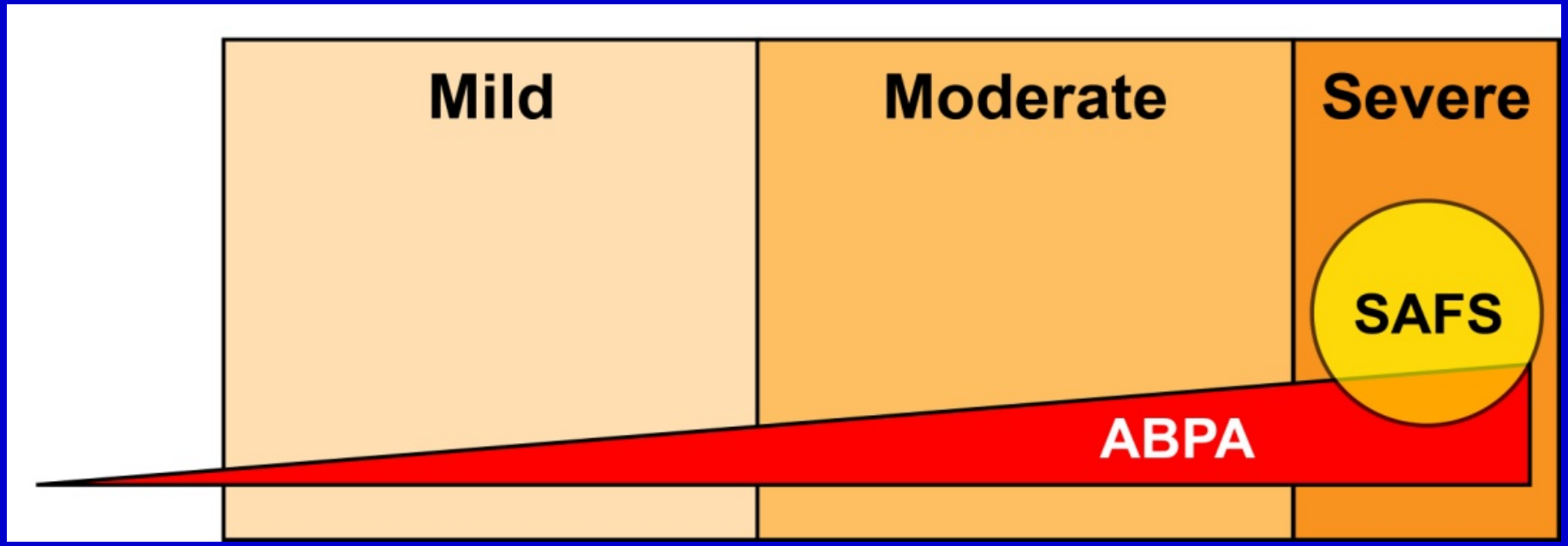
Endpoints for antifungal clinical trials for fungal asthma

David W. Denning
The University of Manchester
Global Action Fund for Fungal Infections

'Fungal asthma'
ABPA versus SAFS



SAFS = severe asthma with fungal sensitisation

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
Exacerbations
Corticosteroid usage/reduction

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

Disease	Antifungal, duration	Benefit?	Author, year
ABPA	Natamycin inh, 52 wks	No	Currie, 1990
ABPA	Itraconazole, 32 wks	Yes	Stevens, 2000
ABPA	Itraconazole, 16 wks	Yes	Wark, 2003
"Trichophyton" asthma	Fluconazole, 20 wks	Yes	Ward, 1999
SAFS	Itraconazole, 32 wks	Yes	Denning, 2009
A. fumigatus-associated asthma	Voriconazole, 12 wks	No	Agbetile, 2014
Acute stage ABPA	Itraconazole, 16 wks	Yes	Agarwal, 2016
Acute stage ABPA	Voriconazole, 16 wks	Yes	Agarwal, 2018
Steroid resistant, severe asthma	Itraconazole, 16 weeks	Yes	Mirsadraee, 2019

The NEW ENGLAND JOURNAL of MEDICINE

A RANDOMIZED TRIAL OF ITRACONAZOLE IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

DAVID A. STEVENS, M.D., HOWARD J. SCHWARTZ, M.D., JEANNETTE Y. LEE, PH.D., BRUCE L. MOSKOVITZ, M.D., DENNIS C. JEROME, M.D., ANTONINO CATANZARO, M.D., DAVID M. BAMBERGER, M.D., ALLISON J. WEINMANN, M.B., B.S., CARMELITA U. TUAZON, M.D., MARC A. JUDSON, M.D., THOMAS A.E. PLATTS-MILLS, M.D., PH.D., AND ARTHUR C. DEGRAFF, JR., M.D.

TABLE 3. DEFINITION OF A RESPONSE IN THE DOUBLE-BLIND TRIAL.*

Reduction in the dose of corticosteroid by 50 percent or more
Decrease in the total IgE concentration by 25 percent or more
At least one of the following
Increase in exercise tolerance by at least 25 percent
Improvement by 25 percent in results of at least one of five pulmonary-function tests†
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‡

*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.

Stevens et al, New Engl J Med 2000; 342:756

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

Stevens et al, New Engl J Med 2000; 342:756

Randomised trial of itraconazole in ABPA

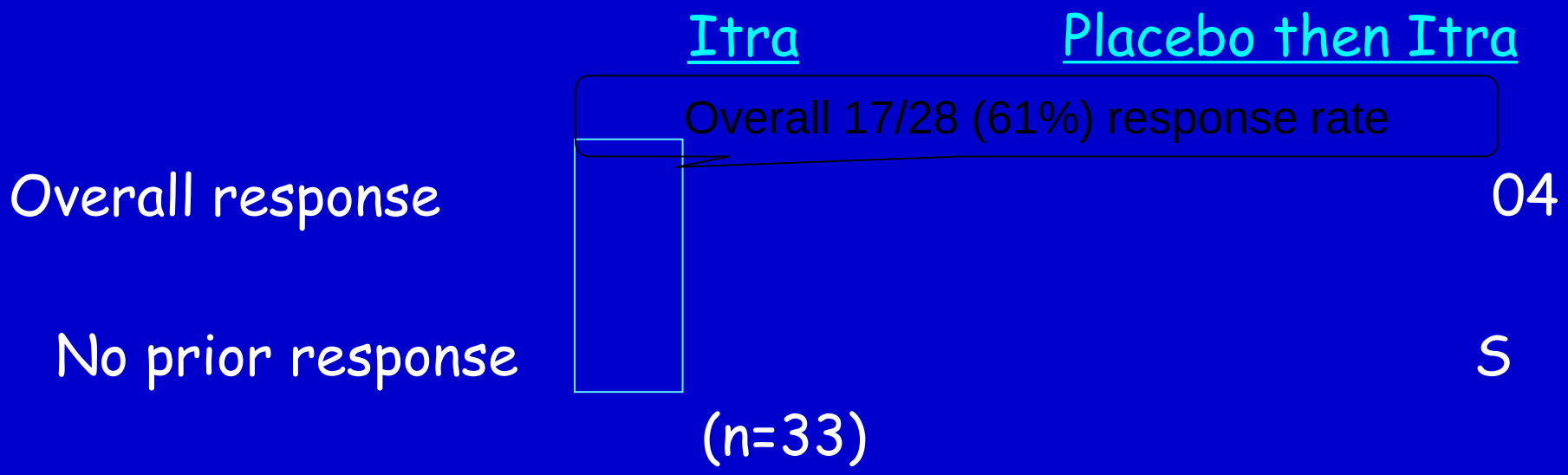
Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

	Itra	Placebo then Itra
	Phase 1	
Overall response	13/28 (46%)	5/27 (19%) p = 0.04
	Phase 2	
No prior response	4/13 (31%) (n=33)	8/20 (40%) NS

Stevens et al, New Engl J Med 2000; 342:756

Randomised trial of itraconazole in ABPA

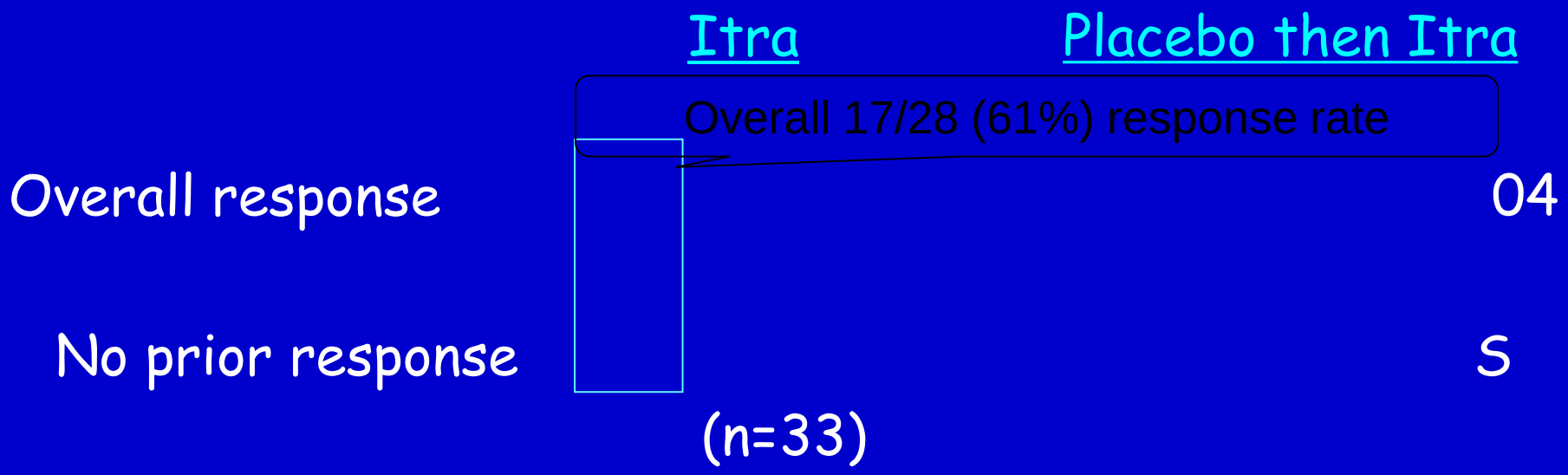
Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks



Stevens et al, New Engl J Med 2000; 342:756

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



Number needed to treat = 3.58

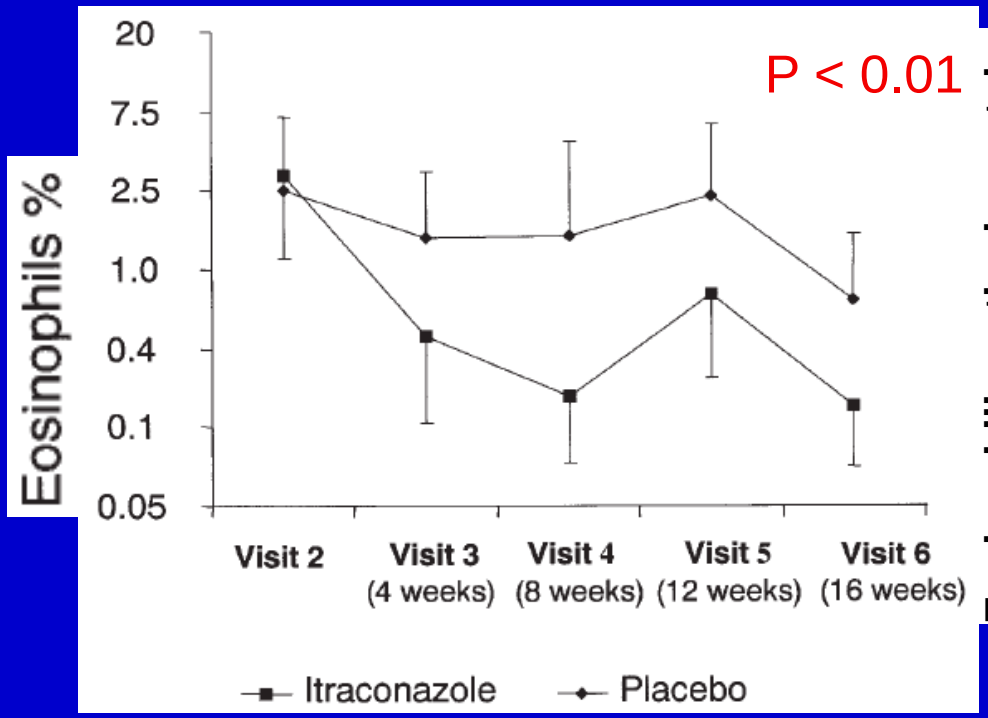
Stevens et al, New Engl J Med 2000; 342:756

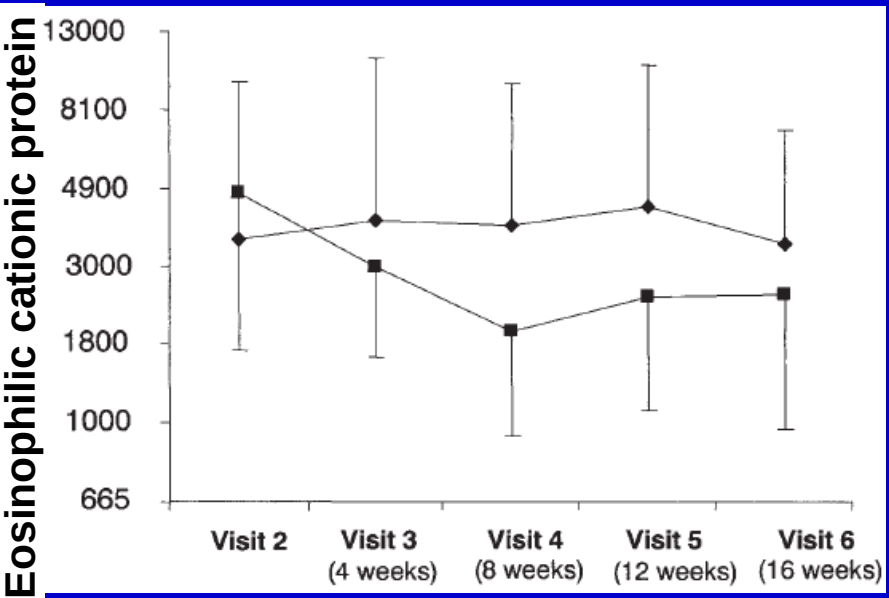
Randomised trial of itraconazole in ABPA

ABPA with asthma, n = 29

Phase 1 - 200mg BID v placebo, 16 weeks

Primary outcome measure – Sputum eosinophil count





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

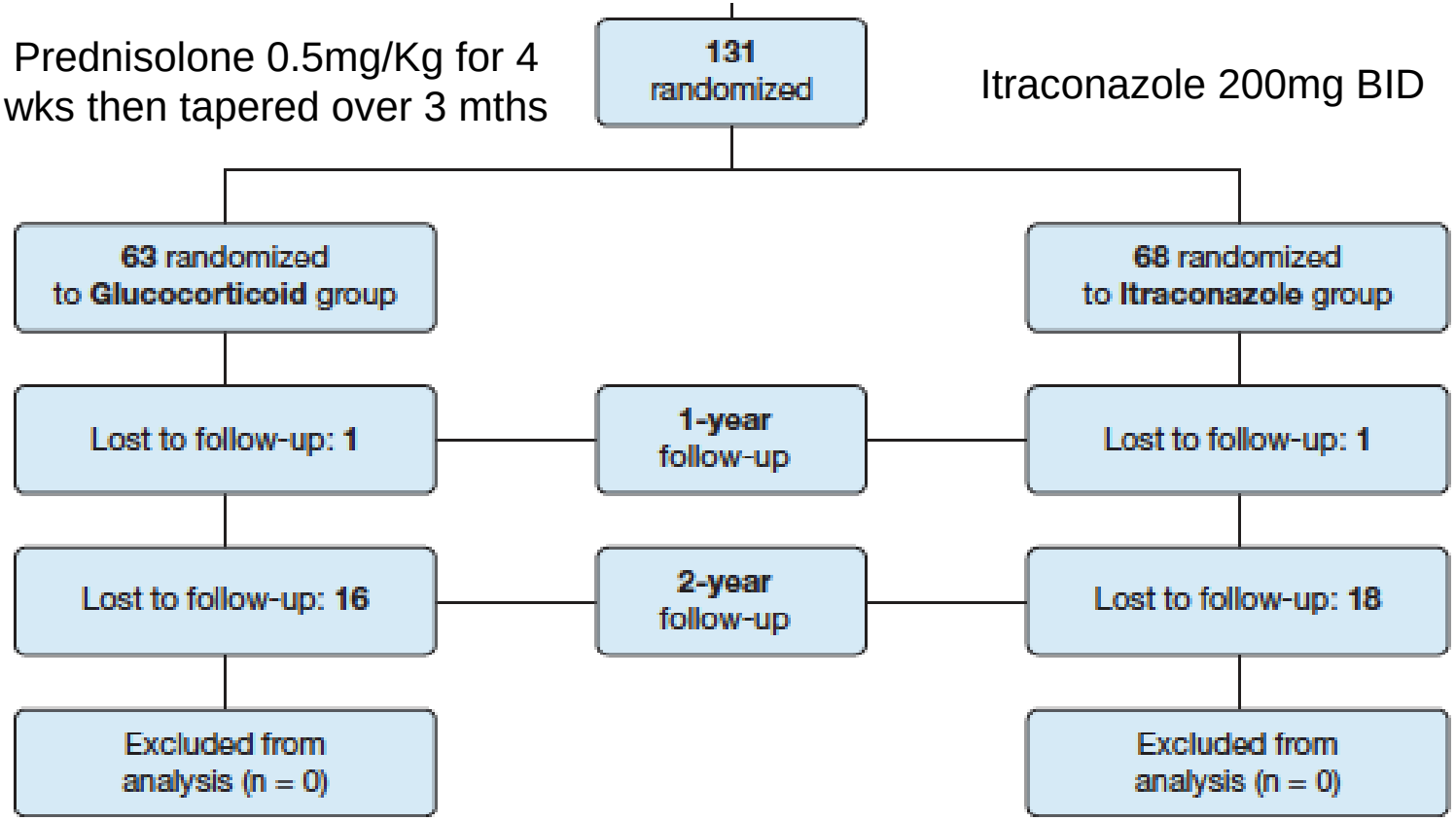
Ward et al, J Allergy Clin Immunol 1999;104:541;

A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

4 months treatment in both arms

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

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



Itraconazole 200mg BID

Agarwal et al, Chest 2018;153:656

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

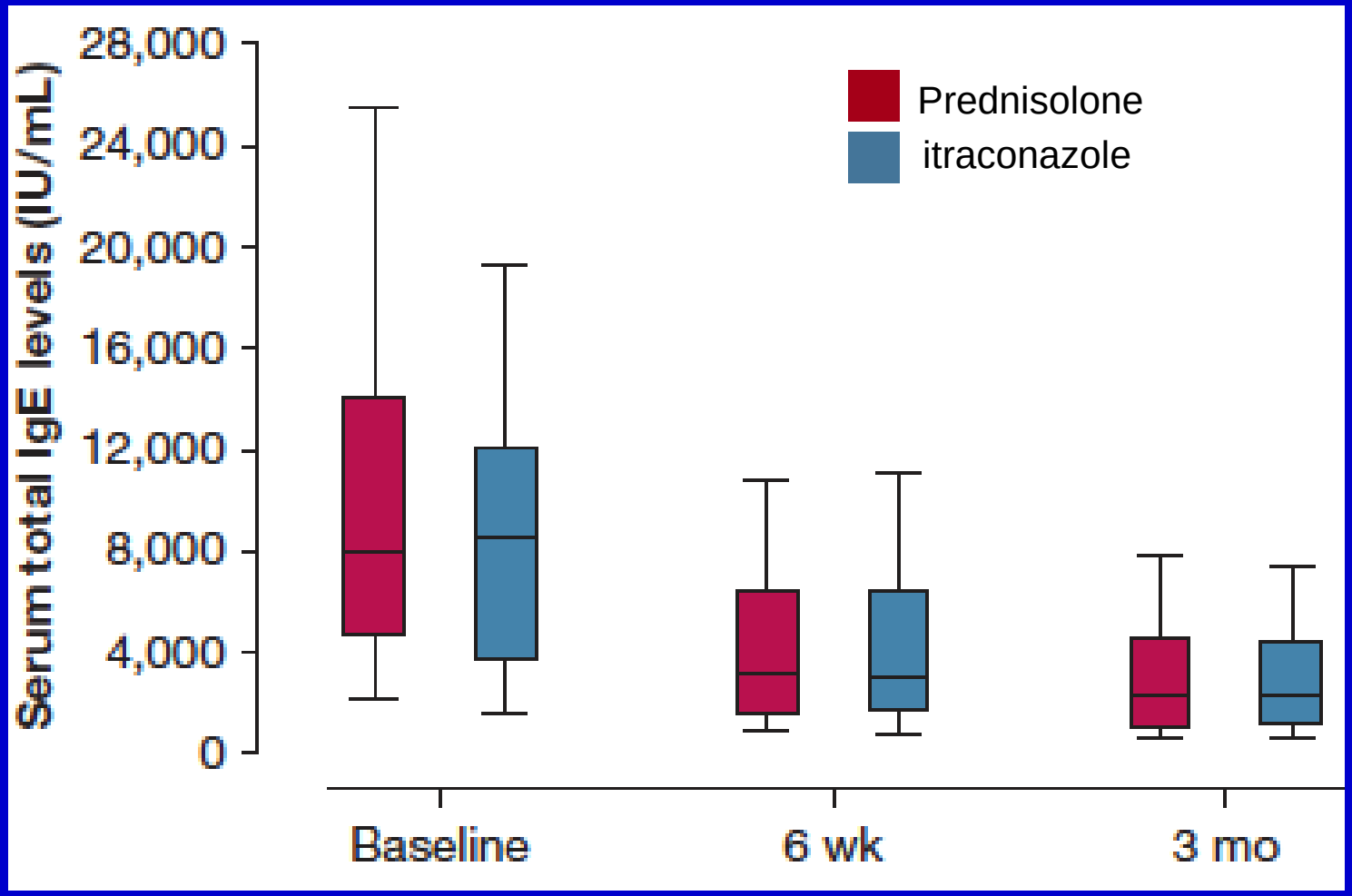
Agarwal et al, Chest 2018;153:656

Primary outcomes

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

Agarwal et al, Chest 2018;153:656

IgE levels over time



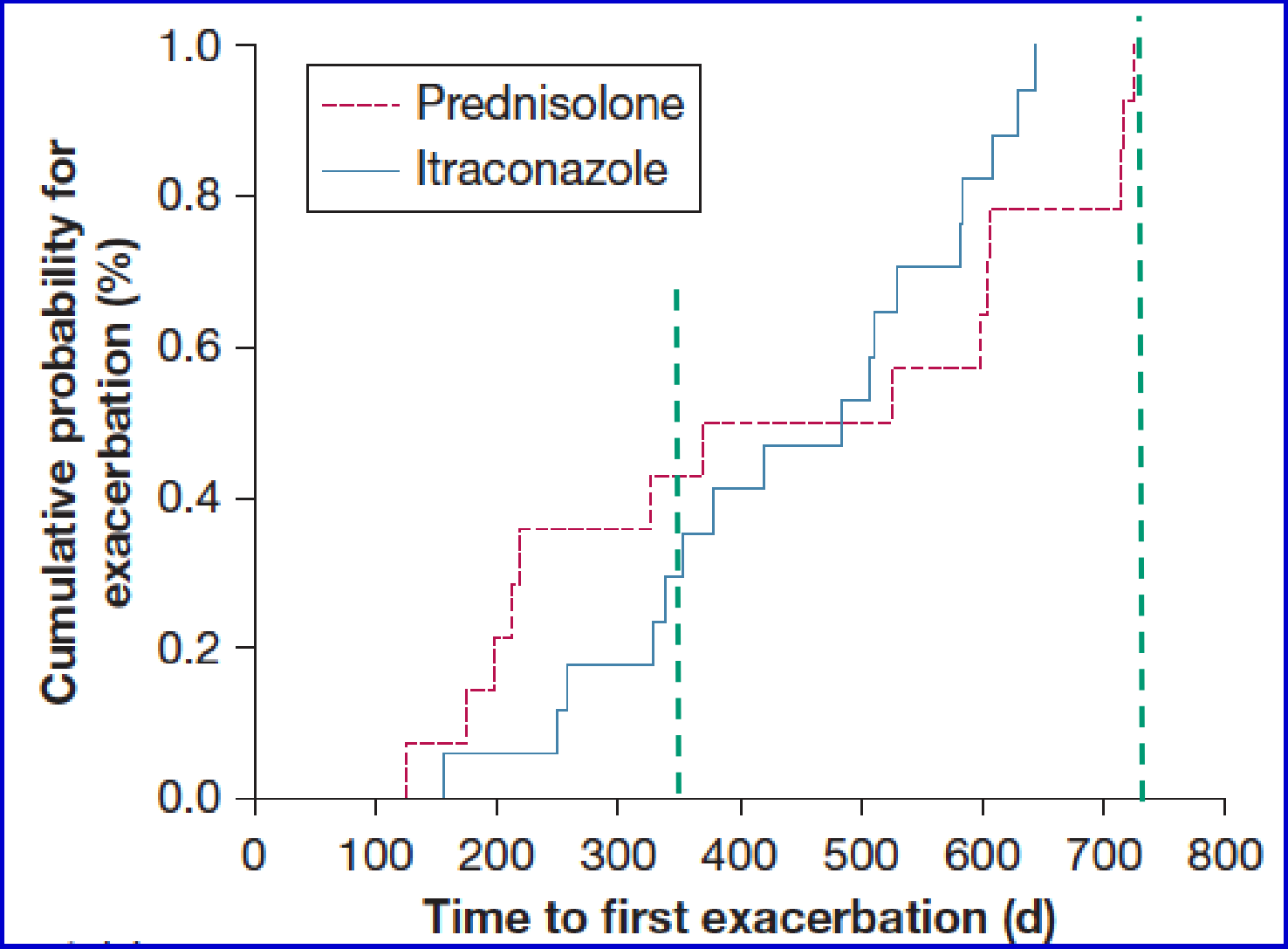
Agarwal et al, Chest 2018;153:656

Primary outcomes

Outcome	Prednisolone Group (n = 63)	Itraconazole Group (n = 68)	Estimated Difference (95% CI)	*P* Value
Secondary outcomes				
Time to first exacerbation (n = 123)	437 (307-567)	442 (369-521)	8 (−76 to 61)	.91
Difference in FEV_1 following 6 wk of treatment (n = 123)	0.33 (0.26-0.41)	0.30 (0.22-0.37)	0.03 (−0.07 to 0.13)	.20
Difference in FVC following 6 wk of treatment (n = 123)	0.37 (0.19-0.54)	0.37 (0.26-0.49)	0.08 (−0.06 to 0.22)	.42
Subjects with exacerbation following 6 mo of treatment	6 (9.5%)	6 (10.0%)	0.01 (−0.11 to 0.12)	.93
Total No. of ABPA exacerbations	0.57 (0.32-0.82)	0.83 (0.48-1.18)	−0.26 (−0.69 to 0.17)	.32
Total No. of asthma exacerbations	0.48 (0.28-0.67)	0.62 (0.36-0.87)	−0.14 (−0.46 to 0.18)	.45

Agarwal et al, Chest 2018;153:656

4 months of therapy and then observation



Agarwal et al, Chest 2018;153:656

Randomized Controlled Trial of Oral Antifungal Treatment for Severe Asthma with Fungal Sensitization

The Fungal Asthma Sensitization Trial (FAST) Study

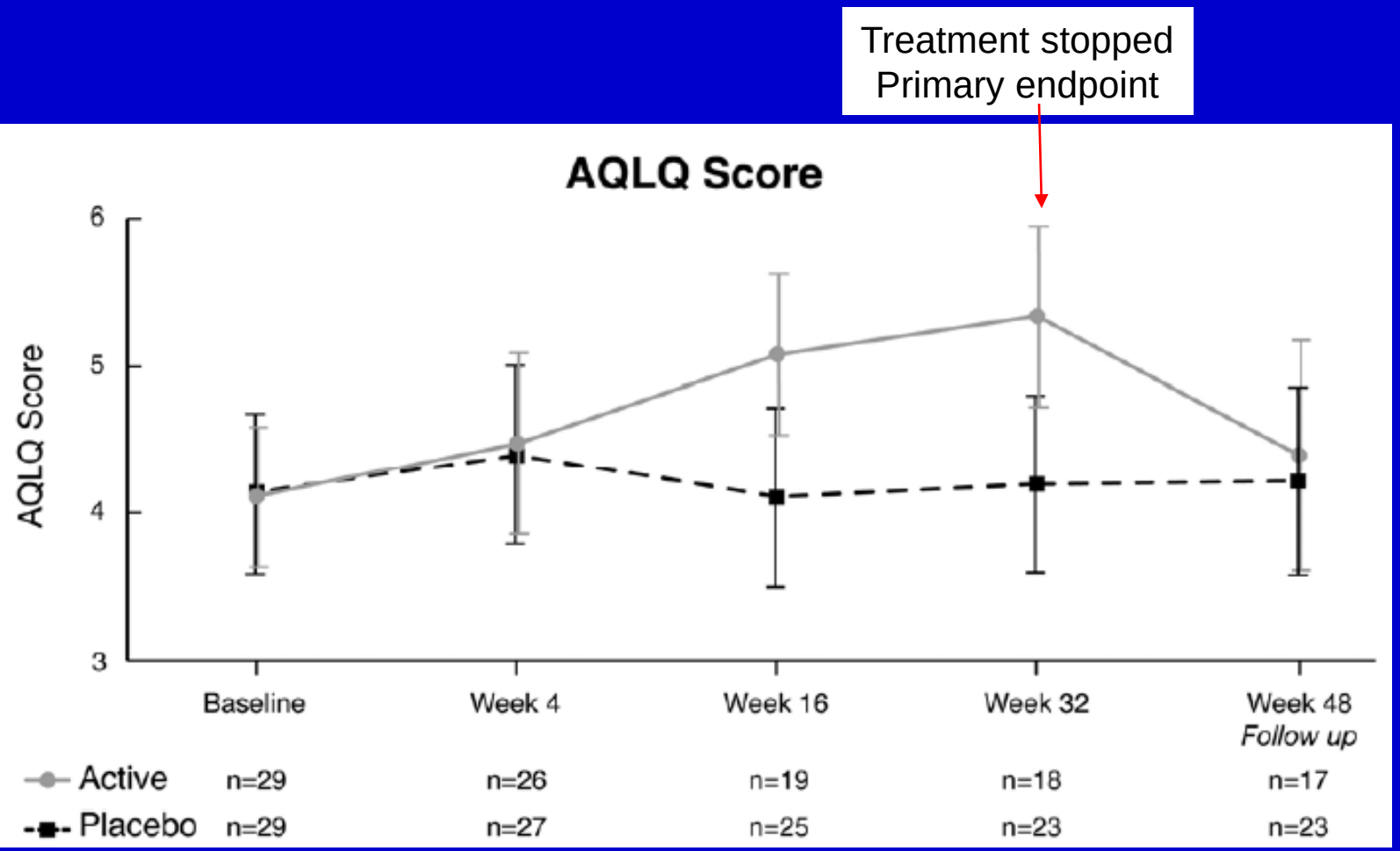
David W. Denning[1,2], B. Ronan O'Driscoll[3], Georgina Powell[1,2], Fiona Chew[1,2], Graham T. Atherton[1,2], Aashish Vyas[4], John Miles[5], Julie Morris[6], and Robert M. Niven[1,2]

Enrolment criteria

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

Denning et al, Am J Resp Crit Care Med 2009; 179:11

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



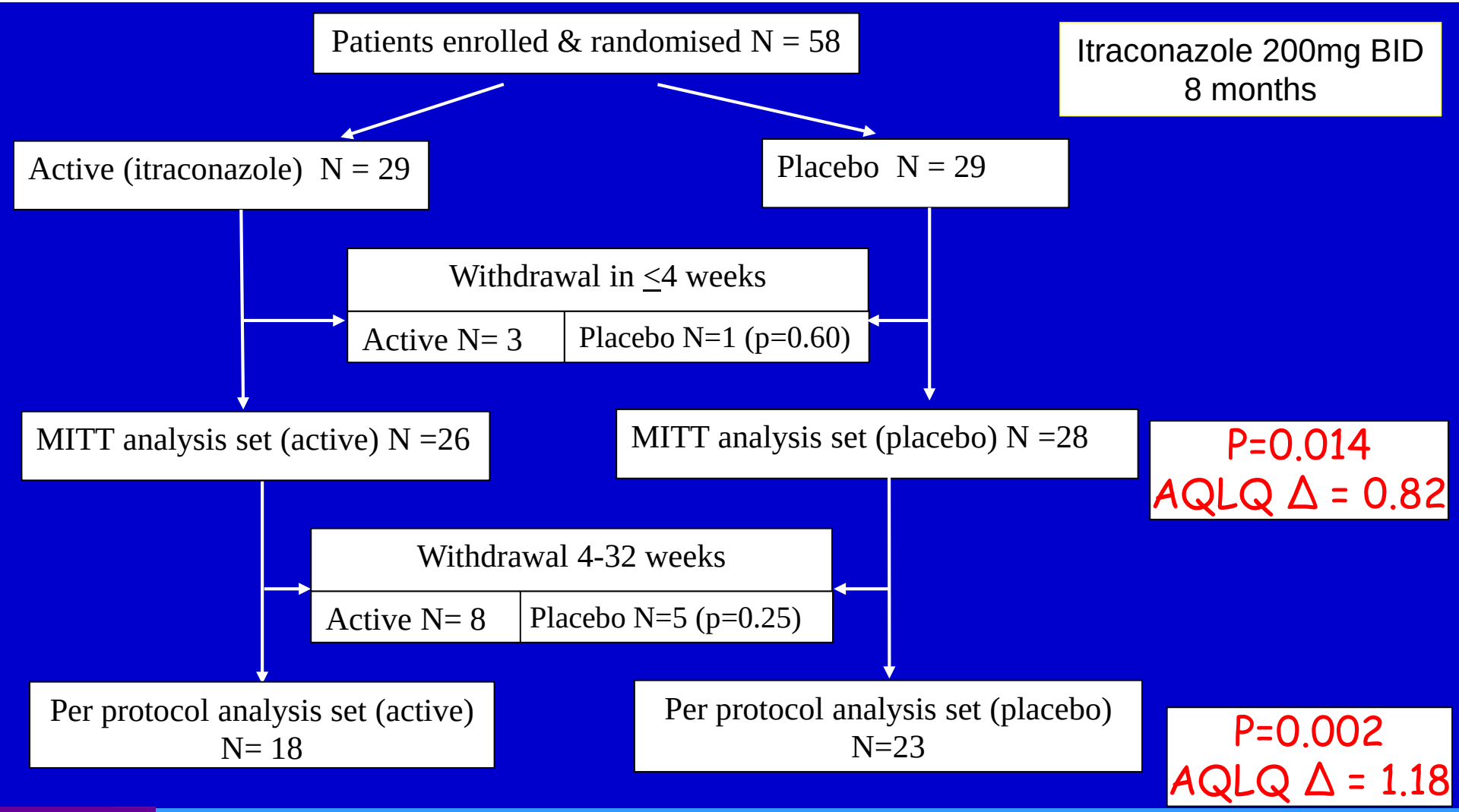
P= 0.014

Denning et al, Am J Resp Crit Care Med 2009; 179:11

Randomized Controlled Trial of Oral Antifungal Treatment for Severe Asthma with Fungal Sensitization

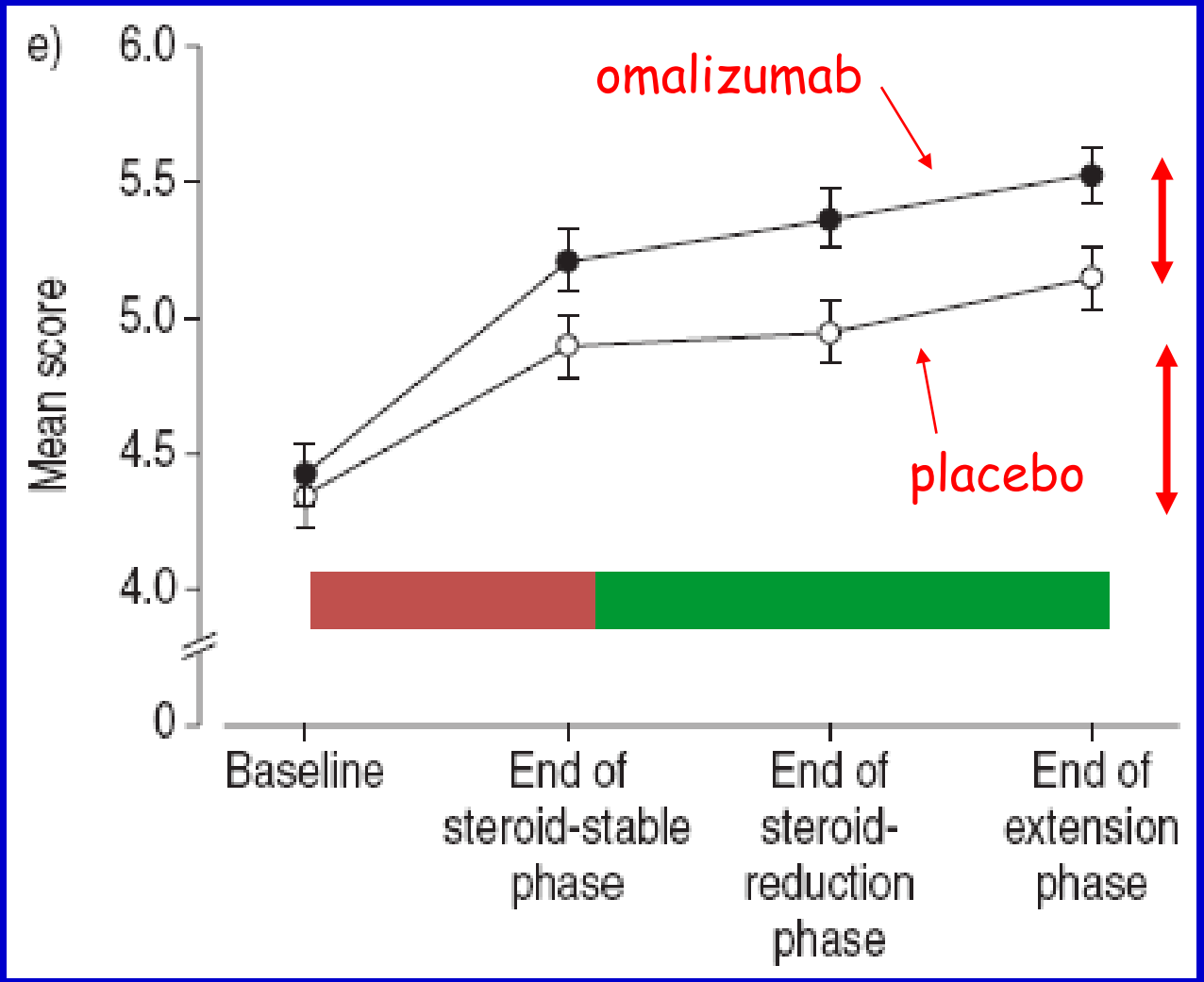
The Fungal Asthma Sensitization Trial (FAST) Study

David W. Denning[1,2], B. Ronan O'Driscoll[3], Georgina Powell[1,2], Fiona Chew[1,2], Graham T. Atherton[1,2], Aashish Vyas[4], John Miles[5], Julie Morris[6], and Robert M. Niven[1,2]



Denning et al, Am J Resp Crit Care Med 2009; 179:11

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



Steroids improvement in AQLQ Δ = ~0.6

Omalizumab improvement in AQLQ Δ = ~0.4

Itraconazole improvement in AQLQ Δ = ~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

	Mean (95% CI) or % (n)		P-value
	Active	Placebo	
Change in AQLQ score	+0.85 (0.28, 1.41)	-0.01 (-0.43, 0.42)	0.014
Improvement in AQLQ score of >0.75	54% (14)	18% (5)	0.013
Percentage change in total IgE (IU/L)	-27% (-14%, -38%)	+12% (-5%, +31%)	0.001
Change in FEV1 (L/min)	-0.22 (-0.56, 0.11)	-0.02 (-0.16, 0.11)	NS
Change in FEV1 (% predicted)	-3.66 (-9.39, 2.08)	0.13 (-3.67, 3.93)	NS
Change in average PEFR (am)	20.8 (3.5, 38.1)	-5.5 (-21.6, 10.7)	0.028
Change in average PEFR (pm)	16.8 (1.5, 35.2)	8.9 (-33.9, 51.8)	NS

Denning et al, Am J Resp Crit Care Med 2009; 179:11

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*

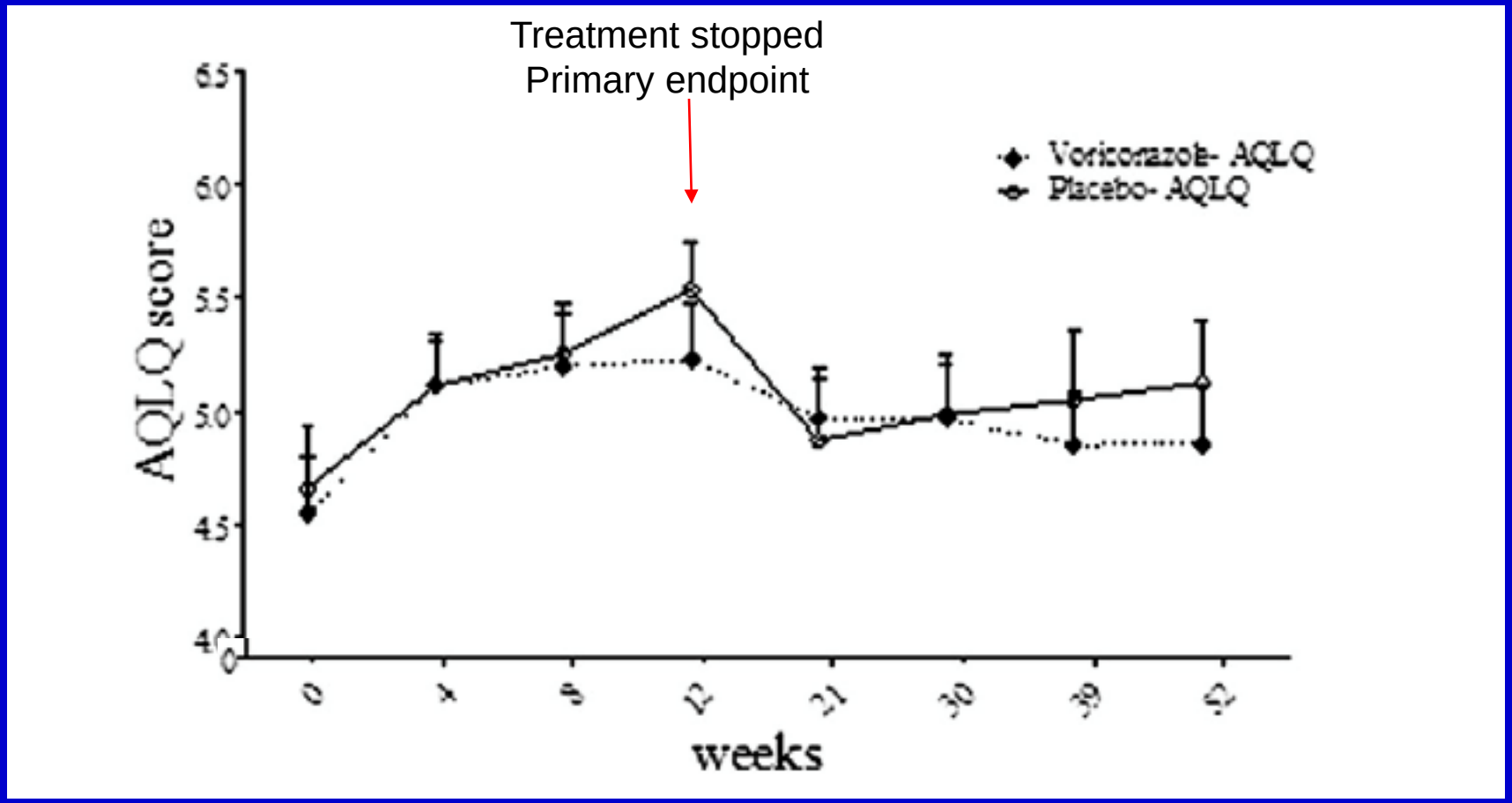
Enrolment criteria

- Asthma
- *A. fumigatus* sensitisation
- 2+ exacerbations in prior year

Agbetile et al, J Allerg Clin Imunol 2014;134:33

Effectiveness of voriconazole in the treatment of *Aspergillus fumigatus*–associated asthma (EVITA3 study)

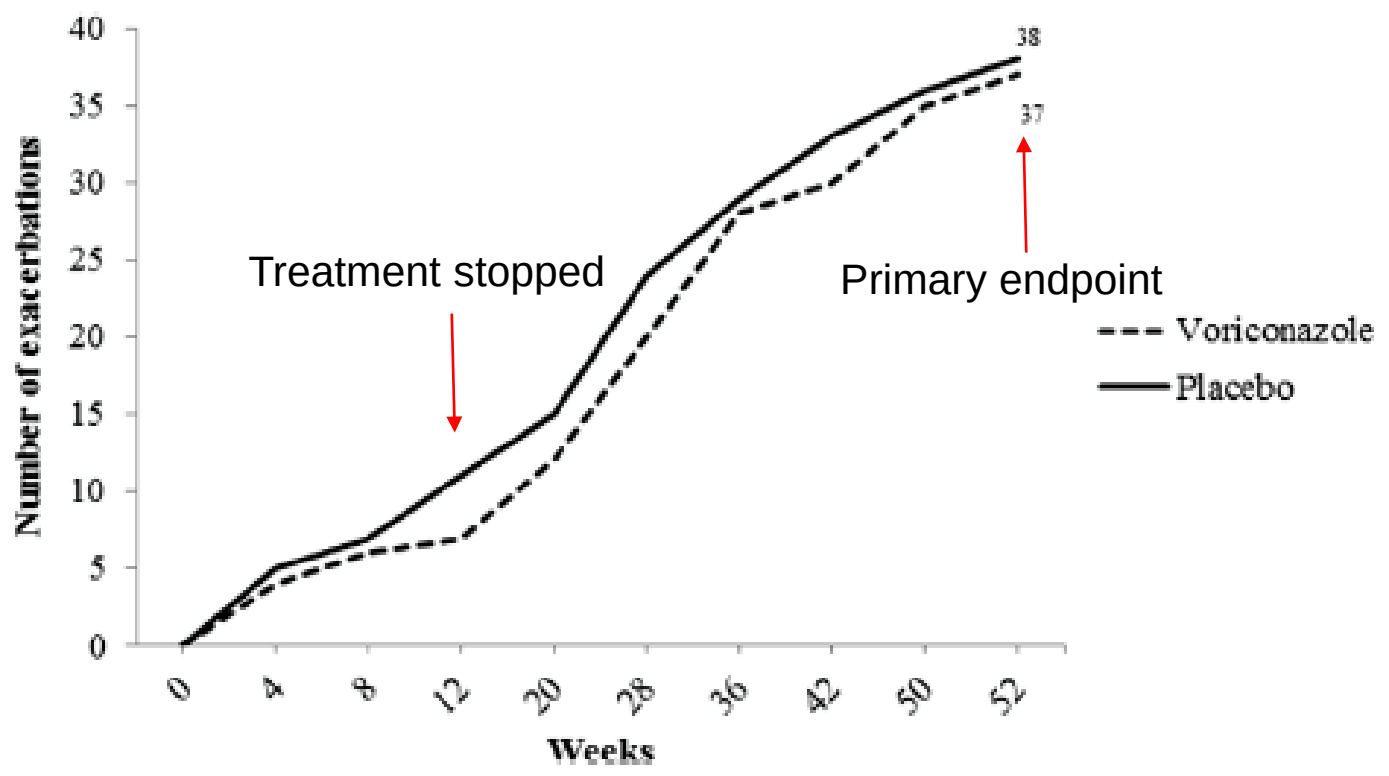
Joshua Agbetile, MD, Michelle Bourne, RGN, Abbie Fairs, PhD, Beverley Hargadon, RGN, Dhananjay Desai, MD, Clare Broad, Joseph Morley, BSc, Peter Bradding, DM, FRCP, Christopher E. Brightling, PhD, FRCP, Ruth H. Green, DM, FRCP, Pranabashis Haldar, DM, MRCP, Catherine H. Pashley, PhD, Ian D. Pavord, DM,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



Agbetile et al, J Allerg Clin Imunol 2014;134:33

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*



Agbetile et al, J Allerg Clin Imunol 2014;134:33

Current Medical Mycology

2019, 5(4): 1-7

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

Majid Mirsadraee[1*], Sanaz Dehghan[2], Shadi Ghaffari[3], Niloofar Mirsadraee[4]

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

†=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)

Current Medical Mycology

2019, 5(4): 1-7

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

Majid Mirsadraee[1*], Sanaz Dehghan[2], Shadi Ghaffari[3], Niloofar Mirsadraee[4]

	Before trial		After one month		After 4 months
	Itraconazole	Prednisolone	Itraconazole	Prednisolone	Itraconazole
FVC (L)	1.6±0.92	1.8±0.7	2.3±0.87†‡	1.69±0.68	3.1±1.84‡
FVC percent	55.2±22.23	60.3±16.65	71.8±18.8†‡	57.7±21.8	79±39‡
FEV1 (L)	1.3±0.73	1.14±0.45	1.9±0.8†‡	1.1±0.2	2.4±1.51‡
FEV1 percent	50.16±22.7	48.2±15.4	71.5±21.8†‡	47.8±17.9	82.5±30.4‡
FEV1/FVC	72.8±12.61	72.1±15.39	79.1±12.7†‡	64.7±10.3	89.5±0.7‡
FENO (PPM)	36.8±29.2	28.6±25.2	34.6±26.5	35.2±22.1	29±17.9
Lukocyte count	9129±3378.8	9900±3093	8900±2524	9000±1414	8397±1596
Eosinophile count	446±699.9	703±676.1	682±773	180±28	1016±203
Eosinophile percent	5.7±7.11	10±12.5	8.1±9.4	2±0.4	5.1±7.5
Serum IgE	482±670	323±88	424±442	332±882	571±116

†=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