5 (48.9-60.1)</td>
<td>51.8 (42.9-60.8)</td>
<td>−2.7 (−7.6 to 13.4)</td>
<td>.87</td>
</tr>
<tr>
<td>Percentage decline in IgE following 3 mo of treatment (n = 123)</td>
<td>66.9 (62.0-71.8)</td>
<td>65.6 (59.1-72.1)</td>
<td>−1.3 (−6.7 to 9.3)</td>
<td>.80</td>
</tr>
<tr>
<td>No. of subjects experiencing exacerbation following 1 y of treatment (n = 123)</td>
<td>6 (9.5%)</td>
<td>7 (11.7%)</td>
<td>−2.1 (−13.8 to 9.2)</td>
<td>.93</td>
</tr>
<tr>
<td>No. of subjects experiencing exacerbation following 2 y of treatment (n = 123)</td>
<td>14 (22.2%)</td>
<td>17 (28.3%)</td>
<td>−6.1 (−21.3 to 9.2)</td>
<td>.44</td>
</tr>
</tbody>
</table>
IgE levels over time

Agarwal et al, Chest 2018;153:656
### Primary outcomes

#### Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prednisolone Group (n = 63)</th>
<th>Itraconazole Group (n = 68)</th>
<th>Estimated Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first exacerbation (n = 123)</td>
<td>437 (307-567)</td>
<td>442 (369-521)</td>
<td>8 (-76 to 61)</td>
<td>.91</td>
</tr>
<tr>
<td>Difference in FEV$_1$ following 6 wk of treatment (n = 123)</td>
<td>0.33 (0.26-0.41)</td>
<td>0.30 (0.22-0.37)</td>
<td>0.03 (-0.07 to 0.13)</td>
<td>.20</td>
</tr>
<tr>
<td>Difference in FVC following 6 wk of treatment (n = 123)</td>
<td>0.37 (0.19-0.54)</td>
<td>0.37 (0.26-0.49)</td>
<td>0.08 (-0.06 to 0.22)</td>
<td>.42</td>
</tr>
<tr>
<td>Subjects with exacerbation following 6 mo of treatment</td>
<td>6 (9.5%)</td>
<td>6 (10.0%)</td>
<td>0.01 (-0.11 to 0.12)</td>
<td>.93</td>
</tr>
<tr>
<td>Total No. of ABPA exacerbations</td>
<td>0.57 (0.32-0.82)</td>
<td>0.83 (0.48-1.18)</td>
<td>-0.26 (-0.69 to 0.17)</td>
<td>.32</td>
</tr>
<tr>
<td>Total No. of asthma exacerbations</td>
<td>0.48 (0.28-0.67)</td>
<td>0.62 (0.36-0.87)</td>
<td>-0.14 (-0.46 to 0.18)</td>
<td>.45</td>
</tr>
</tbody>
</table>
4 months of therapy and then observation

Agarwal et al, Chest 2018;153:656
Enrolment criteria

- Severe asthma (BTS level 4 or 5)
- Sensitisation to any fungus
- IgE < 1,000
- Negative Aspergillus IgG antibody

Proof of concept RCT of antifungal Rx in SAFS - AQLQ change

Treatment stopped
Primary endpoint

P = 0.014

Randomized Controlled Trial of Oral Antifungal Treatment for Severe Asthma with Fungal Sensitization
The Fungal Asthma Sensitization Trial (FAST) Study

Patients enrolled & randomised N = 58

Itraconazole 200mg BID 8 months

Active (itraconazole) N = 29

Placebo N = 29

Withdrawal in ≤4 weeks

Active N= 3

Placebo N=1 (p=0.60)

MITT analysis set (active) N =26

MITT analysis set (placebo) N =28

Withdrawal 4-32 weeks

Active N= 8

Placebo N=5 (p=0.25)

Per protocol analysis set (active) N= 18

Per protocol analysis set (placebo) N=23

P=0.014

AQLQ Δ = 0.82

P=0.002

AQLQ Δ = 1.18

RCT of anti-IgE (omalizumab) vs. placebo, moderate and severe asthma - quality of life

Steroids improvement in AQLQ $\Delta = \sim 0.6$

Omalizumab improvement in AQLQ $\Delta = \sim 0.4$

Itraconazole improvement in AQLQ $\Delta = \sim 0.8-1.2$

Buhl et al Eur Resp J 2002;20:1088
**Proof of concept RCT of antifungal Rx in SAFS - outcomes at 32 weeks MITT**

<table>
<thead>
<tr>
<th></th>
<th>Mean (95% CI) or % (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Change in AQLQ score</strong></td>
<td>+0.85 (0.28, 1.41)</td>
<td>-0.01 (-0.43, 0.42)</td>
</tr>
<tr>
<td><strong>Improvement in AQLQ score of &gt;0.75</strong></td>
<td>54% (14)</td>
<td>18% (5)</td>
</tr>
<tr>
<td><strong>Percentage change in total IgE (IU/L)</strong></td>
<td>-27% (-14%, -38%)</td>
<td>+12% (-5%, +31%)</td>
</tr>
<tr>
<td><strong>Change in FEV1 (L/min)</strong></td>
<td>-0.22 (-0.56, 0.11)</td>
<td>-0.02 (-0.16, 0.11)</td>
</tr>
<tr>
<td><strong>Change in FEV1 (% predicted)</strong></td>
<td>-3.66 (-9.39, 2.08)</td>
<td>0.13 (-3.67, 3.93)</td>
</tr>
<tr>
<td><strong>Change in average PEFR (am)</strong></td>
<td>20.8 (3.5, 38.1)</td>
<td>-5.5 (-21.6, 10.7)</td>
</tr>
<tr>
<td><strong>Change in average PEFR (pm)</strong></td>
<td>16.8 (1.5, 35.2)</td>
<td>8.9 (-33.9, 51.8)</td>
</tr>
</tbody>
</table>

Enrolment criteria

- Asthma
- *A. fumigatus* sensitisation
- 2+ exacerbations in prior year
Effectiveness of voriconazole in the treatment of Aspergillus fumigatus–associated asthma (EVITA3 study)

Joshua Agbetile, MD, Michelle Bourne, RGN, Abbie Fairs, PhD, Beverley Hargadon, RGN, Dhananjay Desai, MD, Clare Broad, Joseph Morley, BSc, Peter Bradding, DM, FRCP, Christopher E. Brightling, PhD, FRCP, Ruth H. Green, DM, FRCP, Pranabashis Haldar, DM, MRCP, Catherine H. Pashley, PhD, Ian D. Pavord, DM, FRCP, and Andrew J. Wardlaw, PhD, FRCP  Leicester, United Kingdom

Treatment stopped
Primary endpoint

AQLQ score

weeks

Voriconazole- AQLQ
Placebo- AQLQ

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![Graph showing number of exacerbations over weeks with treatment stopped and primary endpoint indicated.]

- Treatment stopped
- Primary endpoint
Long-term effect of antifungal therapy for the treatment of severe resistant asthma: an active comparator clinical trial

Majid Mirsadraee1*, Sanaz Dehghan2, Shadi Ghaffari3, Niloofar Mirsadraee4

<table>
<thead>
<tr>
<th></th>
<th>Prednisolone</th>
<th>Itraconazole After 1 month</th>
<th>Itraconazole After 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Become worse</td>
<td>8 (20%)</td>
<td>1 (2.5%)</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>Get better but not complete</td>
<td>22 (55%)</td>
<td>24 (58.5%)†</td>
<td>7 (25%)†</td>
</tr>
<tr>
<td>Complete feeling of healthy</td>
<td>10 (25%)</td>
<td>16 (40%)†</td>
<td>20 (71.4%)†</td>
</tr>
<tr>
<td>Lost during study</td>
<td>11 (22%)</td>
<td>10 (20%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Needs to long term continue</td>
<td>3 (6%)</td>
<td>-</td>
<td>24 (60%)</td>
</tr>
<tr>
<td>Side effects-not discontinued</td>
<td>6 (12%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Side effects-discontinued</td>
<td>6 (12%)</td>
<td>2 (5.7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Well tolerance</td>
<td>36 (76%)</td>
<td>33 (94.3%)</td>
<td>24 (96%)</td>
</tr>
</tbody>
</table>

†=Significant difference between case and control group after a one-month treatment with itraconazole
‡=Significant difference after the trial in the Itraconazole group (paired t-test)
## Long-term effect of antifungal therapy for the treatment of severe resistant asthma: an active comparator clinical trial

Majid Mirsadraee¹*, Sanaz Dehghan², Shadi Ghaffari³, Niloofar Mirsadraee⁴

<table>
<thead>
<tr>
<th></th>
<th>Before trial</th>
<th>After one month</th>
<th>After 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Itraconazole</td>
<td>Prednisolone</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.6±0.92</td>
<td>1.8±0.7</td>
<td>2.3±0.87†‡</td>
</tr>
<tr>
<td>FVC percent</td>
<td>55.2±22.23</td>
<td>60.3±16.65</td>
<td>71.8±18.8†‡</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.3±0.73</td>
<td>1.14±0.45</td>
<td>1.9±0.8†‡</td>
</tr>
<tr>
<td>FEV1 percent</td>
<td>50.16±22.7</td>
<td>48.2±15.4</td>
<td>71.5±21.8†‡</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>72.8±12.61</td>
<td>72.1±15.39</td>
<td>79.1±12.7†‡</td>
</tr>
<tr>
<td>FENO (PPM)</td>
<td>36.8±29.2</td>
<td>28.6±25.2</td>
<td>34.6±26.5</td>
</tr>
<tr>
<td>Lukocyte count</td>
<td>9129±3378.8</td>
<td>9900±3093</td>
<td>8900±2524</td>
</tr>
<tr>
<td>Eosinophile count</td>
<td>446±699.9</td>
<td>703±676.1</td>
<td>682±773</td>
</tr>
<tr>
<td>Eosinophile percent</td>
<td>5.7±7.11</td>
<td>10±12.5</td>
<td>8.1±9.4</td>
</tr>
<tr>
<td>Serum IgE</td>
<td>482±670</td>
<td>323±88</td>
<td>424±442</td>
</tr>
</tbody>
</table>

†=Significant difference between case and control group after a one-month treatment with itraconazole
‡=Significant difference after the trial in the Itraconazole group (paired t-test)
Clinical studies of systemic therapy of antifungal therapy of fungal asthma - thoughts

Precisely who is enrolled is important - active ongoing disease is a key factor, not prevention of exacerbations

Improvement in breathing and reduced coughing with reduction in corticosteroid dosage is what patients want

Modest changes in lung function

Significant changes in total IgE

Longer treatment duration better

Exacerbations may be ABPA and/or asthma and/or bacterial exacerbations of bronchiectasis and are generally infrequent