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*

Background: IgE sensitization to *Aspergillus fumigatus* and a positive sputum fungal culture result are common in patients with refractory asthma. It is not clear whether these patients would benefit from antifungal treatment.

Objectives: We sought to determine whether a 3-month course of voriconazole improved asthma-related outcomes in patients with asthma who are IgE sensitized to *A fumigatus*.

Methods: Asthmatic patients who were IgE sensitized to *A fumigatus* with a history of at least 2 severe exacerbations in the previous 12 months were treated for 3 months with 200 mg of voriconazole twice daily, followed by observation for 9 months, in a double-blind, placebo-controlled, randomized design. Primary outcomes were improvement in quality of life at the end of the treatment period and a reduction in the number of severe exacerbations over the 12 months of the study.

Results: Sixty-five patients were randomized. Fifty-nine patients started treatment (32 receiving voriconazole and 27 receiving placebo) and were included in an intention-to-treat analysis. Fifty-six patients took the full 3 months of medication. Between the voriconazole and placebo groups, there were no significant differences in the number of severe exacerbations (1.16 vs 1.41 per patient per year, respectively; mean difference, 0.25; 95% CI, 0.19-0.31), quality of life (change in Asthma Quality of Life Questionnaire score, 0.68 vs 0.88; mean difference between groups, 0.2; 95% CI, −0.05 to −0.11), or any of our secondary outcome measures.

Conclusion: We were unable to show a beneficial effect of 3 months of treatment with voriconazole in patients with moderate-to-severe asthma who were IgE sensitized to *A fumigatus* on either the rate of severe exacerbations, quality of life, or other markers of asthma control. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Refractory, asthma, exacerbations,* Aspergillus fumigatus*, allergic bronchopulmonary aspergillosis, mold, eosinophils, voriconazole, quality of life, severe asthma with fungal sensitization*

It is well recognized that colonization of the airways with filamentous fungi (molds), together with increased specific IgE levels, can occur in asthmatic patients (and patients with cystic fibrosis), in whom it is associated with a distinct syndrome called allergic bronchopulmonary mycosis.[1,2] The main molds associated with this condition are *Aspergillus fumigatus* and related thermotolerant members of the *Aspergillus* genera causing allergic bronchopulmonary aspergillosis (ABPA).[3,4] The classical clinical features of allergic bronchopulmonary mycosis are fleeting lung shadows, proximal bronchiectasis, and a cough producing viscid mucus. These are associated with laboratory findings of increased total IgE levels, increased fungus-specific IgE levels (and/or a positive skin prick test response) and IgG levels, and peripheral blood eosinophilia.

Up to 50% of patients with refractory asthma have been reported to be IgE sensitized to fungi.[5] However, most patients who are IgE sensitized to *A fumigatus* do not fulfill all the criteria for ABPA. They often have levels of total IgE less than the accepted ABPA threshold (>410 IU/L or 1000 ng/mL, although some investigators use >1000 IU/L),[6-9] concentrations of specific IgG in the normal range, absence of proximal bronchiectasis, and no evidence of fleeting shadows. In a cross-sectional study we have shown that approximately 60% of patients with moderate-to-severe asthma who are IgE sensitized to *A fumigatus* but without ABPA have a positive sputum culture result for the mold, suggesting that airway colonization is commonly associated with sensitization.[10,11] Patients with either sensitization or a positive sputum culture result have a lower postbronchodilator FEV_1 than matched asthmatic patients, and in patients who have both sensitization and a positive sputum culture result compared with those who have neither, the mean difference in postbronchodilator FEV_1 is 20% of the predicted value, suggesting a relationship between lung damage and both fungal allergy and infection.[10,11] A positive sputum culture result and sensitization have also been associated with increased incidence of bronchiectasis.[12]

From the Institute for Lung Health, Department of Infection, Immunity and Inflammation, University of Leicester, and the Department of Respiratory Medicine, University Hospitals of Leicester NHS Trust, Glenfield Hospital.

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Corresponding author: Professor Andrew J. Wardlaw, PhD, FRCP, Institute for Lung Health, Glenfield Hospital, Groby Road, Leicester LE3 9QP, United Kingdom. E-mail: aw24@le.ac.uk.

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Abbreviations used
ABPA: Allergic bronchopulmonary aspergillosis
ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
COPD: Chronic obstructive pulmonary disease
SAFS: Severe asthma with fungal sensitization
VAS: Visual analog score

If, as is thought to be the case in patients with ABPA, persistent colonization of the bronchial tree with *A fumigatus* is contributing to the clinical picture in asthmatic patients with allergy to *A fumigatus* without ABPA, this raises the question of whether treatment with antifungal therapy would be of benefit in this group of patients. Most descriptions of the use of antifungal agents for ABPA in patients with asthma and cystic fibrosis have been limited to case reports. There have been 2 significant placebo-controlled studies of antifungal treatment for ABPA identified in a Cochrane review, both of which reported benefits of itraconazole.[9,13,14] The only other randomized study of antifungal treatment in asthmatic patients was by Denning et al,[15] who treated 58 patients with severe asthma with fungal sensitization (SAFS; a terms coined by the authors to describe patients with severe asthma and fungal IgE who do not meet the criteria for ABPA) with 200 mg of itraconazole twice daily for 32 weeks and observed a significant improvement compared with placebo in Asthma Quality of Life Questionnaire (AQLQ) scores.[16]

One problem with interpreting studies that have used itraconazole is that it can markedly enhance the effects of both endogenous and exogenous corticosteroids.[17] Thus the improvements seen in the above studies could be due to a pharmacokinetic effect on corticosteroid bioavailability rather than antifungal activity. This pharmacokinetic effect has not been reported to occur with voriconazole. It is generally considered that voriconazole is at least as effective as itraconazole in the treatment of invasive infections with *A fumigatus* and is regarded as first-line therapy in many centers.[18] Therefore we undertook a study of voriconazole in asthmatic patients who were sensitized to *A fumigatus* to determine whether this improved their asthma control.

METHODS

Patients

Subjects (all >18 years of age) were recruited during 2010 and 2011, mainly from the respiratory clinics at Glenfield Hospital, although 10 subjects were referred into the study from other hospitals in the East Midlands, United Kingdom. The inclusion criteria were a clinical diagnosis of asthma with at least historical evidence of variable airflow obstruction (short-term variability in FEV_1 >12% or PC_{20} <8 mg/mL), evidence of IgE sensitization to *A fumigatus* (increased specific IgE level >0.35 IU/L or a skin prick test response >2 mm larger than that elicited by the negative control), and at least 2 severe exacerbations (defined as requiring a minimum of 3 days of high-dose oral corticosteroids for asthma symptoms) in the previous 12 months. Exclusion criteria were pregnancy, a diagnosis of chronic obstructive pulmonary disease, a medical condition that would increase the likelihood of an adverse reaction to voriconazole, and treatment with an antifungal agent in the 12 months before entry into the study.

Study design

This was an investigator-led, single-center, double-blind, placebo-controlled, randomized, parallel-group study conducted between 2010 and 2012. The funding agency, Pfizer (New York, NY), provided the drug and placebo but had no role in the accrual or analysis of the data. Ethical approval from the Leicestershire Ethics Committee (UKCRN ID 7763) and the UK Medical and Health Products Regulatory Agency (MHRA 09/H0402/63) was obtained, and each patient provided written informed consent. The clinical trials registration numbers were ISRCTN42366088 and EudraCT 2009-011452-21. The visit schedule, together with the investigations undertaken at each visit, is shown in Table E1 in this article's Online Repository at www.jacionline.org. At a baseline visit, demographic details were collected, including smoking history, treatment, and exacerbation history. If a high-resolution computed tomographic scan had been undertaken for routine clinical purposes, the presence or absence of bronchiectasis on the radiology report was recorded. Spirometry was performed, and quality-of-life measurements were recorded. Blood was drawn for measurement of total IgE, specific IgE, and IgG levels to *A fumigatus*; a full blood count and routine biochemistry; serum cortisol measurement; and cystic fibrosis genotyping. Sputum was obtained either spontaneously or by means of induction for a cell differential and fungal culture. Skin prick tests with a panel of aeroallergens, including *A fumigatus*, was undertaken. After a run-in period of up to 1 month to ensure the subject's condition was stable and to allow measurement of the sputum differential and fungal culture used for randomization, the subjects were started on treatment at visit 2. Treatment was given for 3 months during which subjects were seen at monthly intervals. They were then seen bimonthly until the end of the study. Investigations were repeated at each visit according to the schedule in Fig E1 in this article's Online Repository at www.jacionline.org. Voriconazole levels were measured at visits 3 or 4, which took place 1 or 2 months after starting treatment. Exacerbations were treated either by the patient's personal physician or by the study team and managed according to standard clinical practice. Chronic asthma treatment was not altered during the study period. Randomization was done blocks of 3 with the minimization method using the criteria of sputum eosinophil counts, numbers of exacerbations in the previous 12 months, and sputum fungal culture results for *A fumigatus*.[19] Voriconazole was administered at a dose of 200 mg twice daily, with the drug and matched placebo provided by Pfizer. The 2 primary outcome measures were the change in the Juniper AQLQ score from baseline to the end of the treatment period and the number of severe exacerbations, defined as above, over the 12 months of the study. Secondary outcomes measures were the modified Juniper Asthma Control Questionnaire (ACQ6) score (which excludes FEV_1); a combined visual analog score (VAS) score based on three 100-mm VAS scales, which measured symptoms of cough, breathlessness, and wheeze; the nasal polyp questionnaire score[20]; postbronchodilator FEV_1; sputum eosinophil and neutrophil counts; peripheral blood eosinophil counts; and total IgE and *A fumigatus*–specific IgE and IgG levels.

Investigations

Clinical investigations and measurement of the sputum differential and fungal culture were undertaken as previously described and detailed in the text in this article's Online Repository at www.jacionline.org.[21,22] Measurement of both total and specific IgE levels and IgG levels was undertaken in the University Hospitals of Leicester immunology laboratory by using the ImmunoCAP system (Phadia, Uppsala, Sweden). Serum for voriconazole levels was sent to the Health Protection Agency mycology reference center in Bristol, United Kingdom.

Statistics

The study was powered on severe exacerbations. Twenty-five patients were required in each group, assuming 2 exacerbations per patient per year in the placebo group and 1 exacerbation per patient per year in the voriconazole arm ($\alpha = .05$, $\beta = .02$). The exacerbation data were analyzed by using negative binomial regression. Those patients who received at least 1 week of treatment were analyzed on an intention-to-treat basis. For the quality-of-life data, the mean ACQ6, AQLQ, and VAS scores are shown. Baseline scores were compared with posttreatment data collected at visit 5, and error bars represent the SEM. Within-group data were analyzed by using paired *t* tests; between-group comparisons were analyzed separately at baseline and visit

5 with unpaired *t* tests. Statistical software packages used for various analyses included PASW Statistics 18 (SPSS, Chicago, Ill) and GraphPad Prism (version 4; GraphPad Software, La Jolla, Calif) software.

RESULTS

Recruitment

The details of recruitment are shown in the CONSORT diagram (Fig 1). About a third of the patients contacted and screened agreed to take part. Sixty-five patients were randomized. Six dropped out before taking any drug because they changed their minds about participating in the study between the screening visit and taking the first study medication and took no further part in the study. Therefore 59 patients were entered into the analysis. Of these, 3 in each group did not complete the course of treatment, although 4 of these continued in the study.

Baseline demographics and investigations

Baseline details of patients' demographics and investigations are shown in Table I. The active and placebo groups were generally well matched, with no significant differences between them, although there was a trend toward more men in the placebo group. The patients in both groups had moderate-to-severe disease, with a requirement for high doses of corticosteroids and a substantial degree of fixed airflow obstruction and bronchiectasis. Two patients fulfilled all the criteria for a diagnosis of ABPA.

Primary outcomes

There was no significant difference in the total number of severe exacerbations or in the number of subjects with exacerbations between the 2 groups over the 12-month study period (Fig 2). The voriconazole group had a mean of 1.16 exacerbations per subject over the 12 months of the study compared with 2.5 exacerbations per subject in the 12 months before the study. There were a mean of 1.4 exacerbations in the placebo group compared with 3.0 exacerbations in the previous 12 months. This represented a 54% reduction from baseline in each group. Twenty-seven patients in the voriconazole arm had 1 or more exacerbations compared with 18 patients in the placebo arm. The AQLQ score improved from a mean of 4.55 at baseline in the voriconazole group to 5.22 at the end of the treatment period (Fig 3). It then decreased within 2 months and was 4.85 at the end of the trial. A similar pattern was seen in the placebo group, with the AQLQ score improving from 4.66 at baseline to 5.54 at the end of treatment and 5.13 at the end of the study. There were no statistically significant differences between the voriconazole and placebo groups.

Secondary outcomes

There were no significant differences between the voriconazole and placebo groups in the 3 other quality-of-life measures that we used, the ACQ6, VAS, and nasal polyp questionnaire scores (Fig 3 and data not shown). These measures demonstrated the same pattern as the AQLQ, with an improvement in both groups to the end of the treatment period followed by a rapid return toward baseline values. There were no significant differences between the groups in FEV_1, blood and sputum counts, or total and *A fumigatus*–specific IgE and IgG levels (see the text in this article's Online Repository at www.jacionline.org).

DISCUSSION

As far as we are aware, this is the first report of a randomized controlled study investigating the effects of voriconazole in asthmatic patients complicated by allergy to *A fumigatus*. Voriconazole has a similar *in vitro* minimum inhibitory concentration against *A fumigatus* as itraconazole and posaconazole and a good profile of tissue penetration into the lung tissue and epithelial lining fluid.[23] Its use is generally restricted to invasive infections or situations in which itraconazole treatment has failed, although anecdotally it appeared to have additional benefit.[24] Previous clinical trials of itraconazole in patients with ABPA and SAFS demonstrated improved quality of life, reduced exacerbations, steroid-sparing properties, and reduced inflammatory and immune markers.[9,13,16] We based our outcomes on these studies with a greater emphasis on detecting a reduction in severe exacerbations because of the link between eosinophilic inflammation (which is associated with fungal allergy) and an exacerbation phenotype.[25] It is not clear why our study found no benefit of antifungal treatment compared with the above studies. We recruited a similar number of patients, and the treatment dose was the same, although of shorter duration (12 weeks compared with 16 weeks or 32 weeks in the case of the Fungal Asthma Sensitization Trial study). Our patients were similar to those recruited by the other groups in terms of the severity of asthma, although the patients in the studies by Wark et al[9] and Stevens et al[13] had immunologically more florid disease, particularly with respect to total IgE levels. The patients in the study by Denning et al[16] had a different pattern of fungal allergy as a basis for recruitment, which might have been expected to reduce the power of their study because only a proportion had allergy to thermotolerant, potentially colonizing fungi. We believe it is unlikely that a longer period of treatment would have altered the outcomes on the quality-of-life measures or the secondary outcomes because voriconazole should clear the fungi from the airways in weeks and we did not see any additional effect of treatment on fungal cultures after the first month. However, the fungal colonization did appear to return quite rapidly to baseline levels within a few months of cessation of treatment either as a result of reactivation of dormant spores in macrophages or reinfection, and therefore we cannot exclude the possibility of an effect on exacerbations if we had continued treatment for the full 12 months. However, this would have been prohibitively expensive and resulted in increased adverse events.

We used a fixed dose of voriconazole based on the manufacturer's guidance and the dose of itraconazole used in the studies quoted above. We did not attempt to adjust the dose based on voriconazole levels, not least because of the difficulty of varying the dose while maintaining a double-blind design. Like Denning et al[16] (although unlike Wark et al[9] and Stevens et al[13]), we measured voriconazole levels to provide evidence of compliance (see the text in this article's Online Repository), but we did not rigorously measure trough levels, and we have some missing data. Some patients had levels of less than the recommended trough level of approximately 0.5 μg/mL, and we cannot exclude the possibility that tissue levels were suboptimal in those patients. However, there was no association between voriconazole levels and response to treatment.

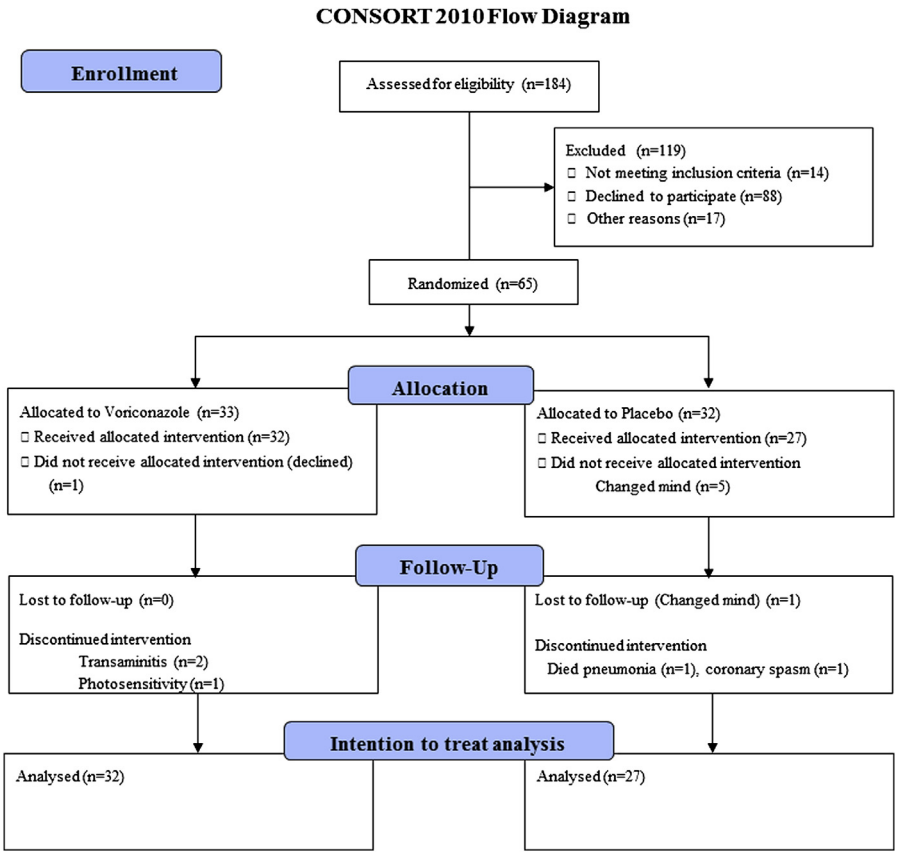

FIG 1. Recruitment of subjects. Of the 184 patients with asthma and IgE sensitization approached to take part in the study, approximately half declined to be involved. A minority did not meet the inclusion criteria, mainly because they had less than 2 exacerbations in the previous 12 months. Of the 65 subjects randomized to drug or placebo, 6 (5 in the placebo group) changed their minds between visits 1 and 2. Of those who took the treatment and were included in the analysis, 1 subject in the placebo group was lost to follow-up between visits 2 and 3, and 2 subjects in the placebo group and 3 in the voriconazole group did not complete the full course of treatment (although 2 of these took >2 months of drug).

As in previous studies, we found high rates of positive sputum culture samples for *A fumigatus*, with 41% of subjects at baseline having a positive sputum result and greater than 80% of subjects having at least 1 positive sputum result over the course of the study (see the text in this article's Online Repository). Rates in healthy subjects are approximately 5% in our subjects on a single visit, but we do not have normal values for more than 2 measurements. There was a trend for more positive sputum samples in the voriconazole group at baseline, but as noted above, the numbers with at least 1 positive sputum sample over the course of the study were well matched between the 2 groups. In terms of sputum culture, there were significantly more responders in the voriconazole group than the placebo group. However, sputum clearance was not complete in 5 of 24 subjects in whom there were positive sputum sample data (although with only 1 colony in each case) at the end of the treatment period. There was also a rapid relapse, with 22 of 31 subjects in the voriconazole group for whom we had data having at least 1 positive sputum sample in the 4 posttreatment visits. Numbers of subjects with definitive sputum data were too small to make a meaningful comparison of the clinical response between sputum responders and nonresponders.

There was a significant improvement in all 3 measures of quality of life at the end of the treatment period compared with baseline, but this was also seen in the placebo group, and the between-group differences were not significant. This contrasts with the study by Denning et al,[16] in which the improvements in AQLQ scores with itraconazole were similar in magnitude to our study, but there was no placebo effect. Benefits with placebo are common in research studies, especially with subjective symptom data caused by optimization of therapy, regression to the mean, or psychological effects. Our patients were stable when recruited and receiving optimal therapy. In addition, the benefits of treatment in both groups were transitory. This suggests that psychological factors were the main explanation for the placebo effect in this study.

The patients were generally well matched apart from differences in sex, which seems unlikely to have had a material effect on the study outcome. Of the 65 subjects who consented to take part in the study and were randomized, 6 changed their minds before receiving any treatment. Five of these were in the placebo group, which skewed the recruitment numbers, but again, it seems unlikely that this affected the outcome. Although a significant number of subjects reported medication side effects, only 1 subject in the voriconazole group received less than 2 months of treatment, and only 2 patients were lost to follow-up, both in the placebo arm.

We were powered to show a 50% reduction in severe exacerbations based on the placebo group having at least 2

TABLE I. Baseline measurements

	Voriconazole (n = 32)	Placebo (n = 27)	*P* value
Demographics			
Men	38% (12)	63% (17)	.07
Age (y), mean (range)	59 (27-80)	59 (38-78)	.90
Age at onset (y), mean (range)	19 (2-60)	20 (2-63)	.50
Body mass index (kg/m^2), mean (range)	27 (18-37)	27 (17-36)	.55
Spirometry			
FEV_1 (% predicted after bronchodilator)	72.6 ± 27.7	62.7 ± 20.3	.13
FEV_1/FVC ratio after bronchodilator	0.61 ± 0.18	0.60 ± 0.17	.70
Leukocyte counts and sputum analysis			
Eosinophil count in blood ($\times 10^{-9}$/L [SE])*	0.46 (0.06)	0.41 (0.04)	.49
Sputum eosinophil counts (%), geometric mean (log SD)	2.88 (1.19)	4.68 (1.04)	.29
Sputum neutrophil counts (%)	66.87 ± 22.17	60.23 ± 23.56	.31
Sputum total cell count ($\times 10^6$/mL)*	6.84 (4.44-10.55)	4.05 (2.41-6.82)	.11
Sputum culture positive for *A fumigatus*, baseline (n)	50% (16)	30% (8)	.06
Patient-reported outcomes			
AQLQ, baseline (SE)	4.55 (0.25)	4.66 (0.28)	.76
Modified Juniper ACQ (ACQ6)	2.15 ± 0.98	2.27 ± 1.20	.68
Average VAS score for asthma symptoms	40.00 ± 4.58	41.45 ± 4.02	.81
Average VAS score for nasal polyps	35.33 ± 19.4	31.41 ± 18.47	.44
Immunoglobulins and radiology			
Total IgE (log_{10} SD)*	459 (3.19)	659 (3.12)	.33
Positive atopic status to common aeroallergens (n)†	69% (22)	70% (19)	1.00
Baseline specific IgE to *A fumigatus* (RAST)*	4.79 (2.38-9.65)	5.69 (2.84-13.01)	.54
Baseline *A fumigatus* IgG*	30.8 (23.54-42.60)	31.7 (21.70-43.80)	.74
Bronchiectasis present or radiology report of CT scan (n)	52% (16)	62% (16)	.59
Smoking and steroid history			
Smoking (pack years) in exsmokers or current smokers	14	11.9	.68
Never smokers (n)	59% (19)	63% (17)	.8
Rescue corticosteroid courses in previous year	2.5 (2-4)	3 (2-5)	.19
Dose of inhaled corticosteroid–beclomethasone equivalent (μg/patient/d), median (IQR)	2000 (900-2000)	2000 (400-2000)	.36
No. receiving maintenance prednisolone (median dose [n])	28% (9)	33% (9)	.89
Median dose of maintenance prednisolone (mg [range])	5 (2.5-10)	5 (5-10)	.89

P values were calculated by using an independent *t* test for parametric values. The Fisher exact test was used for comparison of proportions, and the Mann-Whitney *U* test was used for comparison of nonparametric values.
*Geometric mean (95% CI).
†House dust mite, cat, dog, and grass.

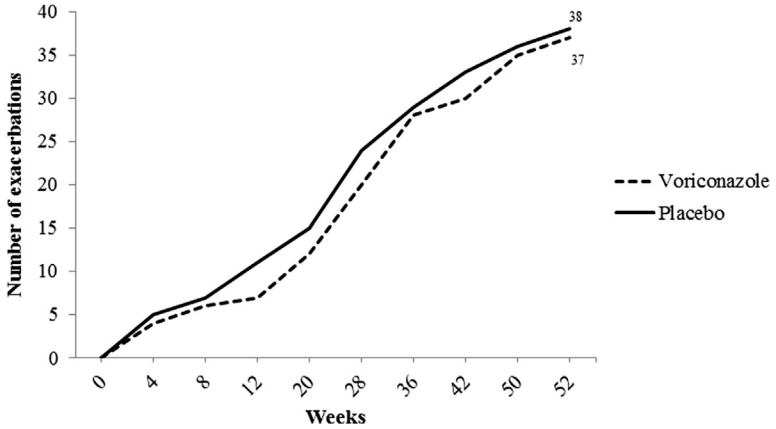

FIG 2. Severe exacerbations. There was a linear increase in the number of severe exacerbations in both groups with no treatment effect. The total number of exacerbations in the placebo group was 38, with 37 in the voriconazole group, which represented a 54% reduction from baseline in both groups. Five patients in the voriconazole group and 9 subjects in the placebo group did not have exacerbations. This difference was not significant.

exacerbations over the 12-month period. The rate of exacerbations in the placebo group was only 1.4, which represented an approximately 50% reduction from the previous 12 months, whereas the rate in the voriconazole group was 1.16, which similarly was an approximately 50% reduction from baseline. Thus although strictly speaking we were underpowered, the lack

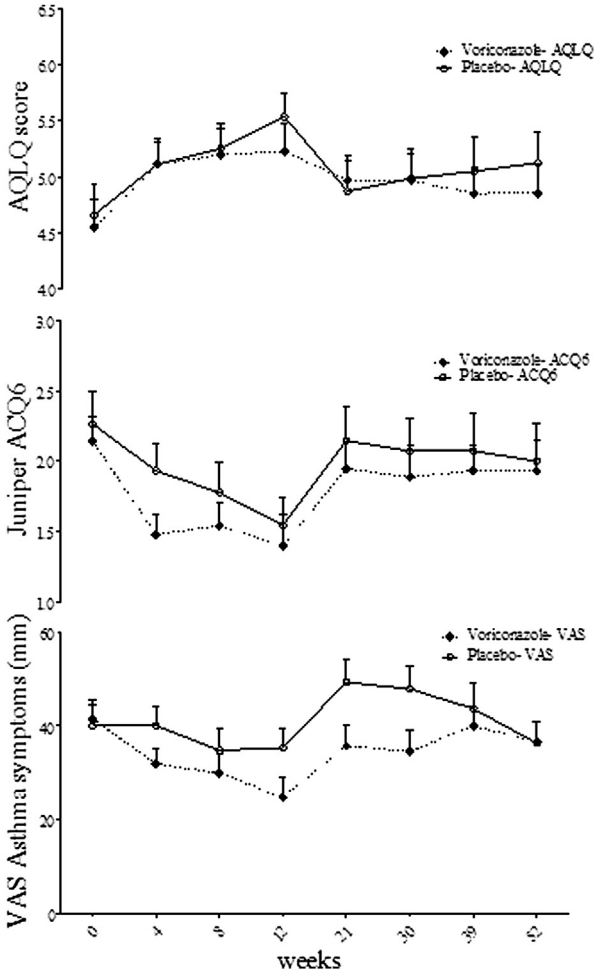

FIG 3. Patient-reported outcomes. There was a significant improvement in quality-of-life scores in both groups from baseline during the course of treatment, with the voriconazole group increasing from a mean of 4.55 to a maximum of 5.3 and the placebo group increasing from a mean of 4.66 to a maximum of 5.6 ($P < .001$). There was no significant difference between groups, and the improvement was not maintained after the treatment period had finished. A similar pattern was observed for both the asthma control score and the mean VAS score, with a significant improvement from baseline in both groups during the treatment period but no significant difference between groups and a return toward baseline value immediately on stopping treatment.

of even a hint of a difference between the 2 groups makes it unlikely that larger numbers of subjects would have resulted in demonstration of a clinically significant reduction in severe exacerbations. The numbers in our study were very similar to those in the Fungal Asthma Sensitization Trial study of Denning et al,[16] in which they observed a significant improvement in AQLQ scores in the itraconazole group. Therefore we do not believe that the failure to show any effect on quality of life in our study was due to a lack of power.

One possible explanation for the lack of any clinical or laboratory benefit in our study compared with those that have used itraconazole is that the benefits of itraconazole in those studies was due to primarily a pharmacokinetic effect on corticosteroid bioavailability, especially considering the high doses of inhaled and oral steroids that tend to be used in patients with ABPA and SAFS. This is a well-recognized problem with itraconazole, which confounds interpretation of the use of this drug.[17,26] This pharmacokinetic effect has not been reported with voriconazole, and in the subset of subjects in which we performed cortisol levels, voriconazole had no discernible effect on serum cortisol levels (data not shown). Denning et a[16] found that half the patients they tested who were taking itraconazole had reduced cortisol levels, but the improvement in AQLQ scores was no different in these patients compared with that seen in patients with unchanged cortisol levels, although numbers were small.

In conclusion, this study does not provide any evidence that patients with moderate-to-severe asthma who are IgE sensitized to *A fumigatus* but do not fulfill all the criteria for ABPA will gain any short- to medium-term benefit in terms of asthma control from a 3-month course of voriconazole.

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Clinical implications: A short course of voriconazole does not benefit patients with asthma associated with allergy to *A fumigatus*. Previously reported benefits of itraconazole in this group of patients could be due to pharmacokinetic effects on endogenous and exogenous corticosteroids.

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