Allergic Bronchopulmonary Aspergillosis and Severe Asthma with Fungal Sensitisation

Dr Rohit Bazaz
National Aspergillosis Centre, UK
Manchester University NHS Foundation Trust/University of Manchester
Figure 1  Interaction of *Aspergillus* with host. ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis.
Allergic Fungal Airway Disease Phenotypes

- AAFS — asthma associated with fungal sensitization
- SAFS — severe asthma with fungal sensitization
- ABPA-S — seropositive allergic bronchopulmonary aspergillosis
- ABPA-CB — allergic bronchopulmonary aspergillosis with central bronchiectasis

Agarwal R, *Curr Allergy Asthma Rep* 2011;11:403
Aspergillus Sensitisation

- Skin testing/specific IgE
- Surface hydrophobins - RodA

- 30% of patients with asthma
- 13% patients with COPD
- 65% patients with CF
ABPA

- ABPA is an exaggerated response of the immune system to Aspergillus
- Complication of asthma and cystic fibrosis (rarely TH2 driven COPD or no identified prior respiratory disease)
- ABPA as a complication of asthma affects around 2.5% of adults. Prevalence in children less but reports variable from 1-8% worldwide.
- Global prevalence of ABPA estimated to be 4.8m
- Characterised by worsening respiratory symptoms, cough, thick sputum, wheeze, chest pain, fever
- Multiple proposed diagnostic criteria

Denning, Med Mycol May 2013
T2 Inflammatory pathways in asthma
Immunopathogenesis of ABPA
A Severe Endotype of T2-High Asthma

Tracy MC et al, J Fungi 2016;2:17
ABPA – diagnostic clues

- Poor asthma control
- History of “recurrent pneumonia”
- Coughing up sputum plugs
### Evolving diagnostic criteria for ABPA

<table>
<thead>
<tr>
<th>Rosenberg-Patterson criteria</th>
<th>Minimal essential criteria</th>
<th>'Truly minimal' criteria</th>
<th>ISHAM Working Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Asthma</td>
<td>1. Asthma</td>
<td></td>
<td>Predisposing conditions</td>
</tr>
<tr>
<td>2. Presence of transient pulmonary infiltrates (fleeting shadows)</td>
<td>2. Immediate cutaneous reactivity to Af</td>
<td>2. Immediate cutaneous reactivity to Af</td>
<td>1. Bronchial asthma</td>
</tr>
<tr>
<td>3. Immediate cutaneous reactivity to Af</td>
<td>3. Total serum IgE &gt; 1,000 ng/mL (417 kU/L)</td>
<td>3. Total serum IgE &gt; 1,000 ng/mL (417 kU/L)</td>
<td>2. Cystic fibrosis</td>
</tr>
<tr>
<td>4. Elevated total serum IgE</td>
<td></td>
<td></td>
<td>Obligatory criteria (both should be present)</td>
</tr>
<tr>
<td>5. Precipitating antibodies against Af</td>
<td></td>
<td></td>
<td>1. Type I Aspergillus skin test positive (immediate cutaneous hypersensitivity to Aspergillus antigen) or elevated IgE levels against Af</td>
</tr>
<tr>
<td>6. Peripheral blood eosinophilia</td>
<td></td>
<td></td>
<td>2. Elevated total IgE levels (&gt;1,000 IU/mL)*</td>
</tr>
<tr>
<td>7. Elevated serum IgE and IgG to Af</td>
<td></td>
<td></td>
<td>Other criteria (at least two of three)</td>
</tr>
<tr>
<td>8. Central/proximal bronchiectasis with normal tapering of distal bronchi</td>
<td>4. Elevated specific serum IgE-Af/IgG-Af</td>
<td>4. CB in the absence of distal bronchiectasis</td>
<td>1. Presence of precipitating or IgG antibodies against Af in serum</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
<td></td>
<td></td>
<td>2. Radiographic pulmonary opacities consistent with ABPA</td>
</tr>
<tr>
<td>1. Expectoration of golden brownish sputum plugs</td>
<td></td>
<td></td>
<td>3. Total eosinophil count &gt; 500 cells/µL in steroid naïve patients (may be historical)</td>
</tr>
<tr>
<td>2. Positive sputum culture for Aspergillus species</td>
<td></td>
<td></td>
<td>*(If the patient meets all other criteria, an IgE value &lt; 1,000 IU/mL may be acceptable)</td>
</tr>
<tr>
<td>3. Late (Arthus-type) skin reactivity to Af</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ABPA, allergic bronchopulmonary asperillosis; Af, Aspergillus fumigatus; CB, central bronchiectasis; CF, cystic fibrosis; IgE, immunoglobulin E; IgG, immunoglobulin G; ISHAM, International Society for Human and Animal Mycology.

ABPA Exacerbation.... Mucus Plugging
CT Features

All non-specific, but suggestive
Cystic, Saccular or varicose bronchiectasis
Mostly central
Thickened bronchial walls
Mucous plugging and bronchocele formation
Features of air trapping
‘Tree in bud’ – centrilobular nodules with a linear branching patterns - implies small airway obstruction – impaction within the bronchioles
Areas of collapse
Complications of ABPA

- Poor asthma control
- Complications related to bronchiectasis
  - Recurrent chest infections
  - Haemoptysis
  - Respiratory failure
- Chronic pulmonary aspergillosis
- Pulmonary fibrosis
- Invasive aspergillosis (rare)
Current therapy for ABPA

• Aimed at controlling acute inflammation and limiting lung injury
• Individualised therapy

• Main treatment options:
  – First line
    - Inhaled and oral corticosteroids
  – Second line
    - Antifungal therapy
  – Third line
    - Omalizumab
A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

Ritesh Agarwal, MD, DM • Sahajal Dhooaria, MD, DM • Inderpal Singh Sehgal, MD, DM •...
Birman Saikia, MD • Digambar Behera, MD • Arunaloke Chakrabarti, MD • Show all authors

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
and one had Aspergillus sensitisation with cavitating nodules. Among these 18 patients, sputum fungal culture results went from positive to negative in five patients, became positive in one patient, remained positive in three patients, and remained negative in seven patients. Nebulised Fungizone® appears to be a poorly tolerated treatment for pulmonary Aspergillosis with high dropout rates. There appears to be both clinical and serological benefits following sustained treatment with nebulised Fungizone® in some patients.
The future?

New therapies in ABPA
Itraconazole DPI for ABPA: Single Dose PK in Asthmatics

Plasma exposure 100-400x lower, sputum 70x higher, vs po itraconazole

Dotted line at 500 ng/mL = \text{Af MIC}_{90}

Phase II 4-arm DBPC 28 day PUR1900 RCT Initiated

Phase 2 Study Underway is Expected to Support Proof of Mechanism in Patients with Asthma-ABPA

28-day Safety, Tolerability, Pulmonary Function and Biomarker Study in Patients with Asthma and ABPA

Randomized, Double-blind, Placebo Controlled Study
(1:1 Randomization; N=16 Per Arm)

Patient Profile
(M/F, ages 18–65) with confirmed/stable asthma and ABPA

Placebo
Pulmazole (10 mg)
Pulmazole (20 mg)
Pulmazole (35 mg)

Endpoints
Safety Tolerability Pulmonary Function Biomarkers

Primary Endpoint
• Safety & tolerability
• Biomarkers

Other Endpoints
• Pulmonary function (FEV₁)
• Plasma and sputum PK
• Sputum and plasma eosinophils
• Serum IgE
• IgE and IgG (specific to A. fumigatus antigens) plasma concentrations
• Aspergillus burden in sputum
• Disease control (ACQ-6)
• FeNO

Pulmatrix Corporate Presentation, Jan 2020
Pulmocide (PC945)

- Nebulised Azole
SAFS – Key diagnostic criteria

• Severe asthma
• Total IgE < 1000 kU/L
• Positive skin prick test for *Aspergillus* or another fungus and/or raised *Aspergillus* or another fungal specific IgE level eg. Cladosporium, Alternaria, Mucor, Rhizopus, Penicillium, Candida, Trichophyton
• Peripheral eosinophil count (normal or high)
• No central bronchiectasis
SAFS - Treatment

• Antifungal therapy:
  Itraconazole, Voriconazole, Posaconazole

SAFS: FAST study - itraconazole for 32 weeks improvement in AQLQ, morning peak flow and fall in total IgE

  Denning D et al. Am J Respir Crit Care Med 179(1):11-18

SAFS: voriconazole and posaconazole over 6 months – 75% stopped oral corticosteroids, 40% downgraded asthma severity, sig reduction in B2 agonist use and health care utilization

  Chishimba et al. J Asthma 49(4):423-433

• Monoclonal antibody therapy
AFAD trial

- Randomised, double blind, placebo control trial evaluating GSK3772847
- Human Immunoglobulin that binds Domain 1 of the cell surface interleukin-33 receptor (IL-33R).
- Phase IIa
Study duration (approx. 28 weeks)

Treatment period

- GSK3772847 (IV) 10mg/kg, n=20
- Placebo, n=20

Screening (28 days prior to V3) - Run-in (14 days prior to V3)

- V1
- V2
- V3
- V4
- V5
- V6
- V7
- V8

Week 0: Dose 1, No Dose
Week 2: Dose 2
Week 4: Dose 3
Week 8
Week 12
Week 24: No Dose

Standard of Care (SoC)

Follow up

Randomisation
Inclusion Criteria

- 18 years old and above
- Moderate or severe asthma (GINA, 2017) treated with inhaled corticosteroid (ICS) and long-acting beta-2-agonist (LABA) for at least 4 months (≥500 µg/day fluticasone propionate or equivalent)
- Pre-bronchodilator FEV1 35-79% of predicted value for participant inclusive
- FeNO ≥25ppb at Screening (Visit 1)
- ACQ-5 score ≥1.5 at Screening (Visit 1)
- Blood eosinophils ≥300 cells/microliter at Screening (Visit 1)
- Evidence of allergic fungal airway disease:
  - Fungal sensitisation to at least one of the following fungi: *Aspergillus fumigatus*, *Penicillium chrysogenum (notatum)* at screening
- A history of exacerbations (at least 1 severe exacerbation - defined as requiring a minimum of 3 days of high-dose oral corticosteroids for asthma symptoms) in the previous 12 months.
Exclusion criteria

- Concurrent respiratory diseases
- Chronic or recurrent non-pulmonary infectious disease or ongoing non-pulmonary infection
- Serious infection within 8 weeks of enrolment
- Cardiovascular disease or malignancy
- Current smokers or former smokers with a smoking history $\geq 10$ pack years
- Eosinophilic diseases
<table>
<thead>
<tr>
<th>Medication</th>
<th>Time interval prior to Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational drug</td>
<td>30 days or 5-half-lives (whichever is longer)</td>
</tr>
<tr>
<td>Biologic agents (such as monoclonal antibodies including marketed drugs)</td>
<td>130 days or 5 half-lives whichever is longer</td>
</tr>
<tr>
<td>Live or attenuated vaccines</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Experimental anti-inflammatory drugs (nonbiologics)</td>
<td>3 months</td>
</tr>
<tr>
<td>Corticosteroids intramuscular, long acting depot</td>
<td>3 months</td>
</tr>
<tr>
<td>Immunomodulatory/suppressive agents (e.g. Methotrexate, troleandomycin,</td>
<td>3 months</td>
</tr>
<tr>
<td>oral or parenteral gold, cyclosporin, azathioprine, cyclophosphamide,</td>
<td></td>
</tr>
<tr>
<td>tacrolimus, mycophenolate mofetil, D-penicillamine)</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>3 months</td>
</tr>
<tr>
<td>Chemotherapy and radiotherapy</td>
<td>12 months</td>
</tr>
<tr>
<td>Anti-fungal medications (oral)</td>
<td>3 months (see Section 7.7.1 for permitted uses)</td>
</tr>
</tbody>
</table>
Recruitment Target

WORLDWIDE - 46

LOCAL - 5
Actual recruitment

WORLDWIDE - 18

LOCAL - 0
### Description of Change

<table>
<thead>
<tr>
<th>Change in Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional therapy: with low dose oral corticosteroid (( \leq 10 \text{ mg/day} )) prednisolone or equivalent is permissible. High dose oral corticosteroid is defined as ( &gt;10 \text{ mg/day} ) prednisolone or equivalent.</td>
</tr>
<tr>
<td>Blood eosinophils of 250-299 cells/µl at screening but with documented evidence of ( \geq 300 ) cells/µl within 5 months of screening will be accepted.</td>
</tr>
</tbody>
</table>
Screen fails

- 8 patients failed screening
  - 4 too low FeNO
  - 3 too low eosinophil count
  - 1 smoking history
“Pre screen” fails

343 patients
- Declined: 29%
- No exacerbation in previous 12 months: 19%
- Smoking history: 6%
- Inhalers: 4%
- Weight: 4%
- Co-morbidities or con-meds: 38%
Summary

• Limited treatment options
• Engaged group of patients
• Concomitant medications criteria can be a significant barrier to recruitment