CORRESPONDENCE

High-Dose Itraconazole for the Treatment of Cerebral Aspergillosis

SIR—Invasive aspergillosis is an opportunistic infection that occurs in patients with severely compromised host defenses. The prognosis for patients with invasive aspergillosis is poor, especially for those with disseminated infection, and depends on a large number of variables (e.g., remission of the underlying disease, the definitive diagnosis being made at an early stage, the extent of disease, the early administration of antifungal treatment [1], and, importantly, the recovery of granulocytes) [2]. Therefore, the evaluation of therapeutic regimens, especially those that include novel antifungal agents, is particularly difficult because many known and unknown factors may bias observed treatment success or failure.

The difficulty of evaluating these regimens is well illustrated by the recent report of Sánchez and colleagues, who described a patient who developed cerebral aspergillosis while receiving corticosteroid therapy for bronchial asthma [3]. After having shown no clinical response to treatment with low-dose amphotericin B (0.65 mg/[kg·d]), therapy with itraconazole (800 mg/d) was started, which resulted in the patient's gradual recovery. Although pretreatment with amphotericin B may have influenced the outcome of the itraconazaole therapy, treatment of cerebral aspergillosis with a high dose of itraconazole alone or in combination with amphotericin B may be effective therapy in these difficult-to-treat infections.

In their review of the literature, Sánchez et al. suggested that treatment of cerebral aspergillosis with high-dose itraconazole may be superior to treatment with the conventional dose (400 mg/d) since three of four patients treated with high doses of itraconazole survived while seven of eight patients treated with the conventional dose died. However, the authors failed to take two important factors into account, namely remission of the underlying disease and the presence of granulocytopenia. The conditions of two of the four patients who received a high dose of itraconazole were diagnosed as hematologic malignancy, as were the conditions of seven of eight patients who were treated with low-dose itraconazole. The investigators did not state whether the underlying disease was in remission in these patients despite the fact that this is an important prognostic factor.

Table 1. Clinical characteristics of 12 patients with cerebral aspergillosis who were treated with itraconazole and who did or did not have granulocytopenia.

Patient no.†	Granulocytopenia	Procedure or underlying condition(s)	Dosage of itraconazole*	Outcome
1	No	Heart transplantation	Low	Cured
6	No	Acute leukemia	High	Cured
11	No	Chronic granulomatous disease	High	Cured
12	No	Bronchial asthma	High	Cured
9	Yes	Acute leukemia	Low	Died
3	Yes	Acute leukemia, diabetes mellitus	Low	Died
4	Yes	Acute leukemia	High	Died
7	Yes	Acute leukemia, BMT	Low	Died
10	Yes	Acute leukemia	Low	Died
2	Yes	Acute leukemia	NA	Died
5	Yes	Multiple myeloma	Low	Died
8	Yes	Multiple myeloma, BMT	Low	Died

NOTE. BMT = bone marrow transplantation. This table was adapted from [3].
* Dosage of itraconazole: low, 400 mg/d; high, 800 mg/d.
† Patients' numbers are those in original table.

Furthermore, careful examination of the clinical characteristics of the patients reviewed by Sánchez et al. shows that all patients who remained granulocytopenic during treatment died whereas those who did not remain granulocytopenic survived (table 1), irrespective of the dosage of itraconazole that they received. Therefore, the investigators' conclusion that high-dose itraconazole may be beneficial in the treatment of cerebral aspergillosis seems premature.

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References

1. Aisner J, Schimpff SC, Wiernik PH. Treatment of invasive aspergillosis: relation of early diagnosis and treatment to response. Ann Intern Med 1977;86:539–43.

2. Gerson S, Talbot G, Huwitz S, Strom B, Kusk E, Cassileth P. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med **1984**;100: 345–51.

3. Sánchez C, Mauri E, Dalmau D, Quintana S, Aparicio A, Garau J. Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? Clin Infect Dis **1995**;21:1485–7.

Reply

SIR—Verweij and colleagues suggest that remission of the underlying disease and the presence of granulocytopenia must be taken into account in the prognosis for patients with cerebral aspergillosis. We agree with Verweij and colleagues that even though remission of the underlying disease plays a role in the prognosis for patients with cerebral aspergillosis, the persistence of granulocytopenia is the most important factor that influences the final outcome. However, among the seven patients who received itraconazole therapy for cerebral aspergillosis and granulocytopenia and who died, only one patient was treated with a high dose of itraconazole. Moreover, even those patients who do not have granulocytopenia have a poor response.

As we mentioned before, in the review by Kim and colleagues [1], only five of 36 patients who had cerebral aspergillosis without immunocompromising diseases survived after surgery plus chemotherapy. In addition, among the 33 cases reviewed by Denning and Stevens [2], there were no differences between responders and nonresponders according to the host factor considered (e.g., neutropenia, bone marrow transplantation recipients, and other [OR, 0.23; 95% CI, 0.03–1.65]). In contrast, in our review all four patients with cerebral aspergillosis who did not have granulocytopenia and who were treated with itraconazole (three with high doses of the drug) survived. Since data concerning the treatment of cerebral aspergillosis are scarce and there are few agents that can be used to treat this disease, more studies are needed to establish a better therapeutic approach.

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References

1. Kim DG, Hong SC, Kim HJ, et al. Cerebral aspergillosis in immunologically competent patients. Surg Neurol 1993;40:326–31.
2. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. Rev Infect Dis 1990;12: 1147–201.

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Rifabutin Prevents Campylobacter Infection in Patients with AIDS

SIR—In a recent issue of *Clinical Infectious Diseases,* Chaisson suggested that, based on its in vitro spectrum of activity, rifabutin might have prophylactic efficacy for bacterial infections in HIV-infected patients [1]. At present, as he pointed out, there are no clinical data indicating that rifabutin prophylaxis prevents such bacterial infections in vivo. However, we recently observed a decreased incidence of campylobacter infections in our cohort of HIV-infected patients who received prophylaxis with rifabutin [2].

Rifabutin has activity against *Campylobacter jejuni* in vitro [3]. Patients with AIDS are at an increased risk of acquiring campylobacter infections [4]. Since atypical, severe, and persistent or relapsing campylobacter infections and acquired resistance to the antibiotics used during treatment of these infections have been reported, campylobacteriosis in patients with AIDS is of clinical concern.

We retrospectively examined the incidence of campylobacter infections in a prospective trial of rifabutin prophylaxis for *Mycobacterium avium* complex (MAC) infection and compared it to the incidence that we observed in the preprophylaxis period.

Between February 1992 and July 1993, we cared for 73 patients whose CD4 cell counts were $<100/\mu L$ (mean CD4 cell count, $30/\mu L$) and who were not receiving rifabutin prophylaxis; the mean number of days of follow-up was 345.2, which corresponded to 840 patient-months. From July 1993, every patient with a CD4 cell count of $<100/\mu L$ began receiving rifabutin (300 mg/d) in a trial of primary prophylaxis for MAC bacteremia.

Between July 1993 and November 1995, 90 patients with a mean CD4 cell count of $22/\mu L$ received rifabutin prophylaxis; the mean number of days of follow-up after treatment was 397, which corresponded to 1,191 patient-months. The two groups were matched for age, sex, and demographic characteristics. A total of 20 episodes of campylobacter infection were observed in 13 of the 163 patients (the 13 patients had a mean CD4 cell count of $31/\mu L$). Seventeen episodes (in 12 patients) were observed in the group who did not receive prophylaxis, and three episodes (in two patients) were observed in the group who received rifabutin prophylaxis ($P < .0005$). The rate of symptomatic infection per 100 patient-months was 0.251 in the group of patients who received rifabutin prophylaxis and 2.02 in the group of patients who did not receive rifabutin prophylaxis.

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