EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

A randomized trial of voriconazole and prednisolone monotherapy in acute-stage ABPA complicating asthma

Ritesh Agarwal, Sahajal Dhooria, Inderpaul Singh Sehgal, Ashutosh N. Aggarwal, Mandeep Garg, Biman Saikia, Arunaloke Chakrabarti

Please cite this article as: Agarwal R, Dhooria S, Singh Sehgal I, *et al*. A randomized trial of voriconazole and prednisolone monotherapy in acute-stage ABPA complicating asthma. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01159-2018).

RESEARCH LETTER

A randomized trial of voriconazole and prednisolone monotherapy in acute-stage ABPA complicating asthma

[3]Ritesh Agarwal MD, DM
[1]Sahajal Dhooria MD, DM
[1]Inderpaul Singh Sehgal MD, DM
[3]Ashutosh N. Aggarwal MD, DM
[2]Mandeep Garg MD[*]
[3]Biman Saikia MD[#]
[3]Arunaloke Chakrabarti MD[§]

[1]Assistant Professor, [2]Additional Professor and [3]Professor
Department of Pulmonary Medicine, Department of Radiodiagnosis and Imaging[*], Department of Immunopathology[#] and Department of Medical Microbiology[§]
Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Address for Correspondence
Dr. Ritesh Agarwal MD, DM
Professor
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research (PGIMER)
Chandigarh. India. 160012
Phone: +91 172 275 6825 (Work)
Fax: +91 172 274 8215
Email: agarwal.ritesh@outlook.in

Funding: Cipla pharmaceuticals (Mumbai, India). The funding agency provided the study drugs but had no role in the study design, data collection, data analysis or preparation of the manuscript.

Take home message

Voriconazole monotherapy is as effective and safer than glucocorticoids in the treatment of allergic bronchopulmonary aspergillosis

Glucocorticoids are the most widely used agents in the treatment of allergic bronchopulmonary aspergillosis (ABPA), a disorder characterized by immunologic reactions mounted against *Aspergillus fumigatus* colonizing the airways of patients with asthma and cystic fibrosis.[1, 2] Unfortunately, the use of glucocorticoids is associated with several adverse reactions.[3] A novel treatment strategy in ABPA would be the use of antifungal triazoles as monotherapy. Recently, we have shown that itraconazole was effective as monotherapy in acute-stage ABPA.[4] Whether voriconazole monotherapy is also efficacious in acute-stage ABPA remains unknown.

We conducted a single-center, unblinded, randomized controlled trial between January 2014 and July 2015 in the Chest Clinic of this Institute. The Institute Ethics Committee approved the study protocol, and written consent was obtained from all subjects. The study was registered at clinicaltrials.gov (NCT01621321). We included consecutive subjects of ABPA, if they met all the following: (a) asthma; (b) immediate cutaneous hyperreactivity to *Aspergillus* antigen; (c) elevated total IgE >1000 IU/mL; (d) *A.fumigatus*-specific IgE >0.35 kUA/L; and two of the ensuing: (a) presence of serum precipitins against *A fumigatus*; (b) fixed or transient radiographic pulmonary opacities; (c) peripheral blood eosinophil count >1000 cells/µL; (d) bronchiectasis on CT chest.[5] We excluded the following: (a) failure to provide consent; (b) intake of systemic glucocorticoids or azoles for >3 weeks in the preceding 6 months; (c) omalizumab therapy; (d) immunosuppressive therapy and immunosuppressive states; (e) enrollment in another trial of ABPA; and, (f) pregnancy.

Subjects were randomized 1:1 sequentially using a computer-generated randomization sequence (assignments placed in opaque sealed envelopes) to either the voriconazole or the glucocorticoid group (Figure 1). Patients in the glucocorticoid arm received oral prednisolone (Omnacortil tablets, Macleod's Pharmaceuticals, India) 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks; then tapered by 5 mg/2 weeks and discontinued (total duration, 4 months)**.** In the voriconazole arm, subjects received oral voriconazole (Voritek capsules, Cipla, India) 200 mg twice daily one hour before or after a meal, for 4 months**.** Adherence to

therapy was ensured by instructing patients to bring the empty pill covers. We also measured voriconazole levels at 6 weeks and 3 months. For the control of asthma, treatment with inhaled corticosteroids, long-acting β2 agonists (formoterol) and montelukast, was allowed in both groups. We recorded the demographic, clinical, immunological, spirometric and radiological details, at the baseline visit. The subjects were followed with clinical examination, chest radiograph and serum total IgE every 6 weeks for 6 months. At the first follow-up visit, we also performed spirometry and assessed the health status using the St. George's Respiratory Questionnaire (SGRQ) score. Subsequently, the patients were followed up every 6 months, or earlier if there was worsening in symptoms. We clinically evaluated all the subjects for adverse reactions and also monitored fasting plasma glucose, blood pressure and liver function test every 6 weeks.

The treatment effects were classified as: (a) **composite response**: improvement in cough and dyspnea (>75% of baseline) accompanied by at least 50% clearance of chest radiographic opacities (if present prior to treatment initiation) along with decline in serum total IgE by ≥25%, after six weeks of treatment;[4, 6] (b) **ABPA exacerbation**: clinical and/or radiological worsening along with doubling of the serum total IgE over the previous baseline value; and, (c) **asthma exacerbation**: clinical worsening in cough and dyspnea with no radiological worsening or doubling of serum total IgE. The first ABPA exacerbation in both the arms was treated with oral prednisolone at a dose of 0.5 mg/kg/day for 4 weeks, 0.25 mg/kg/day for 4 weeks, 0.125 mg/kg/day for 4 weeks, then decreased by 5 mg/2 weeks (total of 4 months). All subsequent exacerbations were treated with prednisolone at the dose above along with itraconazole 400 mg/day for 6 months. Asthma exacerbations were treated with oral prednisolone 0.5 mg/kg/day for 5-7 days.[7] The ***primary outcomes*** were: (a) composite response rates in the two groups after initiation of treatment (6 weeks and 3 months); and (b) ABPA exacerbation rates in the two groups after completion of treatment (12 and 24 months). The ***secondary outcomes*** were: (a) treatment-related adverse effects in the two groups.

Fifty subjects (Figure 1) were randomized to receive either prednisolone (n=25) or voriconazole (n=25). The baseline characteristics including the immunological parameters were similar in the two groups (Supplemental Table 1). The participants were followed up for a mean (SD) of 77 (32) months; however, all analyses were performed till 2 years of follow-up. The proportion of subjects demonstrating a composite response after 6 weeks and 3 months (prednisolone vs. voriconazole, 25 [100%] vs. 24 [96%]; p=0.31) was similar in the two groups (Figure 1). The trough levels of voriconazole were >1, >0.5 and <0.5 mg/L in 19, 3 and 3 subjects, respectively. In the only subject who failed initial treatment with voriconazole, the drug levels were in the therapeutic range (>1 mg/L). The numbers of subjects with exacerbations after 1 and 2 years were similar in the two groups (Figure 1). The incidence of adverse events in the two groups is shown in Figure 1. The occurrence of cushingoid habitus and weight gain were significantly higher in the glucocorticoid group. Transient derangements in liver functions occurred in eight (32%) subjects in the voriconazole group. Three subjects each receiving voriconazole developed transient visual disturbance and photosensitive skin rash (disappeared after avoidance of sunlight exposure). The percentage decline in IgE and the change in lung function was similar in the two groups after six weeks of treatment (Figure 1). There was a considerable decline in SGRQ score at six weeks (mean, 23.9), and was not different in the two groups (Figure 1). The time to first exacerbation (prednisolone vs. voriconazole; mean, 339 vs. 248 days) was similar in the two groups (Figure 1). The total number of asthma and ABPA exacerbations was also similar in the two groups at two-year follow-up.

Only a few randomized trials have evaluated triazoles in patients with ABPA. Two small placebo-controlled trials have previously demonstrated the usefulness of itraconazole (400 mg/day for 4 months) in glucocorticoid-dependent ABPA.[8, 9] Recently, we have published the results of itraconazole monotherapy in acute-stage ABPA complicating asthma.[4] In that study, 131 patients with ABPA were randomized to receive either itraconazole 400 mg/day or prednisolone for 4 months.[4] While prednisolone was superior to itraconazole in inducing a composite response,

itraconazole was also effective in a considerable number (88%). The exacerbation rate at two years was also similar in the two groups.[4] The efficacy of voriconazole monotherapy in the current study was 96%, which is higher than the efficacy of itraconazole.[4] The better outcomes with voriconazole (vs. itraconazole) could be due to its better intrinsic activity against *A.fumigatus*, lesser incidence of resistance or due to better bioavailability.[10]

Finally, our study has a few limitations. This was a single-center, unblinded study with a small sample size (156 subjects were required for the current study to have a 90% power of detecting significance at the 5% level). Thus, our conclusions are hypothesis-generating. For instance, there was a trend towards lesser time to first exacerbation, and more ABPA and asthma exacerbations in the voriconazole arm, which might have proved statistically significant had we included a larger study population. Finally, we used a fixed dose of voriconazole and did not adjust the dose based on levels.

In conclusion, voriconazole appears to be as effective as glucocorticoids in acute-stage ABPA. Larger trials are required to confirm our study results.

AUTHOR CONTRIBUTIONS

RA- conceived the idea, involved in patient management, drafted and revised the manuscript for intellectual content
SD- involved in patient management and data collection, revised the manuscript for intellectual content
ISS- involved in patient management, revised the manuscript
ANA- involved in patient management, statistical analysis, revised the manuscript for intellectual content
MG- involved in patient management, revised the manuscript
BS- involved in patient management, revised the manuscript
DB- involved in patient management, revised the manuscript
AC- involved in patient management, revised the manuscript for intellectual content

AUTHOR DISCLOSURES

RA- has received consultancy fees from Pulmatrix Inc., USA
SD- none
ISS- none
ANA- none
MG- none
BS- none
AC- none

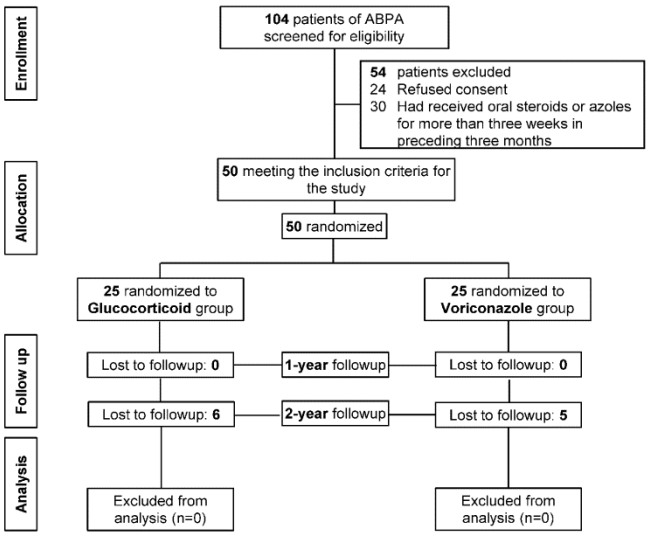
REFERENCES

1. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, Moss R, Denning DW, group AcaIw. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013: 43(8): 850-873.
2. Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Expert Rev Respir Med* 2016: 10(12): 1317-1334.
3. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. *Expert Opin Drug Saf* 2016: 15(4): 457-465.
4. Agarwal R, Dhooria S, Singh Sehgal I, Aggarwal AN, Garg M, Saikia B, Behera D, Chakrabarti A. A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma. *Chest* 2018: 153(3): 656-664.
5. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest* 2006: 130(2): 442-448.
6. Agarwal R, Aggarwal AN, Dhooria S, Singh Sehgal I, Garg M, Saikia B, Behera D, Chakrabarti A. A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J* 2016: 47(2): 490-498.
7. Agarwal R, Dhooria S, Aggarwal AN, Maturu VN, Sehgal IS, Muthu V, Prasad KT, Yenge LB, Singh N, Behera D, Jindal SK, Gupta D, Balamugesh T, Bhalla A, Chaudhry D, Chhabra SK, Chokhani R, Chopra V, Dadhwal DS, D'Souza G, Garg M, Gaur SN, Gopal B, Ghoshal AG, Guleria R, Gupta KB, Haldar I, Jain S, Jain NK, Jain VK, Janmeja AK, Kant S, Kashyap S, Khilnani GC, Kishan J, Kumar R, Koul PA, Mahashur A, Mandal AK, Malhotra S, Mohammed S, Mohapatra PR, Patel D, Prasad R, Ray P, Samaria JK, Singh PS, Sawhney H, Shafiq N, Sharma N, Sidhu UP, Singla R, Suri JC, Talwar D, Varma S. Guidelines for diagnosis and management of bronchial asthma: Joint ICS/NCCP (I) recommendations. *Lung India* 2015: 32(Suppl 1): S3-S42.
8. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, Bamberger DM, Weinmann AJ, Tuazon CU, Judson MA, Platts-Mills TA, DeGraff AC, Jr. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000: 342(11): 756-762.
9. Wark PA, Hensley MJ, Saltos N, Boyle MJ, Toneguzzi RC, Epid GD, Simpson JL, McElduff P, Gibson PG. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. *J Allergy Clin Immunol* 2003: 111(5): 952-957.
10. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin Infect Dis* 2003: 36(5): 630-637.

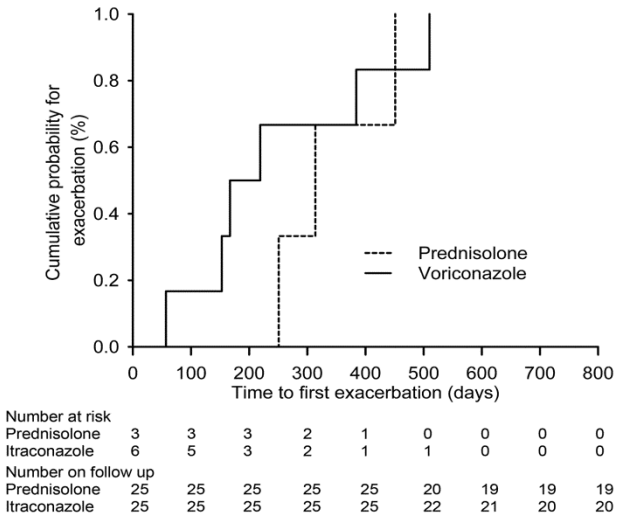
LEGEND TO FIGURES

Figure 1: **(a)** CONSORT diagram demonstrating the flow of participants in the study; **(b)** Time to first exacerbation in subjects receiving voriconazole (solid line) versus prednisolone (dotted line) in subjects with ABPA. The time to first exacerbation was similar in the two groups. The number at risk in each group denotes the numbers of patients still at risk of experiencing the first exacerbation; **(c)** Outcomes of study subjects treated with prednisolone or voriconazole. All values are presented as n (%) or mean (95% CI) unless otherwise stated. ABPA- allergic bronchopulmonary aspergillosis; CI- confidence intervals; FEV1- forced expiratory volume in the first second; FVC- forced vital capacity

a)



b)



Number at risk									
Prednisolone	3	3	3	2	1	0	0	0	0
Itraconazole	6	5	3	2	1	1	0	0	0
Number on follow up									
Prednisolone	25	25	25	25	25	20	19	19	19
Itraconazole	25	25	25	25	25	22	21	20	20

c)

	Prednisolone group (n=25)	Voriconazole group (n=25)	Estimate difference (95% CI)	P value
Primary outcomes				
Subjects with composite response				
After 6 weeks of treatment	25 (100%)	24 (96.0%)	0.04 (-0.10 – 0.20)	0.31
After 3 months of treatment	25 (100%)	24 (96.0%)	0.04 (-0.10 – 0.20)	0.31
Number of subjects experiencing exacerbation				
After 12 months of treatment	2 (8.0%)	3 (12.0%)	0.04 (-0.23 – 0.15)	0.64
After 24 months of treatment	3 (12.0%)	5 (20.0%)	0.08 (-0.29 – 0.13)	0.44
Other outcomes				
Percentage decline in IgE after 6 weeks of treatment	47.9 (37.3-58.4)	45.4 (36.4-54.4)	2.48 (-11.04 – 16.00)	0.66
Time to first exacerbation	339 (85-593)	248 (73-424)	91 (12 – 170)	0.30
Difference in FEV1 (mL) after 6 weeks of treatment	271 191-350)	370 (205-536)	-99 (-269 – 71)	0.69
Difference in FVC (mL) after 6 weeks of treatment	312 (234-389)	395 (262-528)	-83 (-229 – 63)	0.67
Change in score after 6 weeks of treatment	-25.1 (-17.9 to -32.3)	-22.7 (-14.2 to -31.3)	2.4 (-8.3 – 13.1)	0.99
Total number of ABPA exacerbations	0.24 (0.02-0.46)	0.52 (0.23-0.81)	-0.28 (-0.63 – 0.07)	0.12
Total number of asthma exacerbations	0.36 (0.13-0.59)	0.48 (0.27-0.69)	-99 (-0.43 – 0.19)	0.32
Adverse reactions				
Cushingoid habitus	11 (44.0%)	0	0.44 (0.22 – 0.63)	0.0001
Hypertension	0	0	-	-
Hyperglycemia	0	0	-	-
Hypertrichosis	2 (8.0%)	0	0.08 (-0.07 – 0.25)	0.49
Acne	2 (8.0%)	0	0.08 (-0.07 – 0.25)	0.49
Striae	1 (4.0%)	0	0.04 (-0.10 – 0.20)	0.99
Weight gain (%) at six weeks	6.9 (3.7 to 10.3)	0.74 (-1.4 to 2.9)	6.23 (2.14 – 10.05)	0.002
Weight gain >5%	13 (52%)	6 (24%)	0.28 (0.01 – 0.50)	0.04
Mood changes	0	0	-	-
Fatigue	0	0	-	-
Visual disturbance	0	3 (12.0%)	-0.12 (-0.30 – 0.04)	0.24
Skin rash	0	3 (12.0%)	-0.12 (-0.30 – 0.04)	0.24
Liver function test abnormalities	0	8 (32.0%)	-0.32 (-0.52 – -0.12)	0.004
Nausea	0	2 (8.0%)	-0.08 (-0.25 – 0.07)	0.49
Discontinuation of study drug	0	0	-	-
Any adverse effect	29	22	-	-