CASE REPORTS

Prolonged Therapeutic Response to Voriconazole in a Case of Allergic Bronchopulmonary Aspergillosis

Rafael Bandrés Gimeno and María José Muñoz Martínez

Servicio de Neumología, Hospital Xeral de Vigo, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain.

Allergic bronchopulmonary aspergillosis is a lung disease characterized by an immune response to several antigens of Aspergillus species. Corticosteroids are the treatment of choice in the acute phase, although some studies have shown the efficacy of itraconazole. We describe the case of a favorable, prolonged therapeutic response to voriconazole in a patient with allergic bronchopulmonary aspergillosis who did not tolerate itraconazole.

Key words: *Bronchopulmonary aspergillosis. Aspergillosis.* Aspergillus *species. Voriconazole. Therapeutics.*

Respuesta terapéutica prolongada a voriconazol en un caso de broncoaspergilosis

La aspergilosis broncopulmonar alérgica es una enfermedad pulmonar que se caracteriza por una respuesta inmunológica a múltiples antígenos de la especie *Aspergillus*. El tratamiento de elección en la fase aguda son los corticoides, pero algunos estudios han demostrado la eficacia del itraconazol. Describimos un caso de respuesta terapéutica favorable y prolongada con voriconazol en una paciente con broncoaspergilosis alérgica que no toleró el itraconazol.

Palabras clave: *Aspergilosis broncopulmonar alérgica. Aspergilosis.* Aspergillus. *Voriconazol. Tratamiento.*

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease characterized by an immune response to several antigens of *Aspergillus fumigatus* and other related species that colonize the bronchi. It affects between 1% and 2% of patients with asthma[1] and between 1% and 15% of patients with cystic fibrosis.[2,3] Corticosteroids are the treatment of choice in the acute phase, although their long-term role in controlling the progression of the disease has not been determined and they may cause multiple side effects. Although antifungal treatment with natamycin, ketoconazole, and clotrimazole has not been shown to be effective,[4-6] the response to treatment with itraconazole has been shown to be positive.[7-9] The new triazoles, such as voriconazole, have recently been found effective in the treatment of fungal infections.[10-12]

We considered that the new triazoles might also be useful in the treatment of ABPA.

Correspondence: Dr. R. Bandrés Gimeno.
Servicio de Neumología. Hospital Xeral de Vigo. Complexo Hospitalario Universitario de Vigo.
Pizarro, 22. 36204 Vigo. Pontevedra. España.
E-mail: rafaelbandres@yahoo.es

Manuscript received February 2, 2006. Accepted for publication April 4, 2006.

Case Description

A 54-year-old woman who had suffered from asthma since childhood and had been frequently admitted to hospital with exacerbations was diagnosed with ABPA based on the presence of asthma, lung infiltrates, peripheral eosinophilia, and a high serum immunoglobulin (Ig) E level with elevated IgE specific to *Aspergillus* species, IgG precipitins for *Aspergillus* species, and central bronchiectasis. The patient's main symptom at the time of presentation was shortness of breath that showed no clear improvement on treatment with corticosteroids. The IgE count was between 1000 and 2000 kU/L. The clinical response to treatment with 100 mg itraconazole twice daily for 3 months was good and IgE levels fell. The corticosteroids were gradually reduced and eventually withdrawn. Four years later, fatigue, intermittent fever, general malaise, and sweating developed. Sputum contained hematic bronchial casts, whereas the sibilant dyspnea remitted. Several years later, an infiltrate appeared in the right upper lobe and the IgE count rose to 7700 kU/L. Bronchoscopy revealed signs of diffuse inflammation and a mucus plug in a segmental bronchus of the right upper lobe. A bronchial biopsy showed eosinophilic inflammation of the bronchial mucosa with no *Aspergillus* species filaments. A fungal culture grew colonies of *A fumigatus* and *Aspergillus niger*. Treatment with itraconazole was reinstated (200 mg twice daily) and was followed by clinical improvement and reduction of IgE levels. Nevertheless, the patient developed edema in the face and legs and the drug was therefore temporarily withdrawn. Lower dosages of itraconazole (100 mg twice daily) and 30 mg/d of prednisone for 1 month produced no significant improvement of symptoms, although

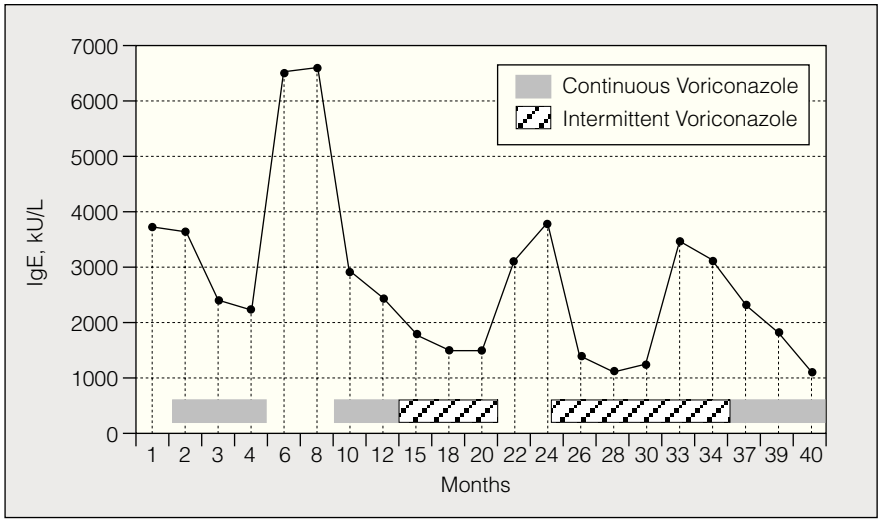

Figure 1. Variations of immunoglobulin (Ig) E concentrations over 40 months of treatment with voriconazole.

there was a slight reduction in IgE levels (from 4250 to 3542 kU/L). Finally, treatment with voriconazole (200 mg twice daily) and 20 mg/d of prednisone was initiated. The patient experienced rapid improvement under this treatment regime, with a rapid drop in IgE levels to 2226 kU/L. When voriconazole was withdrawn 3 months later, both the fatigue and productive cough reappeared, together with a renewed increase in IgE levels to 6612 kU/L.

Treatment with voriconazole was restarted at the same dosage and maintained for 3 months. At the end of this period, a dosage of 200 mg twice daily in alternate weeks was established. This treatment regime maintained both the clinical improvement and the low IgE levels, as shown in the Figure. The corticosteroid dosage was gradually reduced to 5 mg/d.

The was admitted to hospital for a hypertensive crisis and transient ischemic attack. Treatment with voriconazole was suspended for 4 months and this led to a renewed increase in IgE levels, reappearance of fatigue, and poor temperature regulation. Alternate-week treatment was reinstated and maintained for 1 year. This produced a good response for 6 months, with a subsequent exacerbation that was overcome with continuous treatment. Continuous treatment is maintained at present. The last IgE count was 1089 kU/L (G). The mean daily dose of prednisone administered for 40 months from initiation of treatment with voriconazole was 15 mg (range, 5-30 mg).

Discussion

The classic diagnostic criteria for ABPA were established by Rosenberg et al.[13] More recently, Greenberger and Paterson,[14] citing an aim of earlier diagnosis of the disease to prevent it from progressing, defined the minimum essential criteria as follows: asthma, immediate skin reaction to *A fumigatus*, high serum levels of IgE (>417 kU/L or 1000 ng/mL), high levels of IgE or IgG specific to *A fumigatus*, and proximal bronchiectasis. The term seropositive ABPA, where proximal bronchiectasis is absent, has been proposed. Other nonessential criteria include infiltrates evident in a chest x-ray and precipitins for *A fumigatus* antigens.

Denning et al[7] described clinical improvement and reduction of IgE levels in 6 patients treated with itraconazole for 3.9 months. These authors hypothesized a primary antifungal effect rather than an immunomodulatory effect of itraconazole, considering the negative results of the fungal cultures. Salez et al[8] found clinical and functional improvement in 14 patients treated with itraconazole, together with a reduction in IgE and IgG antibodies to *Aspergillus* species, compared to data from the previous 2 years of treatment. These authors were also able to reduce the dosage of oral corticosteroids after 12 months of treatment with itraconazole.

In a randomized, double-blind trial enrolling 55 patients who received 200 mg of itraconazole twice daily or a placebo for 16 weeks,[9] 13 of 28 patients in the itraconazole group responded positively compared to 5 of 27 in the placebo group. In a later open phase, in which all patients received 200 mg/d of itraconazole for 16 weeks, a therapeutic response was achieved in 36% of the patients who had not responded in the first, double-blind phase.

Voriconazole is a new antifungal triazole derived from fluconazole. It has good bioavailability when taken orally[10] and has been shown to be clinically effective against *Aspergillus* species in invasive aspergillosis[12]; some authors[11] therefore consider it to be the treatment of choice for this disease. The mean minimum inhibitory concentrations are 0.25 mg/L for *A fumigatus* and 0.5 mg/L for *A niger*.[10]

No other cases of ABPA treated with voriconazole have been reported to date. Our patient received treatment with itraconazole twice with a good clinical response and reduced IgE serum levels, but a subsequent course of this drug with prednisone produced no effect. With regard to the inefficacy of itraconazole in this case, we can only speculate that it may have been due to serum levels below the minimum inhibitory concentration, or fungicidal levels, for *Aspergillus* species. It was not possible, however, to determine serum concentrations of itraconazole.

The clinical and analytical response to voriconazole and the reappearance of symptoms and increase in IgE levels when the drug was withdrawn, followed by the renewed response when it was reinstated, strongly support a cause-effect relationship for the improvements observed. One finding that surprised us was the fact that the response was maintained with a treatment regime in alternate weeks. Other treatment options could have been continuous higher doses 2 or 3 times per week or high daily doses for 1 week followed by 2 weeks without treatment. However, the patient suffered an episode of exacerbation while under the intermittent treatment regime, requiring voriconazole to be administered continuously. There were no changes in lung function during the period this patient's treatment with voriconazole was followed; longer treatment might be required for significant improvement, however.

The objective of the treatment would be to keep the *Aspergillus* species under control and thus reduce the antigen load responsible for the exacerbated immune reaction.

In our opinion, the choice of an antifungal agent in ABPA should be based on the pharmacokinetic properties, in vitro activity against *Aspergillus* species, proven clinical results against ABPA and other forms of aspergillosis, and tolerance of the drug and an oral route of administration.

In conclusion, we believe that voriconazole could be a candidate treatment for patients with ABPA who fail to respond to corticosteroids or itraconazole or who do not tolerate itraconazole. Nevertheless, controlled trials will be required to determine whether voriconazole can be useful in the treatment of ABPA.

REFERENCES

1. Greenberger PA, Patterson R. Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma. J Allergy Clin Immunol. 1988;81:646-50.
2. Skov M, Hoiby N, Koch C. Itraconazole treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Allergy 2002;57:723-8.
3. Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2002;110:685-92.
4. Currie DC, Lueck C, Milburn HJ, et al. Controlled trial of natamycin in the treatment of allergic bronchopulmonary aspergillosis. Thorax. 1990;45:447-50.
5. Shale DJ, Faux JA, Lane DJ. Trial of ketoconazole in non-invasive pulmonary aspergillosis. Thorax. 1987;42:26-31.
6. Crompton GK, Milne LJ. Treatment of pulmonary aspergillosis with clotrimazole. Br J Dis Chest. 1973;67:301-7.
7. Denning DW, van Wye JE, Lewiston NJ, Stevens DA. Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. Chest. 1991;100:813-9.
8. Salez F, Brichet A, Desurmont S, et al. Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis. Chest. 1999;116: 1665-8.
9. Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med. 2000;342:756-62.
10. Murphy M, Bernard EM, Ishimaru T, Armstrong D. Activity of voriconazole (UK-109,496) against clinical isolates of Aspergillus species and its effectiveness in an experimental model of invasive pulmonary aspergillosis. Antimicrob Agents Chemother. 1997; 41:696-8.
11. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347:408-15.
12. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis. 2002;34:563-71.
13. Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med. 1977;86:405-14.
14. Greenberger PA, Patterson R. Diagnosis and management of allergic bronchopulmonary aspergillosis. Ann Allergy. 1986;56:444-8.