Editorial Response: A Comparison of Itraconazole Versus Fluconazole as Maintenance Therapy for AIDS-Associated Cryptococcal Meningitis

Fluconazole at a dosage of 200 mg daily has again been demonstrated to be highly effective in reducing the risk of relapse after recovery from cryptococcal meningitis [1]. Unfortunately, Dr. Saag and his colleagues were not able to demonstrate that itraconazole, at the doses tested, could be used as an alternative therapy to fluconazole. The measured rate of recurrent meningitis with itraconazole (23%) is similar to that found with weekly infusions of amphotericin B (18%) and placebo (15%) [2, 3]. Thus, at the present time, fluconazole appears to be the only agent with proven efficacy for preventing relapse of cryptococcal meningitis. Neither itraconazole nor weekly infusions of amphotericin B appear to be superior to placebo, although neither itraconazole nor weekly infusions of amphotericin B have been directly compared with placebo. For the patient unable to tolerate fluconazole, albeit a rare event, there appears to be no suitable alternative.

The caveats associated with prevention of relapse of cryptococcal meningitis are twofold. First, it is imperative that the CSF be rendered sterile. All clinical trials conducted have required that the CSF be culture-negative at study entry. Persistence of viable cryptococcal organisms in the completely asymptomatic patient is well documented, including those with negative serum and CSF cryptococcal antigen titers [3–5]. Second, the failure of fluconazole to prevent relapse of cryptococcal meningitis is higher among patients with persistent urinary cryptococcosis, even when using fluconazole at a dosage of 400 mg daily [6]. Thus, it is clinically necessary and desirable to obtain an end-of-therapy sample of CSF and a urine sample following prostatic massage before suspending more intensive initial therapy. These end-of-therapy samples should be negative after a 2-week incubation period before instituting daily fluconazole as lifelong preventive therapy. During that 2-week incubation period, initial induction therapy should continue, for it is difficult for patients to recover lost ground if they should prove to have positive cultures and receive only fluconazole at 200 or 400 mg daily as treatment for active meningitis. Be mindful that only one-third of patients with active meningitis respond to therapy with fluconazole alone [4, 7]. For those without uritary tract involvement, fluconazole at 200 mg daily is effective, while those with persistent urinary cryptococcosis should receive at least 400 mg daily of fluconazole.

An interesting note in the clinical study reported by Dr. Saag and colleagues was the possible adjuvant role of flucytosine in the initial therapy for cryptococcal meningitis. While not a controlled element of this clinical investigation, those who received flucytosine in their initial chemotherapy did better. It seems most likely that such an outcome was the result of selection bias, that is, those who can tolerate flucytosine are healthier, or was because subjects who received flucytosine as part of their initial therapy had a more rapid conversion of their CSF from positive to negative and a longer interval receiving intensive initial chemotherapy with a negative CSF culture before their enrollment in the prevention-of-relapse study. It seems most prudent and highly desirable to rapidly gain control of the CNS infection by use of combinations of flucytosine with amphotericin B or fluconazole [8] and to obtain CSF to demonstrate that the CSF culture has converted from positive to negative before beginning prevention-of-relapse therapy with fluconazole.

Not addressed by any of the prevention-of-relapse studies is the non–AIDS-associated cryptococcal meningitis population. The only controlled clinical trial evaluating relapse in this population randomized subjects to receive 4 weeks vs. 6 weeks of amphotericin B plus flucytosine and then followed patients expectantly [9]. The rate of CNS relapse was 15% in those who received 6 weeks of therapy vs. 27% among those who received 4 weeks. While untested, fluconazole should prove to be as effective in the non-AIDS population as among those infected with HIV, and I see no reason why patients with AIDS should have a lower risk of relapse, because of receiving fluconazole, than do those without AIDS, who receive no prevention-of-relapse therapy. The duration of such therapy in the non-AIDS population is unknown, but it is well established that the risk of relapse remains for several years. For practical purposes, I use fluconazole for 2 years or until the risk factor for disseminated cryptococcal disease abates, for example, stopping immunosuppressive therapy. The cost of such an approach, while several thousand dollars yearly, is well justified given that the majority of non-AIDS patients who have relapse die.


