Recent Advances in the Management of Cryptococcal Meningitis in Patients with AIDS

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The optimum regimen for the treatment of cryptococcal meningitis in patients with AIDS is still not totally clear. The triazoles fluconazole and itraconazole are associated with response rates of 50%-60%. Amphotericin B appears to be associated with a more rapid clearance of organisms, and there are some data suggesting that initial therapy with amphotericin B is preferable to that with triazoles; however, this finding has not been definitively shown in large comparative trials. Results of a recently completed large trial suggested that initial treatment with amphotericin B followed by triazole therapy is associated with an acute mortality rate (~6%) that is substantially less than that in previous studies. Relapse is common (20%-60% of cases) if the patient does not receive chronic suppressive therapy. The drug of choice for maintenance therapy is fluconazole (200 mg/d). A recent trial showed that fluconazole was superior to itraconazole (200 mg/d) as suppressive therapy. Prophylactic use of fluconazole (200 mg/d) significantly decreases the incidence of cryptococcosis and mucosal candidiasis, especially in patients with CD4 cell counts of <50/mm^3. However, because of the lack of a survival benefit and the risk of the selection effect on fluconazole-resistant Candida, it is difficult to make the recommendation of routine prophylaxis with fluconazole for all patients with AIDS; the decision to use prophylaxis should be based on more selective criteria.

Cryptococcal infections, especially meningitis, are important opportunistic complications of AIDS; these infections occur in 5%-10% of patients with AIDS [1]. Herein, the management of cryptococcal meningitis in patients with AIDS will be discussed, and the areas of controversy and the recent advances will be highlighted.

Azole Antifungal Agents

The triazole antifungal agents fluconazole and itraconazole have contributed greatly to our ability to treat cryptococcal infections in patients with AIDS; however, there has been some uncertainty as to their precise place in therapy for meningitis. The initial published data on these drugs were from noncomparative studies of different groups of patients [2-4]. The response rates (which were defined variably from study to study) associated with either fluconazole or itraconazole ranged from 50% to 60%. Many patients in these studies had received some prior therapy with amphotericin B initially, thus making the true effectiveness of azoles as initial therapy difficult to ascertain.

There have been three prospective, randomized trials [5-7] that have compared triazole antifungal agents with amphotericin B as initial therapy for first episodes of cryptococcal meningitis in patients with AIDS. There has also been a study [8] in which itraconazole and fluconazole were compared as therapy for patients with cryptococcal meningitis who had normal mental status (a factor that has previously had prognostic significance). In all of these trials (table 1), the response rates associated with the triazoles (measured clinically or microbiologically at the end of at least 10 weeks of treatment) were never >50%. Furthermore, the mortality rates among the triazole-treated patients ranged from 7% to 29%. None of the studies identified risk factors that could truly distinguish patients who were more likely to respond to therapy.

Is amphotericin B therapy more effective than triazole therapy? In the two smaller comparative trials [6, 7], amphotericin B was associated with a better outcome (response rates, 80%-100%). In contrast, the largest comparative study [5], which was sponsored by the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) and AIDS Clinical Trials Group (ACTG), failed to show a difference in the response rates associated with amphotericin B and fluconazole. To many observers, the most surprising result of this study was the low response rate associated with amphotericin B, which has been attributed to inadequate dosages in many patients.

Further analysis of the MSG/ACTG trial suggested that although there was not a statistically significant difference between the response rates associated with amphotericin B and fluconazole, there were interesting trends, especially microbiologically. Although the overall microbiological responses were equivalent, the CSF in amphotericin B-treated patients who responded to therapy tended to clear more rapidly (median...
time: 16 days for amphotericin B–treated patients vs. 30 days for fluconazole–treated patients). This more rapid microbiological response was also noted in other studies [6].

Since the major limitations of amphotericin B therapy are toxic effects and parenteral administration, the microbiological observations led the MSG/ACTG investigators to propose a trial studying initial therapy with amphotericin B (with or without concomitant flucytosine) for 2 weeks followed by a "consolidation" period of therapy with high doses of triazoles (MSG 17/ACTG 159). Patients were initially randomized to 2-week courses of treatment with amphotericin B (0.7 mg/ [kg · d]) and either flucytosine (100 mg/[kg · d]) or placebo. Fourteen days after initiation of the study (if the patients successfully completed the first phase of treatment), they were rerandomized to therapy with either fluconazole (400 mg/d) or itraconazole (400 mg/d) for a further 8 weeks. Although all the results of this study have not yet been published, preliminary analysis of the pooled data indicates that the mortality rate is <8%, which is almost one-half that seen in prior controlled trials [9]. Furthermore, following initial therapy with amphotericin B, both fluconazole and itraconazole appear to be equally effective in controlling infection for the next 2 months.

Further support for this approach to management of cryptococcal infections comes from an Italian study [10]; all patients were treated with high-dose amphotericin B (1 mg/[kg · d]) for 14 days followed by maintenance treatment with fluconazole or itraconazole. Of 31 patients who received this treatment, 29 (94%) responded to therapy, and none died of cryptococcosis. On the basis of these results, I recommend that all patients with acute cryptococcal meningitis and AIDS be treated initially with amphotericin B (0.7 mg/[kg · d]) plus flucytosine for 2 weeks followed by fluconazole (400 mg daily) for a further 8–10 weeks. Although some patients may respond to initial therapy with triazoles, the overall response rate is only about 50%, and it is difficult to predict with any accuracy which patients will respond. Furthermore, the toxic effects associated with a relatively short course of amphotericin B treatment are relatively minor and usually tolerable.

There is still an interest in finding effective alternatives to amphotericin B. Three currently investigational options include some form of an alternative formulation of amphotericin B, higher doses of fluconazole, and novel combination therapies. In a preliminary report of liposomal amphotericin B as treatment for 26 patients with cryptococcosis [11], a mycologic and clinical response rate of ~60% was noted, as were minimal toxic effects. There are also preliminary data on the use of higher doses of fluconazole. Berry et al. [12] used fluconazole (800 mg/d) as salvage therapy for seven patients for whom previous therapy had failed and noted responses in four. Hau-brich et al. [13] reported complete responses in five of six patients with cryptococcal meningitis who were treated with 800 mg of fluconazole/d. The median time to conversion of culture results to negative was 21 days.

Initial experience with combination therapy with fluconazole and flucytosine is also encouraging. In a study conducted by the California Collaborative Treatment Group [14], 32 patients were treated with fluconazole (400 mg/d) and flucytosine (150 mg/[kd · d]). Complete clinical responses were noted in 63% of patients (with four patients dying in the first 10 weeks), and mycologic responses were noted in 75% of patients. Furthermore, the median time to sterilization was 23 days. Although many patients experienced some toxic effects from flucytosine therapy (including one death due to gastrointestinal hemorrhage possibly associated with this treatment), most tolerated at least 2 weeks of treatment. These data clearly suggest that this combination merits more extensive investigation.

Once patients have completed initial therapy for acute disease, some form of maintenance treatment is required because of the high probability of relapse in the absence of continuous suppression of cryptococcal growth. The drug of choice for maintenance therapy is fluconazole (200 mg daily), and in randomized, controlled trials [15, 16], this triazole has been

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### Table 1. Summary of data from four randomized, comparative trials of triazole antifungal agents as initial treatment of cryptococcal meningitis in patients with AIDS.

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**NOTE.** ··· = drug not evaluated.

* Defined as mycologic clearance and clinical improvement by the end of treatment (6–10 weeks depending on study).

1 Flucytosine was used in combination with amphotericin B in the studies of Larsen et al. and de Gans et al. and in 14% of patients in the study of Saag et al.
shown to be superior to placebo or weekly administration of amphotericin B. A recent MSG trial (MSG 25) [17] compared fluconazole (200 mg daily) with itraconazole (200 mg daily) as treatment for patients who had successfully completed initial therapy for cryptococcal meningitis (defined by sterile CSF cultures). This trial was halted on the recommendation of the MSG data and safety monitoring committee, because the relapse rate among the itraconazole-treated patients (24%) was significantly greater than that among the fluconazole-treated patients (4%). Thus, it appears that itraconazole should be regarded as second-line therapy in this setting.

Adjunctive Measures for Acute Infection

It is important to note that most deaths due to acute cryptococcal meningitis occur in the first 2 weeks after diagnosis [5]. Many patients who present with acute meningitis have raised intracranial pressures, and there are many anecdotal reports of sudden deterioration in the conditions of and/or catastrophic visual loss in patients with elevated intracranial pressures and cryptococcal meningitis [18–20]. Consequently, many investigators believe that routine measurement of intracranial pressure and management of raised intracranial pressure are critical components of therapy for such patients. Although the most effective therapeutic approach is unclear, anecdotal data suggest that spinal taps removing ~30 mL of spinal fluid that are repeated daily while the pressure is elevated are often very effective in these situations. Occasionally, the placement of lumbar drains or intracranial shunts is needed. The role of corticosteroid therapy in this situation is controversial and is not routinely recommended.

Prophylaxis

Although the epidemiology of cryptococcal infection in patients with AIDS is unclear, it is believed that most cases represent acute primary infection that has disseminated because of the host’s immune defect. Cryptococcus is ubiquitous in the environment and can be isolated from many environmental sites. It is particularly associated with pigeon droppings, and in a recent study from New York City [21], some strains found in pigeon excreta were similar to clinical isolates from patients with AIDS. However, even if avian excreta is the primary source of environmental exposure for most patients, given the ubiquity of the organism and its environmental niche, avoidance of exposure is generally impractical.

Consequently, prophylaxis has concentrated on the use of antifungal agents in patients at greatest risk. When fluconazole was first available in the United States, Nightingale and colleagues [22] routinely administered the drug to patients in Dallas who had CD4 cell counts of <68/mm³; they compared the outcomes for these patients with those for a cohort of former patients who had not received fluconazole therapy. Only one case of cryptococcosis was found in the 329 patients who had received fluconazole treatment, while 16 cases were found in 337 control patients; these findings suggest the possibility that chemoprophylaxis for cryptococcosis might be effective.

The ACTG conducted a randomized, prospective trial (ACTG 981) [23] that compared fluconazole (200 mg daily) with clotrimazole troches as treatment for >400 patients with CD4 cell counts of <200/mm³ who were followed for a median of 35 months. In this study, cryptococcal disease was most likely to occur in patients with CD4 lymphocyte counts of <50/mm³ and was over seven times more likely to occur in the clotrimazole-treated patients (15 of 211) than in the fluconazole-treated patients (two of 217). Fluconazole prophylaxis also reduced the incidence of candidal infection, including esophageal disease; however, a protective benefit against other fungal pathogens was not observed. The beneficial effect of fluconazole prophylaxis for cryptococcal infections seen in this trial is supported by data from observational studies [24, 25] that found that patients with AIDS who received fluconazole treatment in the previous months were less likely to have cryptococcosis. Indeed, the data from these studies suggest that relatively low doses of fluconazole (perhaps even intermittent dosing) might be protective.

Do these results mean that all patients with advanced HIV disease should receive routine antifungal prophylaxis with fluconazole? The answer is unclear. Unlike the situation with prophylaxis for Pneumocystis carinii pneumonia, demonstration of the clinical effectiveness does not automatically translate into a recommendation that fluconazole should be always administered in this setting. Indeed, the situation with antifungal prophylaxis clearly illustrates the difficult decision making that is involved in choosing whether to start preventive therapy for opportunistic infections other than P. carinii pneumonia. This decision making will involve issues of the risk and importance of the opportunistic infection in question, the tolerability of the therapy as well as its potential for drug-drug interactions, the possibility of the selection effect, and the cost-effectiveness of the therapy.

It is difficult to assess the overall importance of fungal infections in patients with AIDS. Candidal infections are very common but are usually confined to the oral and vaginal mucosa. The most severe manifestation of candidiasis in patients with AIDS is esophageal disease, which occurs in ~20% of patients; although esophageal candidiasis is associated with considerable morbidity, it infrequently causes death. Cryptococcal infections account for ~6% of AIDS-defining illnesses; however, there is some suggestion that this incidence is decreasing. In a recent study of patients with CD4 lymphocyte counts of <50/µL by the Community Program for Clinical Research on AIDS (W. El-Sadr, personal communication), the 12-month risk of cryptococcal meningitis was 2.1%, 10 times less than the risk of disseminated Mycobacterium avium complex infection. The reported mortality rate of acute cryptococcal meningitis ranges
from 10% to 30%, although, as noted above, there is evidence from recent treatment trials that this rate is decreasing. Thus, while fluconazole therapy may be effective in reducing the risk of cryptococcal infection and candidial disease, it is unclear how great the impact would be. In the ACTG 981 trial [23], there was no survival advantage for the patients assigned to receive fluconazole treatment.

The advantages of antifungal prophylaxis might be greater for patients living in areas in which the systemic mycoses are endemic, where the risk of fungal infection is higher. Indeed, prospective studies from the Southwest [26] suggest that the lifetime risk of disseminated coccidiomycosis in HIV-positive patients in an area of endemcity is >25%. A similar risk for disseminated histoplasmosis has been estimated in certain cities in the Midwest [27]. Unfortunately, there is little evidence that fluconazole therapy is effective in preventing either of these fungal infections in patients with advanced HIV disease, particularly those with disseminated histoplasmosis, and studies of suppressive treatment suggest that fluconazole therapy may be less effective than itraconazole therapy [28].

Fluconazole therapy is well tolerated in most studies. The most important potential toxic effect is hepatitis, which is idiosyncratic and occasionally fatal. However, as important as toxicity issues are, a greater limitation to the use of fluconazole may be the potential for drug-drug interactions. The azole antifungal agents inhibit the cytochrome oxidase system in the liver, thereby leading to increased levels of drugs metabolized by this system. A clinically relevant interaction has already been described between fluconazole and rifabutin [29], and other interactions may occur as patients with advanced disease are treated with multiple drugs. Interactions between itraconazole and the rifamycins are also clinically significant.

The potential for the development of resistance with routine antifungal therapy has been an important factor in tempering enthusiasm for this therapeutic approach. It is clear that the increase in fluconazole usage has been coupled with rising numbers of anecdotal reports of clinical treatment failures for HIV-positive patients with mucosal candidiasis [30]. A few reports have also demonstrated decreased in vitro susceptibility of Candida isolates from patients for whom fluconazole therapy clinically failed [31]. Fluconazole resistance is most likely to be seen in isolates from patients with advanced AIDS (CD4 cell counts, <50/µL) who have had significant prior exposure to the drug. However, there are no data on the true incidence, prevalence, and risk factors for the development of fluconazole resistance. For example, we do not know whether the emergence of more recalcitrant fungal infections is more likely to occur after exposure to continuous or intermittent therapy with fluconazole. At this point, it is impossible to say that the risks and consequences of developing azole-resistant mucosal candidiasis are substantial enough to limit the use of fluconazole, although the emerging data warrant caution in prescribing chronic or intermittent therapy with fluconazole. However, in the absence of data from clinical trials, it is very difficult to know whether the benefit gained by preventing candidial and cryptococcal infections is outweighed by the possible development of fluconazole-resistant thrush or esophagitis 12–36 months later.

These issues, coupled with the cost implications of routine antifungal prophylaxis, led a U.S. Public Health Service/Infectious Diseases Society of America task force to decide that they should not make a recommendation for routine antifungal prophylaxis for patients with advanced HIV disease [32]. Instead, this decision should be made on an individualized basis with consideration of the following: the relative risk of cryptococcosis and the endemic mycoses, the presence or absence of recurrent candidial disease, and the potential for drug-drug interactions, resistance, and cost. Prophylaxis is likely to be of greatest benefit for patients with very low CD4 cell counts, although further cost-effectiveness trials are needed for a clearer answer.

References


