Combination Therapy for Aspergillosis: Is It Needed, and Which Combination?

The current Infectious Diseases Society of America expert panel recommendations call for the use of the standard deoxycholate formulation of amphotericin B for treatment of invasive aspergillosis [1], a regimen proven in a recent study to be inferior to voriconazole [2]. The recommendations also discourage use of combination therapy, a strategy that already has become common [3–5]. But are new therapies still necessary, in view of the recent experience with voriconazole [2]?

In that study, the clinical response to voriconazole was 52%, and survival was 71% [2]. The study was truly remarkable, the finest comparative trial of treatment for invasive aspergillosis to date, enrolling nearly 400 patients at 95 centers in 19 countries from 1997–2000. But does it answer the question “what is the best treatment for aspergillosis”? As often happens in clinical trials, the amphotericin B arm was obsolete before the study was completed, because clinicians had largely replaced amphotericin B with the less toxic lipid formulations. In addition, the majority of patients in the amphotericin B arm quickly stopped the randomized therapy and initiated alternative treatment with other approved agents—a problem that might have been alleviated by blinding or by the use of a lipid formulation of amphotericin B [6]. A better comparison would have been voriconazole versus liposomal amphotericin B [4, 6–11], but today the more relevant question may be whether combination therapy has a role in treatment of aspergillosis [9, 12].

The voriconazole study, despite its shortcomings, raised the bar for future comparative trials involving aspergillosis. To show a 10% improvement in survival over that achieved with voriconazole alone will require 570 evaluable patients and enrollment of >800 subjects (assuming that 70% of enrollees are evaluable [2]), and a less rigorous design would require 328 evaluable patients and enrollment of 470 subjects to demonstrate a 15% improvement in clinical response.

We must ask the right question and choose the best combination before committing limited resources to such a difficult and expensive trial. Preclinical studies, such as that of Petraitis et al. [13] published in this issue of The Journal of Infectious Diseases, offer a way to identify synergistic antifungal combinations for trials in humans. Petraitis et al. [13] demonstrated synergy between ravuconazole and micafungin in vitro and in their animal model, using a variety of elegant outcome measures, complementing the findings of others [14, 15]. But have we identified the most relevant model?

A number of issues should be considered in defining the optimal animal model for evaluation of therapy for invasive aspergillosis. First, animals should be infected by the respiratory route, because infection in humans is caused by inhalation, and the lung is the major site of infection. The lung may not be as heavily infected after hematogenous challenge [14, 16]. Second, the timing, intensity, and duration of therapy should be patterned after the conditions experienced in humans. Namely, therapy should be delayed a few days after the initiation of infection, giving the infection time to establish a significant fungal burden, and therapy should be of sufficient intensity and duration to maximally suppress fungal proliferation. Use of suboptimal doses or durations of therapy to show synergy is undesirable and does not resemble the approach used in patients. Third, fungal burden, not survival, should be the primary outcome measure. Suboptimal therapies may improve survival without greatly reducing fungal burden [17–19]. Failure to sterilize the tissues will permit relapse after treatment is stopped in the persistently immunocompromised host. In addition, fungal burden in the brain should be measured, because the brain is commonly involved in invasive aspergillosis, and brain infection may pose unique challenges to therapy. Although tests for fungal metabolites, antigens, cell-wall chitin, or DNA may be surrogates for fungal burden, quantitative culture is the reference standard and should be retained for determination of the primary end point: sterilization of the tissues at completion of therapy and prevention of relapse 4–7 days later.

Several combinations deserve consideration for treatment of aspergillosis. Echinocandins also have exhibited synergy with amphotericin B [20–22]. However, that they do not greatly reduce fungal burden in aspergillosis, and may even increase it [23, 24], is a cause for concern that requires careful review. Other agents for investigation include liposomal nystatin [25], nikkomycin Z [26], and terbinafine...
The combination of a triazole with amphotericin B is potentially antagonistic [28–32] but has demonstrated efficacy in aspergillosis models [33, 34] and is being used in patients [3, 4]. These regimens should be compared in animal models to provide support for design of future clinical trials.

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References


