Fluconazole Plus Amphotericin B Combinations Are Not Contraindicated and May Add Benefit for the Treatment of Candidemia

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(See the article by Rex et al. on pages 1221–8)

Invasive fungal infections must rank very high on the scale of clinical frustrations. They impede the recovery of many seriously ill patients who have otherwise benefited from cutting-edge medical and surgical techniques. They are often difficult to diagnose with certainty, and mortality rates remain higher than ideal despite a steadily expanding armory of broad-spectrum antifungal agents. In addition to the existing triazole antifungals (fluconazole and itraconazole) and amphotericin B (AmB), newer triazoles (voriconazole, posaconazole, and ravuconazole) and echinocandins (caspofungin, anidulafungin, and micafungin) are being developed for clinical use. This growing diversity of antifungal classes has renewed interest in the possibilities of therapy with antifungal combinations. By analogy with management of tuberculosis and HIV infection, a pharmaceutical attack designed to strike at ≥2 targets in the fungi may improve therapeutic outcomes.

However, evidence for such a conclusion from prospective clinical trials is restricted to the combination of AmB plus flucytosine for treatment of cryptococcal meningitis, dating back to 1979 [1]. Rex et al. [2] have now investigated the use of fluconazole monotherapy versus the combination of fluconazole with AmB for treatment of candidemia. This is a singularly important antifungal trial, because it directly addresses a long-standing controversy: the potentially antagonistic interaction of a triazole antifungal with AmB and its implications for the clinic.

The study reported by Rex et al. [2] included 219 patients with candidemia in a modified intent-to-treat analysis. They were drawn from a population of 236 non-neutropenic patients with a Candida-positive blood culture enrolled at 27 centers during a period of almost 4 years. The trial was randomized, blinded, and placebo-controlled as much as was practicable for the types of patients and drugs being tested. Fluconazole plus AmB or a yellow-colored (vitamin-containing) placebo were provided intravenously for a minimum of 5 days; then treatment was continued with oral fluconazole alone. Medications commonly provided concomitantly with AmB infusions (hydrocortisone or heparin) were ordered to the bedside but only administered to patients actually receiving AmB.

The AmB dosage provided in the study (0.6–0.7 mg/kg per day) is a common choice for intravenous therapy [3], whereas the daily fluconazole dose (800 mg) is twice the recommended level and was chosen to maximize effects against Candida isolates with fluconazole susceptibility approaching the point of resistance [4]. The patient populations in each study arm were generally comparable and, with neutropenic patients excluded, represents candidemia in the least seriously affected groups. Only 5 patients of the 219 analyzed had undergone organ transplantation; approximately one-third in each treatment arm had diabetes, and almost 20% in each treatment arm had cancer. Mean APACHE II scores in the fluconazole plus placebo group were significantly higher than in the fluconazole plus AmB group. The trial was randomized, blinded, and placebo-controlled as much as was practicable for the types of patients and drugs being tested. Fluconazole plus AmB or a yellow-colored (vitamin-containing) placebo were provided intravenously for a minimum of 5 days; then treatment was continued with oral fluconazole alone. Medications commonly provided concomitantly with AmB infusions (hydrocortisone or heparin) were ordered to the bedside but only administered to patients actually receiving AmB.

The principal end point for the trial was time to treatment failure, defined as a switch to alternative antifungal treatment, death, or withdrawal from the study with or without drug-related toxicity. Choice of
end points in antifungal clinical trials is always a difficult decision, and these treatment failure definitions are a good compromise among imperfect alternatives. It may be argued that an antimicrobial agent cannot be expected to do more than eliminate an infecting microorganism (clinical cure may depend on other factors affecting the patient’s condition), so a mycological end point should have a claim to priority. However, the results of blood cultures for candidemia are negative for 40%–50% of patients, even when other evidence points strongly to a diagnosis of invasive *Candida* infection [5], and they are therefore unreliable as sole or primary end points. Resolution of fever and other clinical factors often associated with candidemia are weak factors as a basis for trial end points, because they are too nonspecific to define the condition. Nonculture diagnostic approaches for candidemia, including serological testing and PCR, have been under investigation for many years; thus far, they have not yielded any test adequate to define end points in a clinical trial [6].

The results of the Rex et al. [2] trial are easily summarized. No statistically significant difference was found by analysis of time to failure between the 2 arms of the study. However, in the fluconazole plus placebo group, 44% of 107 infections had failed to respond to therapy by 30 days after the initiation of treatment, significantly more than the 31% of 112 patients who received fluconazole plus AmB. Moreover, positive blood cultures were obtained after treatment in 17% of the fluconazole plus placebo patients versus 6% of those provided fluconazole plus AmB (P = .02). The data effectively demonstrate that coadministration of fluconazole plus AmB resulted in no adverse outcome in this patient population, and there was an unmistakable trend toward a slightly better outcome with the combination. This conclusion withstands efforts to probe for possible weaknesses in the study related to differences in the *Candida* species involved, the total duration of treatment, removal of intravenous catheters, and elevation of liver enzymes. Even nephrotoxic effects did not skew data against the group that was provided fluconazole plus AmB. Although renal dysfunction was noted in 23% of the patients who were provided AmB, it was not a significant primary cause of failure by the study criteria.

Rex and colleagues [2] have provided a clear demonstration that fluconazole and AmB can be provided as combination therapy. Fluconazole, like the entireazole antifungal class, inhibits the biosynthesis of the normal fungal membrane sterol, ergosterol. Their action thus removes the essential target for AmB, and it can be readily demonstrated in vitro that azole-AmB combinations interact antagonistically in their antifungal effects, particularly when fungi are exposed sequentially to an azole then to AmB [7, 8]. However, in animal models of disseminated fungal infections, just 2 agents from the triazole class, ketoconazole and itraconazole, stand out as antagonistic in some combinations in mouse studies [9–12], although not in work with guinea pigs [13] or rabbits [14]. Fluconazole plus AmB has usually shown no antagonism in animal models of mycoses [15–18], although one study found that rates of clearance of *C. albicans* from tissues of infected rabbits was slower when fluconazole was provided before AmB than for the opposite sequence or for simultaneous coadministration [19].

The evidence for a possible class antagonism between azoles and AmB, together with warnings against clinical use of itraconazole plus AmB combinations [20, 21], has created uncertainty about the clinical use of anyazole plus AmB combination. The irony of the situation is that, for many patients at risk for invasive mycoses, sequential treatment with fluconazole (for prophylaxis) and AmB (when an invasive mycosis is proven or suspected) is a common occurrence.

In the study by Rex et al. [2], 111 (50.7%) of the 219 patients analyzed had been treated with fluconazole before their inclusion in the prospective trial. These patients were evenly distributed between the 2 arms of the study, and failure rates were similar in each arm in those who had and had not been preexposed to fluconazole. Therefore, the study lends credence to the notion that treatment of candidemia with fluconazole followed by fluconazole plus AmB is no cause for clinical concern (and may confer slight benefit). However, sequential treatment with fluconazole followed by a switch to AmB alone has still not been evaluated in a prospective trial, nor has the efficacy of the fluconazole plus AmB combination been tested in neutropenic patients, for whom therapy is complicated by host immune status. Future trials should address these issues.

References


