Management of Cryptococcal Meningitis in AIDS: The Need for Specific Studies in Developing Countries

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(See the brief report by Bicanic et al. on pages 76–80)

Cryptococcosis is a deadly opportunistic infection caused by an encapsulated yeast, Cryptococcus neoformans. The major predisposing factor is the profound cellular immune defect caused by HIV infection. Despite major advances in the treatment of HIV infection with HAART, cryptococcosis is still diagnosed in Western countries, especially in patients who have limited access to health care [1, 2]. In sub-Saharan Africa and Southeast Asia, cryptococcosis remains a major concern [3, 4], representing the third most common cause of hospital admission and the cause of 44% of HIV infection–related deaths in South Africa [5]. Meningitis is diagnosed in ∼90% of HIV-infected patients who have cryptococcosis [3, 6], and C. neoformans currently represents the first or second microorganism that causes meningitis in adults in several African countries [7, 8]. Recent data obtained by the French Cryptococcosis Study Group [6] have suggested that the observation of any evidence of cryptococcosis on the basis of positive antigen detection, the presence of encapsulated yeasts during direct examination or histological analysis, and/or the isolation of C. neoformans from any body site should be immediately followed by sampling and culture of CSF, blood, and urine samples and by serum antigen titration, to evaluate fungal burden and to optimize induction treatment.

On the basis of the results of several carefully conducted clinical trials, the 2000 Infectious Diseases Society of America guidelines for the management of cryptococcal meningitis [9] recommends a combination of amphotericin B (AmB; 0.7–1 mg/kg/day or a lipid formulation in the case of renal impairment) and oral flucytosine (100 mg/kg/day) for 2 weeks, followed by fluconazole (400 mg/day) for a minimum of 8 weeks. The proposal to add flucytosine to AmB therapy was made on the basis of the results of the study by van der Horst et al. [10], which showed that 2 weeks of combination therapy was an independent factor that was associated with CSF sterilization. In addition, during the pre-HAART era, Saag et al. [11] demonstrated that the best predictive factor for relapse was the lack of flucytosine administration during the initial 2 weeks of therapy.

Since then, the results of several studies have reinforced the potential value of flucytosine in combination for the management of cryptococcal meningitis in HIV-infected patients. Brouwer et al. [12], in a study performed in Thailand, elegantly pointed out that clearance of cryptococci from the CSF occurred significantly more quickly with AmB plus flucytosine than with AmB alone, with AmB plus fluconazole, or with triple therapy. More recently, in a 4-year French national prospective study (the CryptoA/D study) [6] wherein real-time data were collected during clinical management and 230 adults (including 177 HIV-infected patients) were included, it was found that no flucytosine administration during induction therapy was independently associated with a lack of CSF sterilization at week 2 in HIV-infected patients who had cryptococcal meningitis. In the latter study, the lack of flucytosine—and not only the lack of combination therapy with AmB and flucytosine—during the induction phase was, thus, of major importance. In addition, data obtained in vitro and in a murine model of cryptococcosis showed that synergy can be achieved with AmB–flucytosine combination therapy, even if the isolate is resistant to flucytosine in vitro [13–15]. In addition to antifungal therapy, the diagnosis and management of elevated CSF opening pressure should be systematically sought at the initial stage and potentially during the course of induction therapy to avoid unacceptable early mortality [16]. Finally, among the recent complications that have been recorded during administration of HAART, paradoxical reactions resembling exacerbations of the fungal infection that have been ascribed to immune reconstitution have been qual-

Received 21 March 2007; accepted 21 March 2007; electronically published 25 May 2007.

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Clinical Infectious Diseases 2007;45:81–3
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1058-4838/2007/4501-0015$15.00
DOI: 10.1086/518583
ified as immune reconstitution inflammatory syndrome [17]. Several baseline risk factors for developing immune reconstitution inflammatory syndrome have been reported, such as a low CD4 cell count, initial fungemia, and early initiation of HAART [18]. However, despite available data, the optimal time to initiate HAART during HIV-associated cryptococcosis remains to be precisely documented.

In this issue of Clinical Infectious Diseases, Bicanic et al. [19] comparatively studied early fungicidal activity in CSF samples and outcome of therapy in 54 antiretroviral-naive or antiretroviral-experienced South African patients with HIV infection who were treated with AmB deoxycholate (1 mg/kg/day, 7 days total; \( n = 49 \)) or fluconazole (400 mg/day; \( n = 5 \)) during a first or relapse episode of cryptococcal meningitis. In their nonrandomized study, the patients with less severe cryptococcal meningitis received AmB for 7 days and switched to oral fluconazole, and all patients received appropriate treatment for increased CSF opening pressure. Overall, 2-week early fungicidal activity was significantly higher for AmB than for fluconazole, a difference that remained significant if linear regression modeling was used to adjust for baseline fungal load.

It is tempting to speculate that an explanation of shorter duration of survival is the fact that fluconazole is only fungistatic; however, disease severity can also account for this. Experimental data support the conclusion that administration of fluconazole late in the course of C. neofor mans infection may alter its efficacy [20], and that fluconazole dosage must be increased in the case of severe cerebral cryptococcosis [21]. This is important, given that patients in Africa are often referred to a hospital late in the course of their infection.

Despite these results, debate is not over regarding the induction regimens for cryptococcal meningitis in resource-poor countries facing a pandemic of HIV infection. Indeed, intravenous perfusions of AmB are often difficult to manage, and AmB toxicity is difficult to prevent, thereby precluding a complete induction therapy course in various areas (Doctors without Borders France, personal communication). In addition to the preliminary data obtained here that show a fungistatic effect of fluconazole at 400 mg/day, several data have suggested that fluconazole therapy alone, at least at conventional or low dosages, is inappropriate for the initial management of cryptococcal meningitis in patients with AIDS.

Indeed, Saag et al. [22] have shown that early mortality and median length of time to first negative CSF culture tended to be higher in patients who have received fluconazole, compared with patients who have received AmB. In another study [23], although results were based on a small sample size, the combination of AmB and fluconazole was clinically and mycologically superior to fluconazole monotherapy. Finally, in the 2000 Infectious Diseases Society of America guidelines [9], induction therapy with fluconazole alone at conventional dosages was discouraged. More recently, Bicanic et al. [24], in a recent issue of Clinical Infectious Diseases, also reported that 76% of culture-positive cases of cryptococcosis relapse were caused by isolates with reduced susceptibility to fluconazole in the case of initial azole therapy. Interestingly, in this study, the addition of rifampin played a major role by interfering with the metabolism of fluconazole in patients in South Africa.

Therefore, on the basis of experimental data obtained in animals showing a clear dose response with fluconazole during cryptococcal meningitis [25, 26], data reported by Bicanic et al. [19], and the potential efficacy of higher doses of fluconazole as salvage therapy [27], much higher doses of fluconazole should now be investigated at the initial stages of cryptococcal meningitis in HIV-infected patients.

More precisely, the combination of high-dose fluconazole and flucytosine should, in fact, be studied. Indeed, experimental data have shown that the combination of both drugs was more effective than fluconazole alone [25]. In HIV-infected patients with cryptococcal meningitis, Larsen et al. [28], in an open study, first found that a combination of fluconazole and flucytosine was clinically superior to results that had been previously reported for fluconazole alone. Witt et al. [29] then showed that concomitant use of flucytosine, in addition to fluconazole, was strongly correlated with a better outcome.

Of importance, a randomized Ugandan study [30] demonstrated that the combination of fluconazole (200 mg/day) and flucytosine for 2 weeks was more effective, clinically and on survival, than fluconazole therapy alone.

When considering the current mortality rate of cryptococcosis in South Africa, Bicanic et al. [19] found that it was similar in HAART-naive patients, compared with HAART-experienced patients, at 10 weeks, whereas mortality was reduced in the latter group at 1 year. In a recent study in France [31], early mortality of cryptococcal meningitis did not change over time. Although no data on the incidence of cryptococcosis-associated immune reconstitution inflammatory syndrome are provided here, the same group of authors recently demonstrated that this syndrome is beginning to become a significant cause of mortality in South Africa [32].

In conclusion, a future trial assessing the efficacy of oral high-dose fluconazole and flucytosine in association with an optimal management of increased CSF opening pressure on mycological outcome and survival is mandatory. Results of such a protocol might validate a potential feasible alternative to the classical advocated regimen of AmB and flucytosine for the treatment of cryptococcal meningitis in patients with AIDS in resource-poor countries.

Acknowledgments

I thank Françoise Dromer for her helpful comments.

Potential conflicts of interest. O.L. has given...
keynote lectures for Pfizer, Schering Plough, Gil-ead Sciences, and Merck.

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