Allergic Bronchopulmonary Aspergillosis and Severe Asthma with Fungal Sensitisation

National Aspergillosis Centre

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Manchester University NHS Foundation Trust/University of Manchester

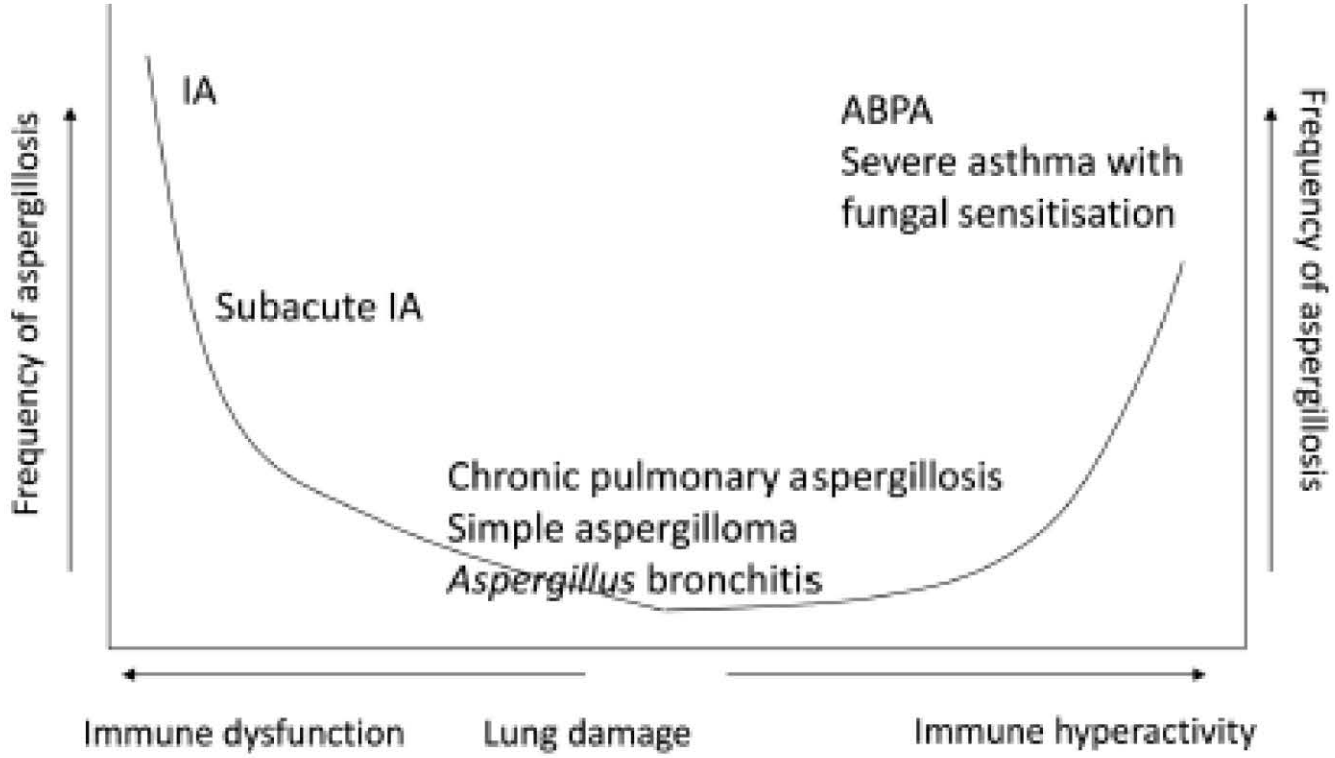
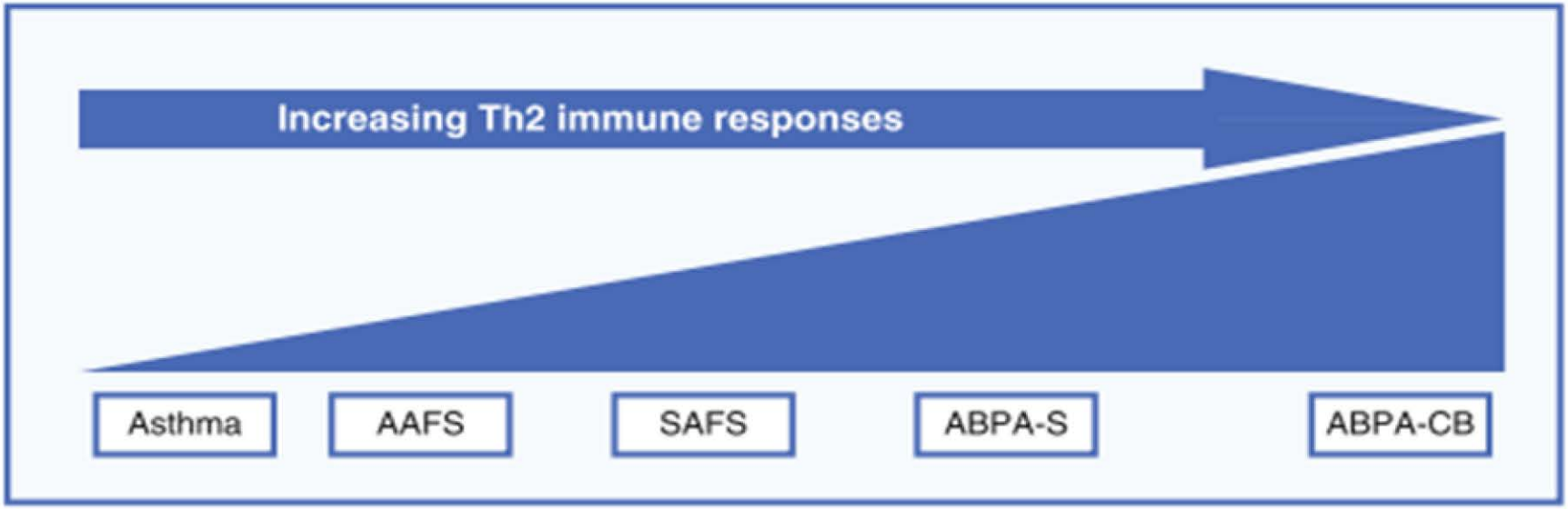


Figure 1 Interaction of *Aspergillus* with host. ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis.

Kosmidis, Denning . Thorax 2015;70:270–277. doi:10.1136/thoraxjnl-2014-206291

Allergic Fungal Airway Disease Phenotypes



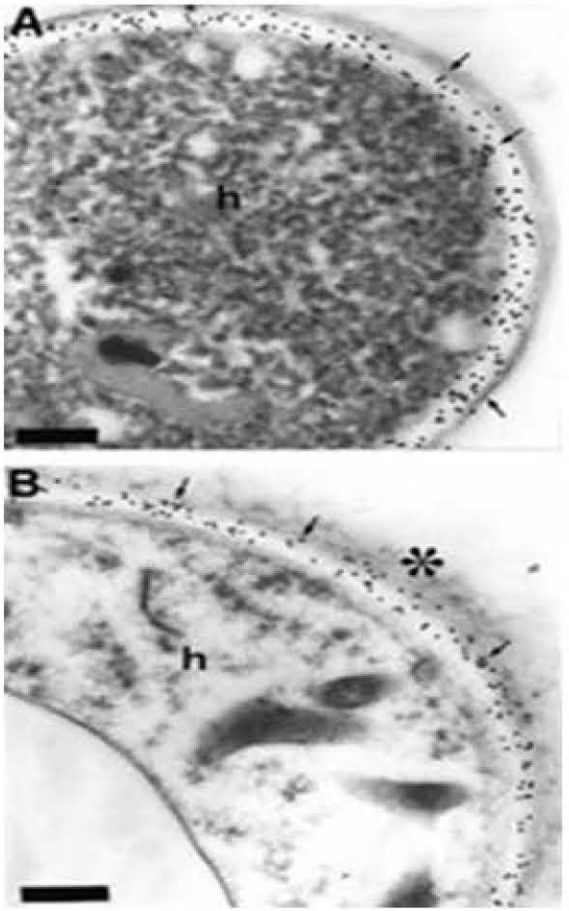
AAFS—asthma associated with fungal sensitization
SAFS—severe asthma with fungal sensitization
ABPA-S—seropositive allergic bronchopulmonary aspergillosis
ABPA-CB—allergic bronchopulmonary aspergillosis with central bronchiectasis

Agarwal R, *Curr Allergy Asthma Rep* 2011;11:403
Woolnough K et al, *Curr Opin Pulm Med* 2015;21:39

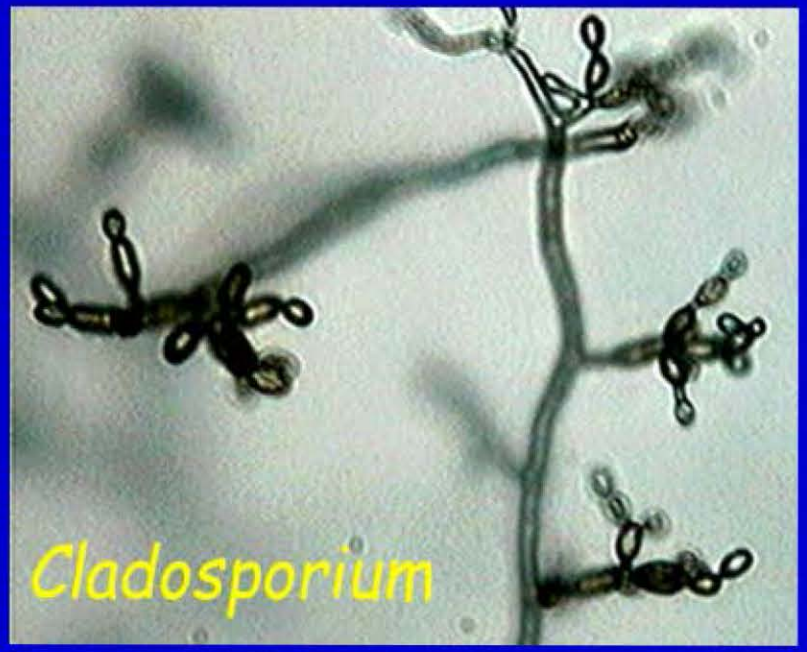
Aspergillus Sensitisation

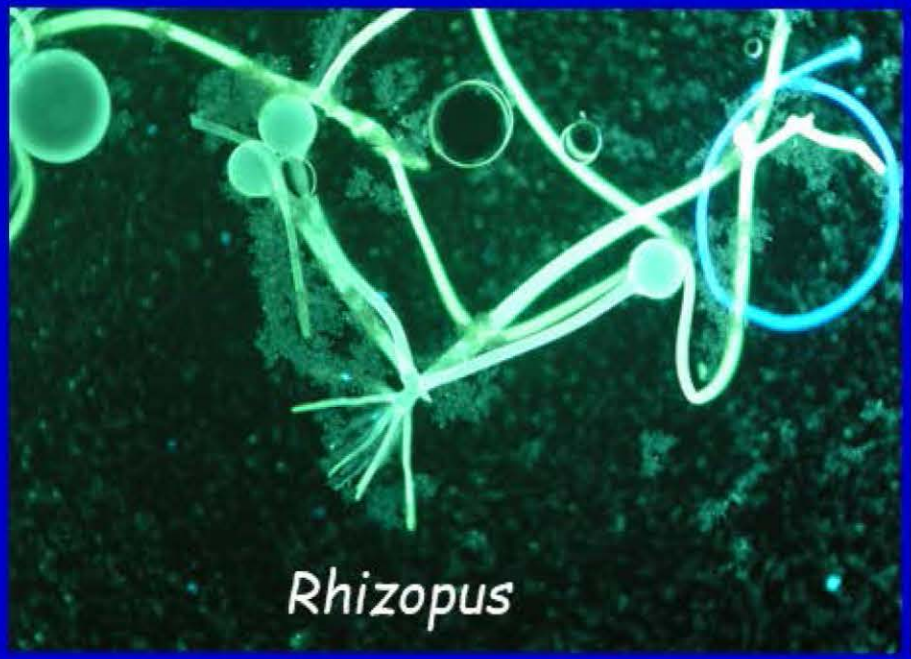
- Skin testing/specific IgE
- Surface hydrophobins - RodA

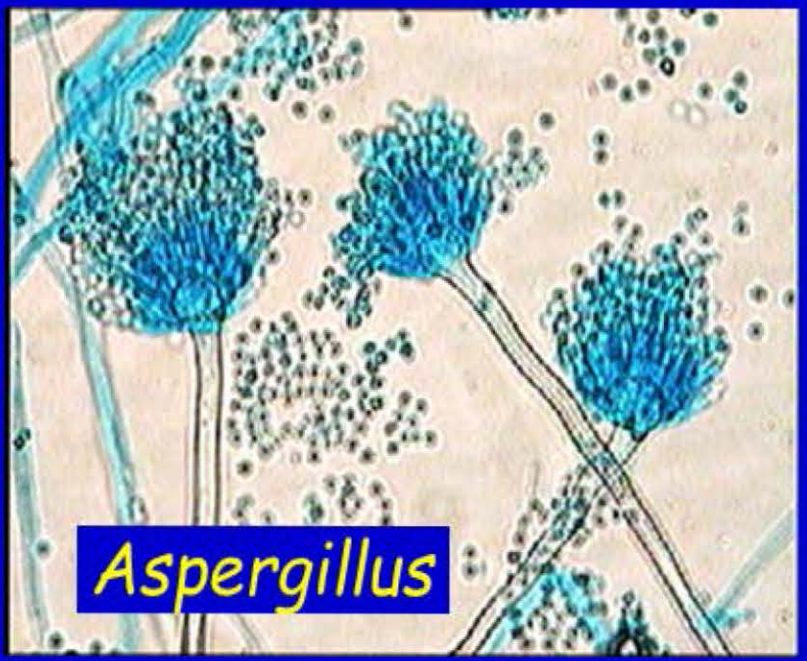
- 30% of patients with asthma
- 13% patients with COPD
- 65% patients with CF




Alternaria


Cladosporium


Rhizopus

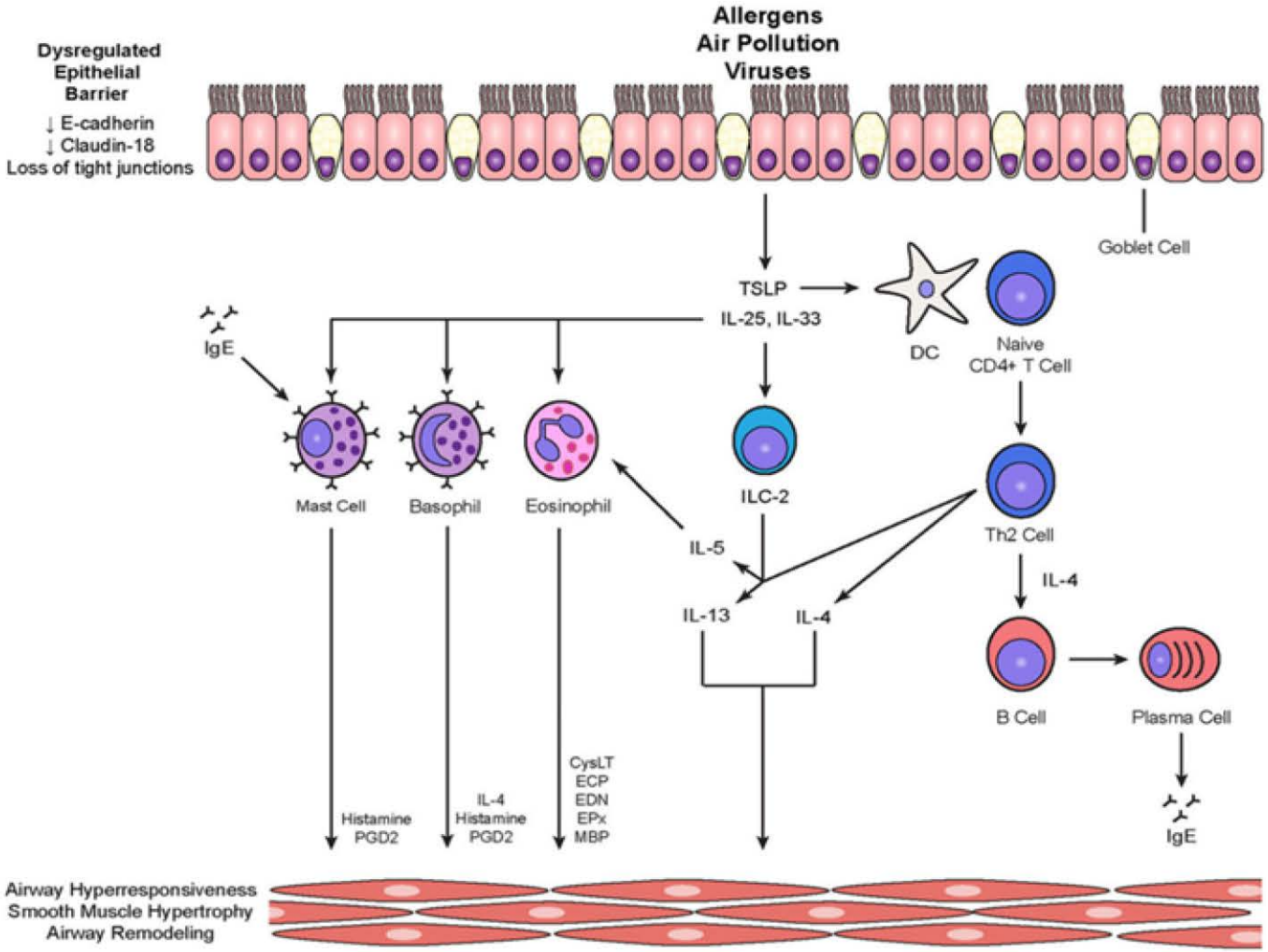

Aspergillus

ABPA

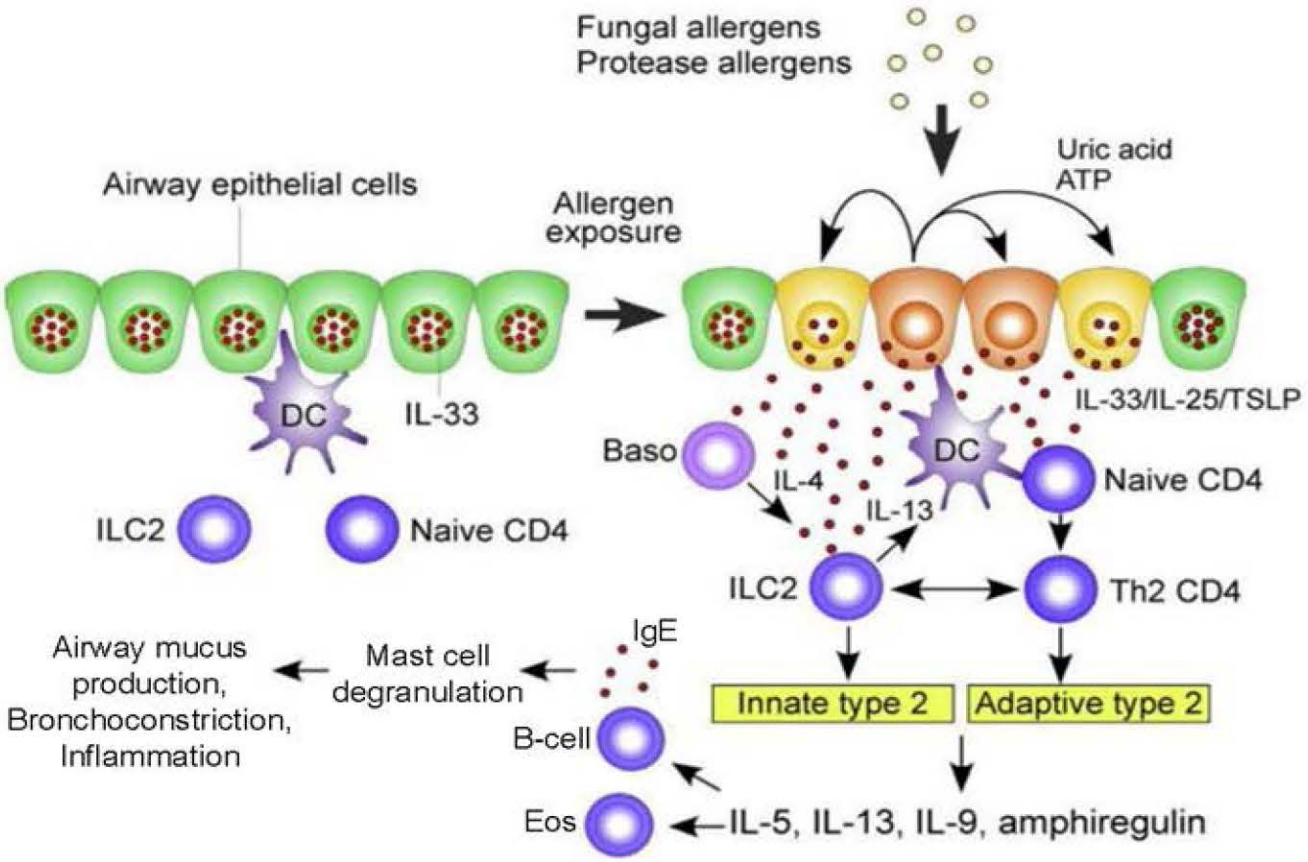
- ABPA is an exaggerated response of the immune system to Aspergillus
- Complication of asthma and cystic fibrosis (rarely TH2 driven COPD or no identified prior respiratory disease)
- ABPA as a complication of asthma affects around 2.5% of adults. Prevalence in children less but reports variable from 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

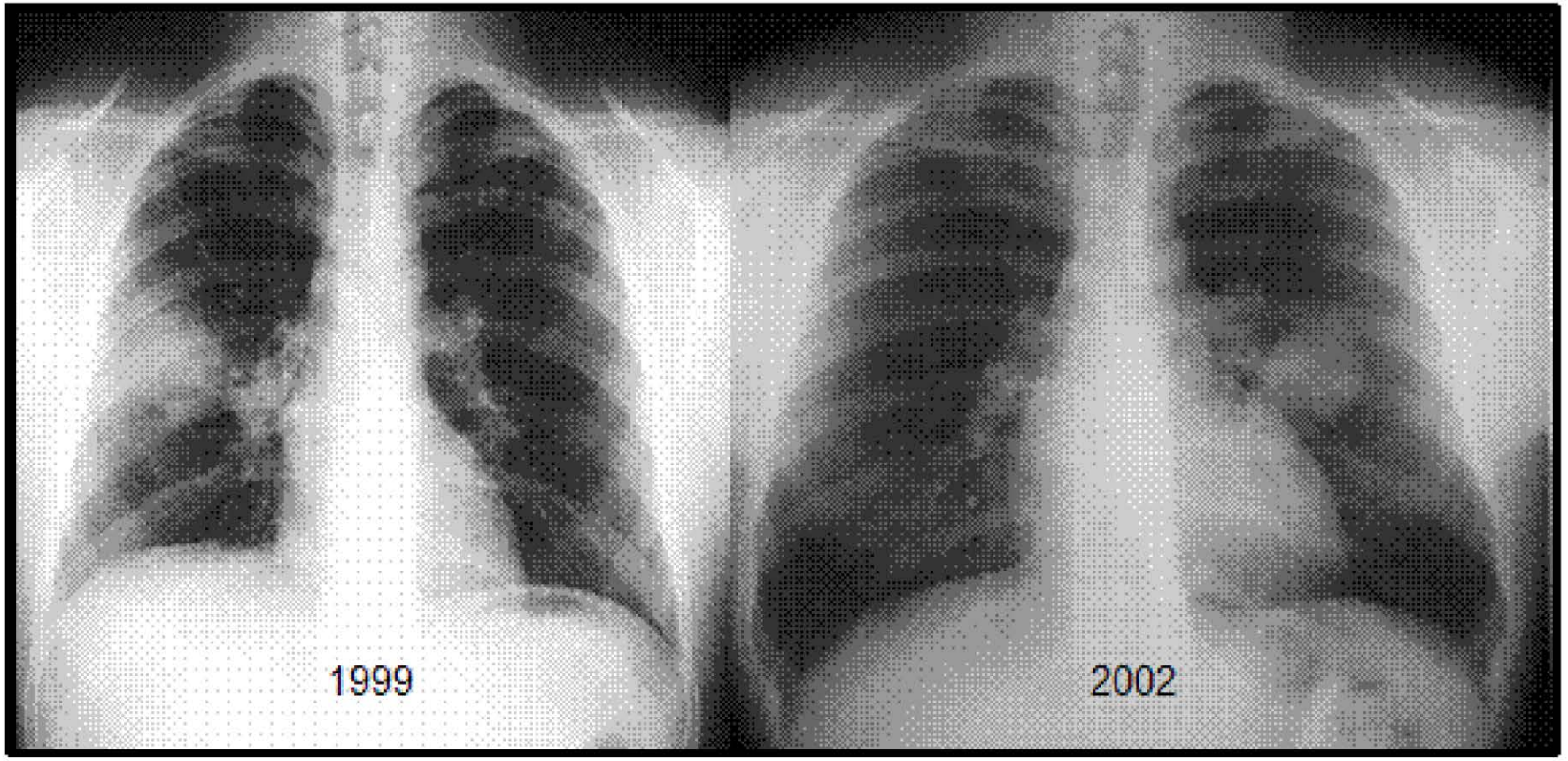
- Poor asthma control
- History of “recurrent pneumonia”
- Coughing up sputum plugs

Evolving diagnostic criteria for ABPA

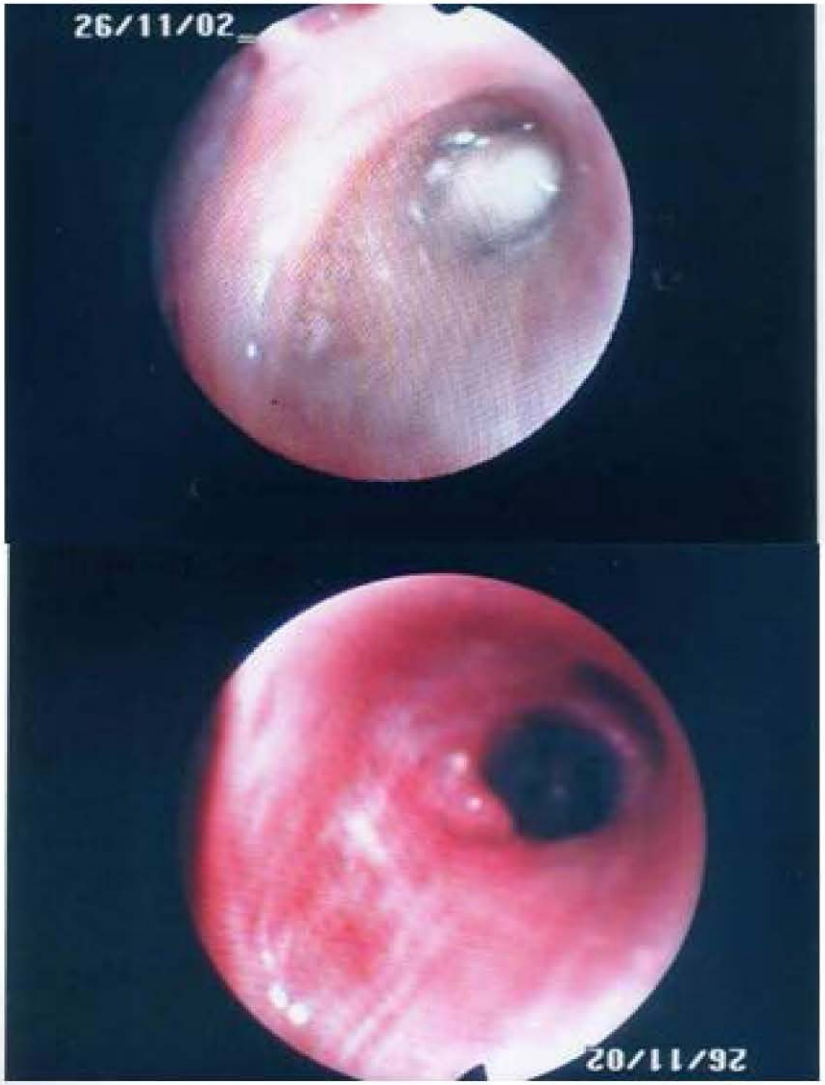
Rosenberg-Patterson criteria[46,47]	Minimal essential criteria[51]	'Truly minimal' criteria[7]	ISHAM Working Group[29]
Major criteria	1. Asthma	1. Asthma	***Predisposing conditions***
1. Asthma			1. Bronchial asthma
2. Presence of transient pulmonary infiltrates (fleeting shadows)	2. Immediate cutaneous reactivity to *Af*	2. Immediate cutaneous reactivity to *Af*	2. Cystic fibrosis
3. Immediate cutaneous reactivity to *Af*	3. Total serum IgE >1,000 ng/mL (417 kU/L)	3. Total serum IgE >1,000 ng/mL (417 kU/L)	***Obligatory criteria (both should be present)***
4. Elevated total serum IgE			1. Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Af*
5. Precipitating antibodies against *Af*			2. Elevated total IgE levels (>1,000 IU/mL)*
6. Peripheral blood eosinophilia	4. Elevated specific IgE-*Af*/IgG-*Af*	4. CB in the absence of distal bronchiectasis	***Other criteria (at least two of three)***
7. Elevated serum IgE and IgG to *Af*			1. Presence of precipitating or IgG antibodies against *Af* in serum
8. Central/proximal bronchiectasis with normal tapering of distal bronchi	5. CB in the absence of distal bronchiectasis		2. Radiographic pulmonary opacities consistent with ABPA
			3. Total eosinophil count >500 cells/μL in steroid naïve patients (may be historical)
Minor criteria			(*If the patient meets all other criteria, an IgE value <1,000 IU/mL may be acceptable)
1. Expectoration of golden brownish sputum plugs			
2. Positive sputum culture for *Aspergillus* species			
3. Late (Arthus-type) skin reactivity to *Af*			

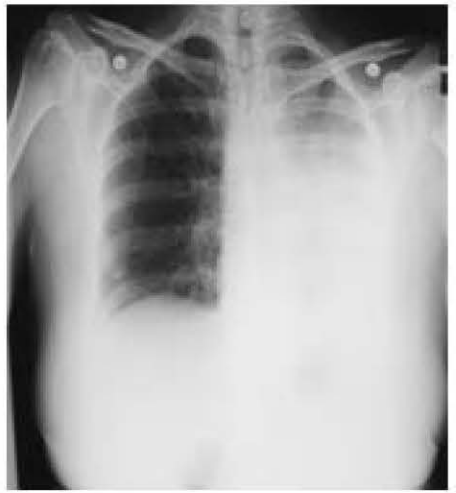
ABPA, allergic bronchopulmonary asperillosis; *Af*, *Aspergillus* fumigatus; CB, central bronchiectasis; CF, cystic fibrosis; IgE, immunoglobulin E; immunoglobulin G; ISHAM, International Society for Human and Animal Mycology.

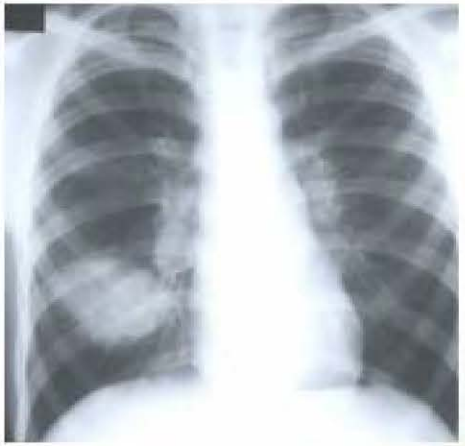
Shah, Allergy Asthma Immunol Res. 2016 Jul; 8(4): 282–297.


1999
2002

ABPA Exacerbation…. Mucus Plugging







CT Features

All non-specific, but suggestive

Cystic, Saccular or varicose bronchiectasis

Mostly central

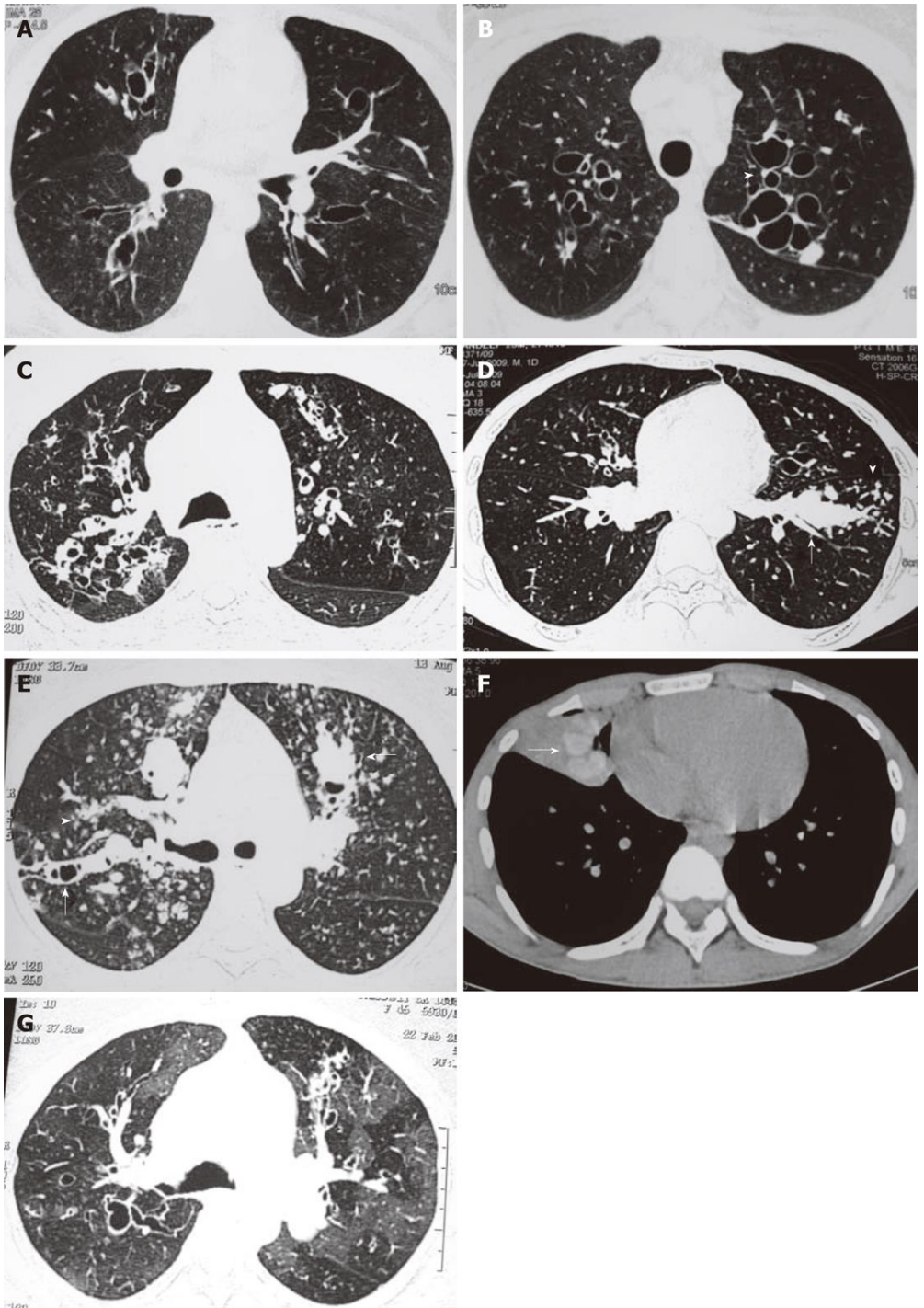
Thickened bronchial walls

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 Dhooria, MD, DM • Inderpaul Singh Sehgal, MD, DM • ...
Biman 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*

Mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

ORIGINAL ARTICLE

An evaluation of nebulised amphotericin B deoxycholate (Fungizone®) for treatment of pulmonary aspergillosis in the UK National Aspergillosis Centre

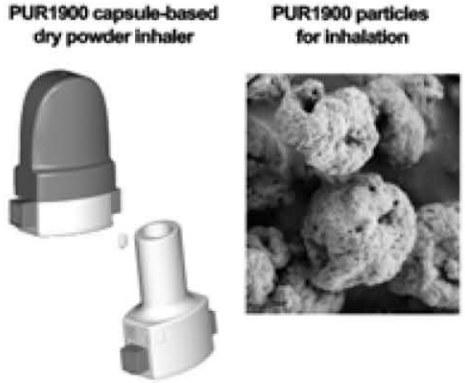
Akaninyene A. Otu, Philip Langridge, David W. Denning

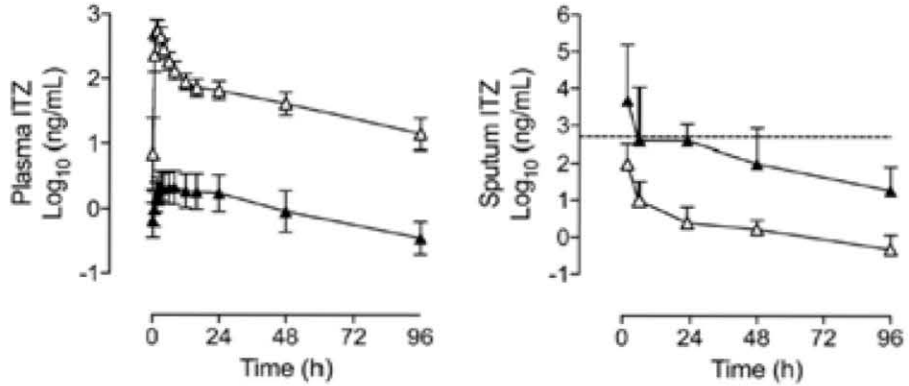
and one had Aspergillus sensitisation with cavitating nodules. Among these 18 patients, sputum fungal culture results went from positive to negative in five patients, became positive in one patient, remained positive in three patients, and remained negative in seven patients. Nebulised Fungizone® appears 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.

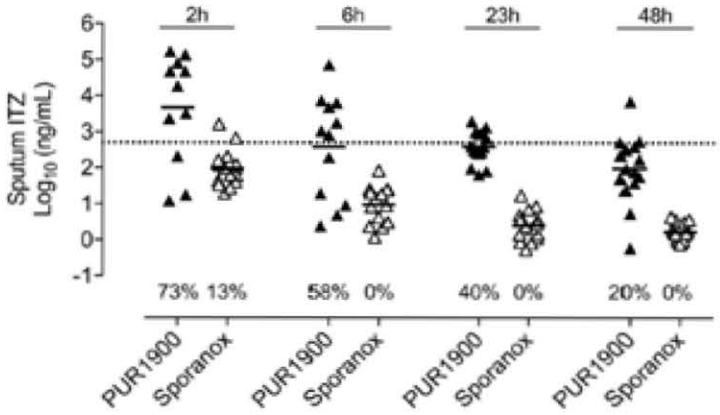
The future?

New therapies in ABPA

Itraconazole DPI for ABPA: Single Dose PK in Asthmatics







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

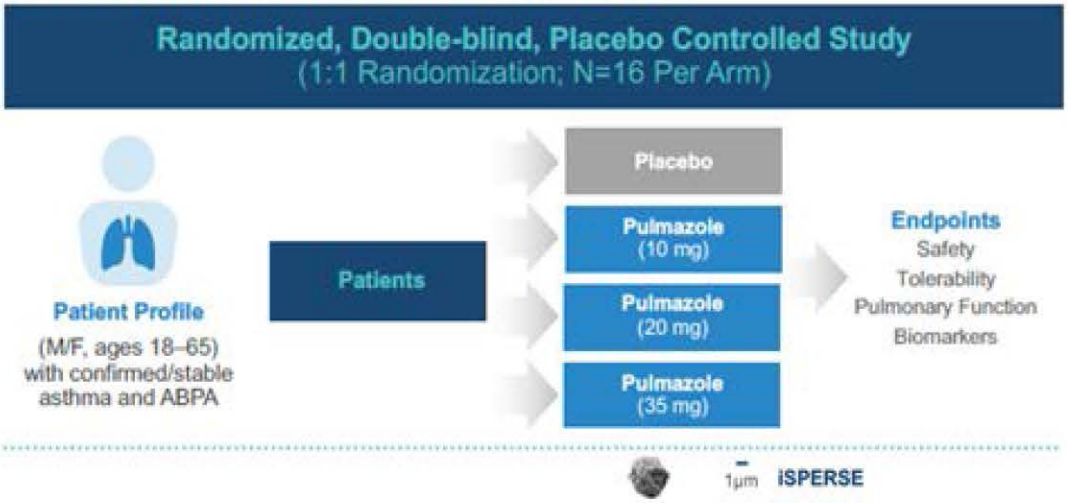
Dotted line at 500 ng/mL = *Af* MIC_{90}

Hava DL et al, Br *J Clin Pharmacol* 2019 Nov 6. doi: 10.1111/bcp.14166

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



Primary Endpoint

- Safety & tolerability
- Biomarkers

Other Endpoints

- Pulmonary function (FEV_1)
- 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

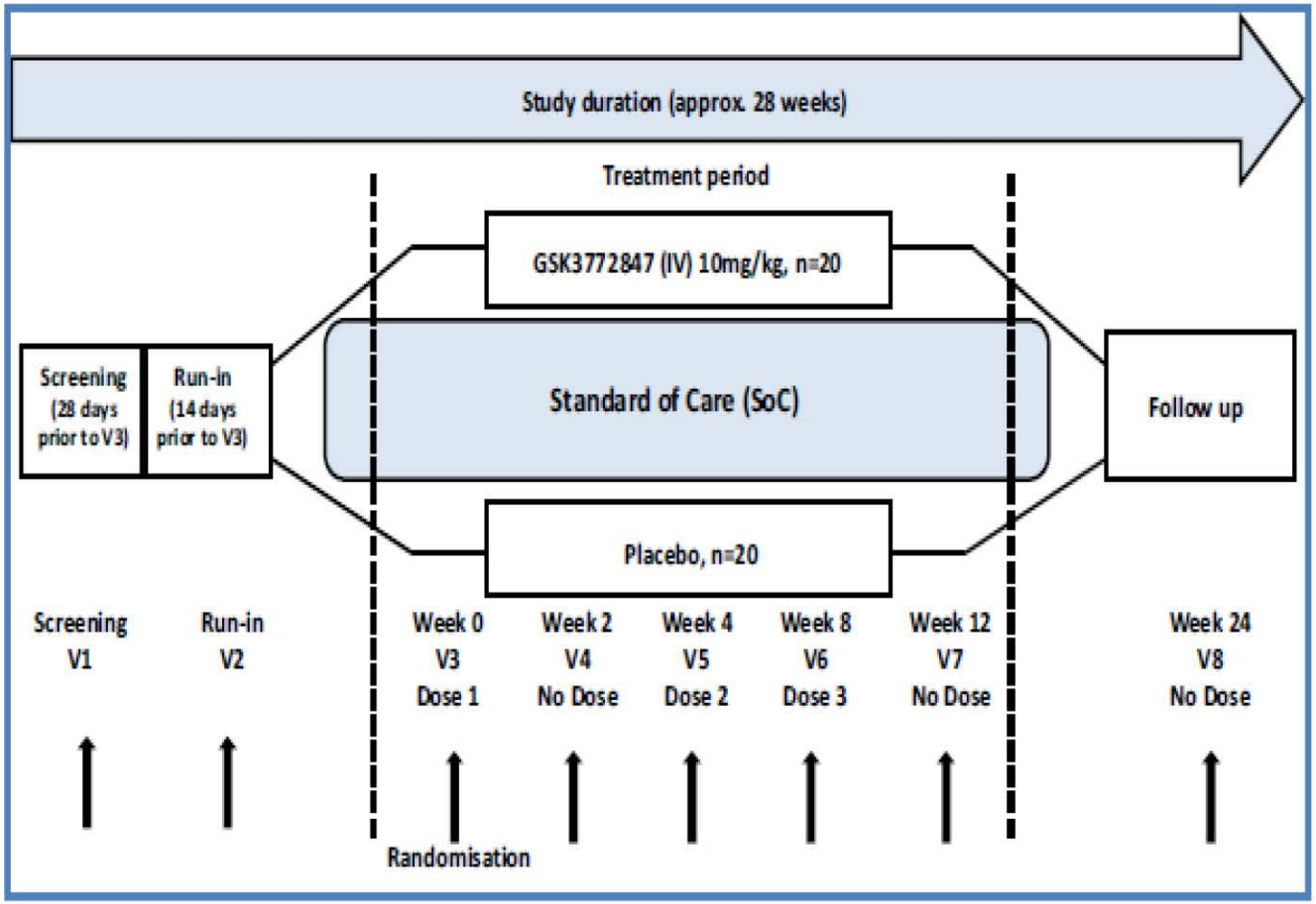
Chishimba et al. *J Asthma* ***49(4):423-433***

- Monoclonal antibody therapy

AFAD trial

Protocol Title: A double blind (sponsor open) placebo-controlled, stratified, parallel group study to evaluate the efficacy and safety of repeat doses of GSK3772847 in participants with moderate to severe asthma with allergic fungal airway disease (AFAD).

- 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
Screening (28 days prior to V3)
Run-in (14 days prior to V3)
Standard of Care (SoC)
Follow up
Placebo, n=20
Screening V1
Run-in V2
Week 0 V3 Dose 1
Week 2 V4 No Dose
Week 4 V5 Dose 2
Week 8 V6 Dose 3
Week 12 V7 No Dose
Week 24 V8 No Dose
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 ≥10 pack years
- Eosinophilic diseases

Table 2 Prohibited Medications

Medication	Time interval prior to Screening
Investigational drug	30 days or 5-half-lives (whichever is longer)
Biologic agents (such as monoclonal antibodies including marketed drugs)	130 days or 5 half-lives whichever is longer
Live or attenuated vaccines	2 weeks
Experimental anti-inflammatory drugs (nonbiologics)	3 months
Corticosteroids intramuscular, long acting depot	3 months
Immunomodulatory/suppressive agents (e.g.	3 months
Methotrexate, troleandomycin, oral or parenteral gold, cyclosporin, azathioprine, cyclophosphamide, tacrolimus, mycophenolate mofetil, D-penicillamine)	
Theophylline	3 months
Chemotherapy and radiotherapy	12 months
Anti-fungal medications (oral)	3 months (see Section 7.7.1 for permitted uses)

Recruitment Target

WORLDWIDE - 46

LOCAL - 5

Actual recruitment

WORLDWIDE - 18

LOCAL - 0

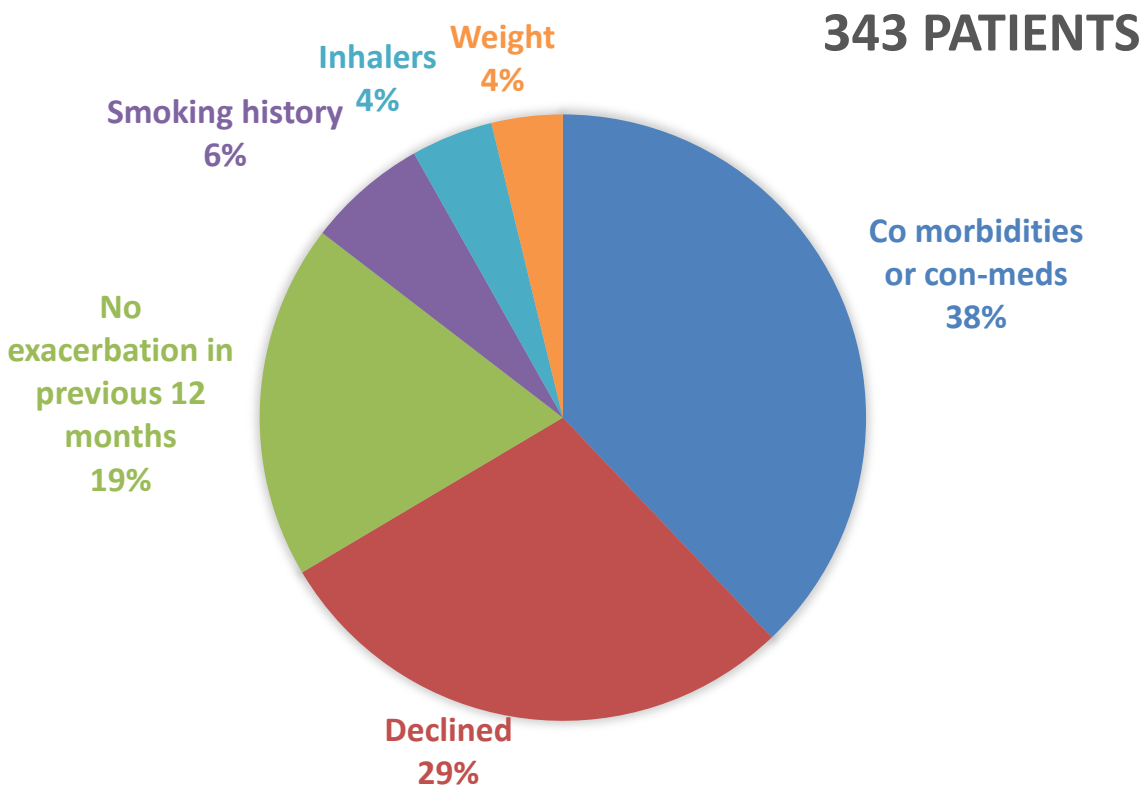
Protocol amendment

Description of Change
Additional therapy: with low dose oral corticosteroid (≤10 mg/day prednisolone or equivalent) is permissible. High dose oral corticosteroid is defined as >10 mg/day prednisolone or equivalent.
Blood eosinophils of 250-299 cells/microliters at screening but with documented evidence of ≥300 cells /microliters within 5 months of screening will be accepted.

Screen fails

- 8 patients failed screening
  - 4 too low FeNO
  - 3 too low eosinophil count
  - 1 smoking history

“Pre screen” fails



Summary

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