Free Fluconazole for Cryptococcal Meningitis: Too Little of a Good Thing?

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(See the article by Bicanic et al. on pages 1069–73)

In 1992, the National Institute of Allergy and Infectious Diseases Mycoses Study Group and the AIDS Clinical Trials Group published the results of a comparison between amphotericin B and fluconazole and concluded that “fluconazole is an effective alternative to amphotericin B as primary treatment of cryptococcal meningitis in patients with AIDS” [1, p. 83]. However, by the time that this article was published, most authorities had enough experience with both of these drugs to realize that fluconazole alone as primary therapy was an unsatisfactory choice for the treatment of this disease [2]. Subsequent studies, which used treatment concepts borrowed from oncologists, demonstrated much improved results using “induction” courses of higher-dose amphotericin B (with or without 5-fluorocytosine), followed by “consolidation” with fluconazole for individuals who had responded favorably, preferably by achieving negative CSF culture results [3]. Because relapse rates exceeded 50%, successfully treated patients required secondary prophylaxis with fluconazole at lower doses for an indefinite period of time [4]. Using these regimens, which have been formally accepted as guidelines endorsed by the Infectious Diseases Society of America [5], the majority of patients were successfully treated, with negative CSF culture results expected in 60% of patients after 2 weeks of therapy and with 70% of cultures expected to be sterile at 10 weeks; the mortality rate was <10%, and patients infrequently experienced relapse [3]. Moreover, when relapses did occur, they were rarely caused by the development of documented fluconazole resistance and more likely the result of poor adherence to the treatment regimen on the part of profoundly immunosuppressed patients.

The introduction of HAART agents contributed even more to the control of cryptococcal meningitis in patients with HIV infection by producing a substantial decrease in its incidence [6] and by finally making “cures” possible, such that secondary prophylaxis could be confidently discontinued when the CD4 cell count adequately responded [7]. In this environment, patients usually developed cryptococcal meningitis only if they were naive to antiretroviral therapy, if therapy had failed, or if they were not adherent to treatment regimens. Up to one-third of patients with recently diagnosed and/or treated cryptococcal meningitis developed immune reconstitution inflammatory syndrome (IRIS) after the initiation of antiretroviral therapy. These patients typically presented with a paradoxical exacerbation of their meningitis following periods of apparent improvement from anticyptococcal therapy, and although they require more-frequent hospitalizations and invasive procedures for management of this complication, they tend to do better in the long run, probably because of the vigorous immunological response derived from their antiretroviral drugs [8].

Therefore, in developed countries, significant progress has been achieved in the management of cryptococcal disease. Unfortunately, this is not the situation in the developing world, where cryptococcal meningitis is still quite prevalent and where resources to treat the disease are wholly inadequate. Despite the fact that Pfizer began to provide fluconazole to African countries in 2000 to treat fungal infections, significant problems still exist with regard to infrastructure, access to medical care, distribution of skilled clinicians, and expertise with managing the intricacies of complications of AIDS and the necessary medications. In sub-Saharan Africa, which bears the brunt of the AIDS epidemic, the situation is par-
ticularly desperate. An estimated 420,000 individuals with AIDS developed cryptococcal meningitis in South Africa in 2004 [9]. A report involving 230 patients with AIDS and acute cryptococcal meningitis at a university teaching hospital in Zaire described a 100% mortality rate within 6 months after diagnosis, even though one-half of the patients were initially treated with fluconazole [10].

In this issue of Clinical Infectious Diseases, Bicanic et al. [11] describe their experience at 2 hospitals in Cape Town, South Africa, with patients who had symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy. This report is particularly instructive in that it reinforces a number of concepts that need to be emphasized in the treatment of patients with AIDS and acute cryptococcal meningitis. First, fluconazole monotherapy is unreliable for the treatment of this disease. Although the authors do not provide precise incidence data for relapses, they saw 7–12 new patients per month with acute cryptococcal meningitis and at least 1 patient with symptomatic relapse each month during the course of their study. Approximately two-thirds of these symptomatic relapses were culture positive. A number of factors are responsible for the inadequate response to fluconazole in this particular patient population, including: (1) profound immunodeficiency, as evidenced by a median CD4 cell count of 27 cells/μL with consequent impaired CSF immunity; (2) the increased microbiological burden in HIV-infected patients, usually evidenced by large numbers of organisms seen in CSF specimens; (3) absence of fungicidal activity of fluconazole (previous reports have shown that fluconazole sterilizes the CSF more slowly than amphotericin B [1, 2]); and (4) likely inadequate CNS levels of fluconazole because of unappreciated drug interactions. Clinicians need to be cognizant of these interactions, particularly when using medications metabolized by hepatic cytochrome enzymes.

Because of the frequent concurrence of tuberculosis along with cryptococcal meningitis in patients with AIDS in sub-Saharan Africa, one-third of the patients in this study were receiving rifampicin along with fluconazole; 44% of the patients infected with fluconazole-resistant isolates received both drugs together, without appropriate adjustments upwards of the fluconazole dose. Rifampicin substantially increases the clearance of fluconazole, such that serum levels may decrease to less than the MICs for Cryptococcus species, likely resulting in even lower CSF concentrations [12]. Mondon et al. [13] have demonstrated heteroresistance within a population of C. neoformans isolates, some with very high MICs to fluconazole, even in the absence of prior experience with the drug. In a patient with continued in vivo exposure to fluconazole and multiple recurrences of meningitis, they were able to show the emergence of a highly resistant clone that persisted as long as fluconazole was present. Under these conditions, then, the ideal environment for the emergence of fluconazole resistance was supported. This is the same clinical scenario that existed in the population described in the present article by Bicanic and colleagues. The unfortunate results of the fluconazole resistance documented in this report were poor subsequent responses and a high mortality rate of >50% at a median of 6 months.

Another important observation in this series was that a minimum of one-third of the symptomatic relapses were culture negative and likely a result of IRIS. This probably represents an underestimation, because it is likely that some of the patients who had a relapse and positive CSF culture results were also experiencing the consequences of an enhanced immunologic response. Approximately one-third of patients treated first for an opportunistic infection and then with active antiretroviral therapy will have paradoxical exacerbations that can be attributed to IRIS [8]. In the present study, sufficient patient data were not obtained to adequately determine the incidence of IRIS, because only 15 of the 27 patients had viral loads and CD4 cell counts determined at the time of the presentation for relapse. As has been demonstrated previously, other than the presence of a negative culture result, CSF parameters are not particularly helpful in differentiating patients with true microbiologic relapse from those who develop IRIS. The patients in this study presented in a manner characteristic of other reports, in that the majority of them were seen early after antiretroviral therapy was started, usually within 60 days; they had all been antiretroviral naïve but had responded favorably to therapy, and most required additional hospital resources to treat this complication [14].

What, then, should be the standard of care for acute cryptococcal meningitis in patients with AIDS in regions of limited resources? Obviously, if amphotericin B is available, patients should be treated with an induction course in an attempt to sterilize the CSF. Bicanic et al. [11] state that, after introduction of amphotericin B–containing regimens, no cases of fluconazole resistance were noted. The data speak for themselves. If resources are not adequate to administer amphotericin B, then much higher doses of fluconazole should be provided. Both murine data [15] and limited human data [16] suggest that there are better microbiological and clinical responses with higher doses. The provision of higher doses should be more feasible than it was in the past, because the cost of fluconazole is substantially lower now that generic versions are widely available. Furthermore, the wide therapeutic index with this drug makes high doses easily tolerable.

Questions regarding the timing of the introduction of active antiretroviral therapy to lessen the impact of IRIS are still unresolved. Studies are presently underway to address this critical issue. Until definitive recommendations are available, because of the profound immunosuppression in this patient population, anti-
retroviral therapy should be started once patients are clinically stable from their acute cryptococcal disease and have evidence of a satisfactory microbiologic response. Clinicians need to be familiar with the presentation of IRIS and to possess the adequate expertise to aggressively manage the elevated intracranial pressures that occur by performing repeated lumbar drainages and judiciously administering corticosteroids.

Until developing countries can obtain adequate resources and the necessary clinical expertise to manage the myriad of complications associated with late-stage patients with AIDS, situations such as that described by Bicanic et al. [11] will continue to occur.

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References