New Agents for Treatment of Invasive Aspergillosis

Thomas F. Patterson
Department of Medicine, University of Texas Health Science Center at San Antonio

(See the article by Bowden et al. on pages 359–66)

Invasive aspergillosis remains a significant clinical challenge. The long-standing “gold standard” of therapy has been amphotericin B (AmB), the usefulness of which is severely limited because of the substantial toxicities associated with the doses of AmB required for treatment of this disease and because of the lack of efficacy of the agent in severely immunosuppressed hosts [1, 2]. Clearly, there exists a major medical need for new antifungal agents for the treatment of invasive aspergillosis; however, the development of effective therapies has been hindered by the lack of diagnostic tools to establish a clear and prompt diagnosis of infection, and outcomes are likely to be poor in the most immunosuppressed patients in whom host immune defects persist [3]. Thus, few randomized trials evaluating therapies for invasive aspergillosis have been conducted successfully [4]. Most new antifungal agents have been evaluated in patients who were receiving salvage therapy for invasive aspergillosis after having received initial therapy with AmB, and few studies have addressed the outcomes associated with use of these drugs as primary therapy for this disease. This approach has left unanswered major questions regarding the efficacy of new agents, including lipid formulations of AmB, especially with regard to their use as primary therapy for this often lethal disease.

Given this background, it is easy to see that Bowden et al. [5] should be congratulated on the completion of a randomized trial in which a lipid formulation of AmB (amphotericin B colloidal dispersion [ABCD]; Amphocet) was compared with AmB for use as primary therapy for invasive aspergillosis. The primary end point of efficacy in the study was assessed by use of an evaluable patient population who met the following criteria: diagnosis of proved or probable invasive aspergillosis and receipt of therapy for >7 days. In addition, successful responses to therapy were classified as complete response, partial response, or stable disease. By use of these parameters, successful responses occurred in 26 (52%) of 50 patients who received ABCD, 6 mg/kg/day, compared with 27 (51%) of 53 patients who received AmB. In addition, toxicity rates that required study drug discontinuation were similar in the 2 treatment groups (22% for the ABCD group vs. 24% for the AmB group). Of note, less nephrotoxicity was seen with the use of the lipid formulation, although greater infusional toxicities also occurred with its use. However, despite these favorable rates of response and decreased rates of renal toxicities, several features of the study design, response evaluation, and assessment of toxicity should be noted.

As the authors clearly state, it should be realized that, after >4 years of study accrual at multiple international sites, the study was closed before target enrollment was met. Because of this early closure, the study was underpowered to show differences in the efficacies of the 2 therapeutic arms. One reason for the slow patient accrual may have been the study’s use of a rigorous diagnostic standard for the establishment of proved and probable cases of disease, which was similar to standards published elsewhere for clinical trials of invasive mycoses [6]. Although these criteria define a study population with well-documented infection, the lack of required serological or radiographic testing of patients for inclusion in the study likely resulted in a study population with more advanced disease and also limited the size of the patient population eligible for a primary evaluation study, because many patients already would have received therapeutic doses of AmB empirically, pending confirmation of a diagnosis. Of note, as might have been predicted by the study design, the study population did include a substantial proportion of patients with proved infection, which is often associated with a poorer outcome. That feature may well have unfavorably biased the results in both treatment arms, although more patients who were receiving AmB were found to have proved infection.

However, even with the substantial pro-
portion of patients with proved infection, the overall efficacy in each of the 2 treatment arms in this study was >50%. The response rate associated with either agent is higher than the rates noted in other recent historical studies, particularly considering that many patients in the study by Bowden et al. [5] were highly immunosuppressed, including >40% who were undergoing bone marrow transplantation [2]. In addition, although no comparative trials of new agents have yet been conducted, several trials of new agents for salvage therapy for invasive aspergillosis have reported efficacy rates of >40%, and the rates of response to AmB are often half those seen in comparative populations [7–12]. Thus, are we to conclude that, for use as primary therapy, both ABCD and AmB were, in fact, substantially more effective in this study?

It is important to realize that, in the efficacy analysis used in the trial, all patients in the evaluable population were required to have received therapy for a minimum of 7 days. Although early deaths may not be preventable with the use of any antifungal agent, the requirement of receipt of therapy for 7 days for evalua-

bility certainly increases the apparent rates of response. By use of an intent-to-treat analysis, the response rates associated with ABCD and AmB in the study of Bowden et al. [5] (in which stable infection was included as a satisfactory response to therapy) decreased to 35.2% and 34.8% in each arm, respectively.

In the trial, satisfactory outcomes included not only complete or partial responses but, also, stable infection, which was defined by clinical improvement and by radiographic findings that did not show >50% improvement. In patients with stable infection, the median duration of administration of either therapeutic agent was ~2 weeks, which may not have been long enough to realistically produce a complete or partial radiographic response, although it is not known how rapidly radiographic evidence of invasive aspergil-

nosis responds to therapy or whether residual disease predicts response.

Although long-term stable disease in highly immunsuppressed patients may, in fact, be considered a clinical success, other recent clinical trials have used more strict criteria to determine success—that is, evidence of a complete or partial response [2, 7–13]. For example, in open-label trials of liposomal AmB, AmB lipid complex, itraconazole, voriconazole, and caspofungin, rates of successful response to these agents as salvage or primary therapy were 33%–52%, although it should be recognized that the criteria for study inclusion and the populations evaluated in each of these open-label trials certainly influenced overall outcomes and made comparisons difficult. In fact, no comparative studies of new agents have been conducted. Although few large comparative trials have evaluated primary therapy in patients with documented invasive aspergillosis, a recent comparison of voriconazole versus AmB as primary therapy for invasive aspergillosis—a comparison that, to date, has been reported in abstract form only—noted complete or partial responses in 52% of patients treated with voriconazole, compared with 31% of those treated with AmB, when either therapy was allowed to be followed by therapy with other licensed antifungals [10]. In the study of Bowden et al. [5], the rate of complete or partial responses among patients in the intent-to-treat population decreased to a disappointing 12.5% among those who received ABCD and to 15.1% among those who received AmB.

Another objective of the study of Bowden et al. [5] was to compare the toxicities of ABCD and AmB. Statistically, less nephrotoxicity occurred among patients who received the lipid formulation of AmB, but more infusion-related toxicity (chills) also was seen among those patients. Hypoxia, which was a limitation in a previous trial [14], was not more frequently associated with ABCD in the study of Bowden et al. [5]. However, neither of these therapies was tolerated in the long

term; the median duration of therapy was 13.0 days for ABCD and 14.5 days for AmB, which suggests poor long-term tolerance of either agent.

In summary, this useful study is one of the few to have evaluated primary therapy for invasive aspergillosis. Although the formulation of AmB chosen for the study may have more toxicity than other lipid preparations [10, 13], the results attained when substantial dosages of a lipid formulation (6 mg/kg/day) were used for primary therapy of this disease do not suggest an overwhelming rate of response. In fact, careful examination of the data shows response rates similar to those associated with AmB and suggests outcomes that may be inferior to those associated with other compounds. Additional evaluation of the optimal use and dosages of lipid formulations of AmB is required to answer the many clinical questions about these topics, but an important finding of the study of Bowden et al. [5] is the additional evidence for the unacceptable outcomes and poor tolerability associated with the use of AmB for treatment of this disease.

References