Combination Therapy for Invasive Aspergillosis

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(See the article by Marr et al. on pages 797–802)

Mortality in patients with invasive aspergillosis (IA) remains unacceptably high, particularly in the subgroup of patients receiving hematopoietic stem cell transplants (HSCTs) [1]. For this reason, when caspofungin and voriconazole, which target different sites within the fungal cell, became available, a great deal of interest was raised by the theoretical possibility of obtaining synergistic effects using the 2 drugs in combination and thereby improving the management of this dreadful disease. However, the assumption that the use of ≥2 effective drugs with different mechanisms of action will produce an improved result, compared with use of a single agent, needs in vitro, in vivo, and clinical validations.

Available data on combination therapy for the treatment of invasive fungal infections have been recently reviewed [2]. In vitro studies have shown that the combination of one of the new triazoles (e.g., voriconazole, posaconazole, and ravuconazole) with an echinocandin (e.g., caspofungin, micafungin, and anidulafungin) is often synergistic but is sometimes indifferent (although never antagonistic) against Aspergillus. Animal models have shown somewhat conflicting results. In a guinea pig model of IA, Kirkpatrick et al. [3] failed to show improved survival in animals treated with voriconazole alone or voriconazole plus caspofungin, although the combination was more effective in sterilizing the studied organs than was monotherapy. On the contrary, in a rabbit model, Petraitis et al. [4] found better results with ravuconazole and micafungin in combination than with either agent alone in terms of improved survival, lower residual fungal burden, and more rapid clearance of serum galactomannan antigenemia. In summary, preclinical data seem promising in terms of ensuring synergistic effects in treating Aspergillus infections, although several methodological aspects need to be clarified (for example, the time relationship between Aspergillus challenge and start of treatment) [5]. Whether these experimental data will translate into a clinical advantage for the patient and will be cost effective for the health care system is a completely different problem and needs to be tested in controlled and carefully planned clinical trials. The available data on clinical experience, although not particularly exciting as pertains to response rates, are very limited and do not allow any definitive conclusions [6, 7].

In the current issue of Clinical Infectious Diseases, Marr et al. [8], from the Fred Hutchinson Cancer Research Center in Seattle, Washington, present an observational study of salvage therapy in patients with IA, in which the 3-month survival rate of only 31 patients experiencing failure of first-line therapy with amphotericin B and subsequently treated with a combination of voriconazole and caspofungin is compared with that observed in a historical group of just 16 patients treated with voriconazole alone under the same clinical circumstances. Salvage therapy was administered for a median of 33 days in the historical control group, compared with 68 days in the combination therapy group. Results show better overall survival in the combination therapy group, with a P value just reaching significance (.05). The probability of death due to aspergillosis, after having excluded patients who died due to relapsing leukemia, was lower in patients who received combination therapy, compared with the historical control group, who received voriconazole alone (P = .02). In multivariate models, combination therapy substantially reduced the risk of death (hazard ratio [HR], 0.27; 95% CI, 0.09–0.78; P = .008). Other variables were tested for their association with the outcome. Surprisingly, in contrast with other studies [1], disseminated aspergillosis was associated with a lower risk of death in the univariate analysis (HR, 0.35; 95% CI, 0.08–1.5), although with a nonstatistically significant P value of .09, and it was not predictive of survival in the multivariate models. Also surprising, and in contrast with most studies, was the fact that, in the multivariate analysis, patients...
with hematological malignancies not receiving HSCBs had a higher risk of death (HR, 3.8; 95% CI, 1.2–12) than did patients who received HSCBs (although with a nonstatistically significant \( P \) value of .32).

In the discussion section, Marr et al. [8] appropriately point out the limitations inherent in observational studies and in the use of historical control subjects. However, their conclusion is not free of some ambiguity. Indeed, they say that further studies are needed to show that combination therapy is better than single-drug therapy for first-line therapy of aspergillosis, as if they were considering their study [8] to have proven that combination therapy is the best choice for salvage therapy; in my opinion, this is not the case, for the following reasons.

First, although the significance of observational studies has recently been reconsidered [9], the results of nonrandomized studies may differ substantially from the results of randomized studies conducted in the same clinical circumstances, even when treatment and control groups are relatively well matched, as in this case, and even when a well-defined and easily measured end point like survival is used. Usually, historical control studies tend to underestimate results in the control group and show larger treatment effects than randomized studies [10]. This bias may be even more important in studies involving iatrogenically immunocompromised patients. Indeed, IA, as any other opportunistic infection, affects patients who are already affected with another severe disease, for which very aggressive and intensive treatments are usually employed. This means that, in these clinical circumstances, the effect of the underlying condition and its treatment may be so significant that it confounds the results of the treatment of the opportunistic infection, even when dealing with a strong end point such as mortality.

Second, research in the field of invasive fungal infections is progressing, and most of the changes in diagnosis and management are very recent. An important change has been the introduction of 2 important diagnostic tools, like the \( \text{Aspergillus} \) galactomannan antigen detection and the sequential use of high-resolution pulmonary CT scan, potentially able to allow earlier diagnosis [11, 12]. These changes suggest another bias potentially affecting historical control studies (not necessarily the study by Marr et al. [8])—because earlier diagnosis might allow earlier treatment, which in turn might be associated with better outcome [12].

Third, as has been the case with all published studies of salvage therapy for IA, this study includes no description of the engagement rules for shifting the patients to salvage therapy. I assume that these rules did not change between the 2 periods of the study, but I do not know the meaning of “progressive infection…after \( \geq 7 \) days of amphotericin-based therapy” (p. 798) in practical terms [8]. Persistence or worsening of respiratory symptoms? Radiological failure with no change or enlargement of the lesions? A combination of clinical and radiological criteria? Definition of treatment failure in patients with IA and the optimal duration of treatment before declaring failure are both important issues on which research groups should try to reach a consensus.

In conclusion, the study by Marr et al. [8] represents a very interesting, well-documented, and meaningful clinical experience that suggests that the administration of voriconazole and caspofungin in patients with IA who experience failure of amphotericin B therapy might be associated with a markedly improved survival rate, compared with voriconazole alone. Even though the size of the observed effect (a 73% reduction in mortality) is striking, the limited size of both the experimental group (31 patients) and the control group (16 patients) and the great potential for important biases arising in historical comparisons substantially undermine any definitive conclusion that one might draw from this study. Furthermore, as Marr et al. [8] correctly underline, combination therapy might increase toxicity and drug interactions. In addition, its cost is extremely high and might be prohibitive for many hospital budgets. Finally, clinical practice in the management of aspergillosis has changed. After the approval of voriconazole as first-line therapy of IA, clinicians are now facing patients who experience treatment failure with or are intolerant to voriconazole, not amphotericin B. How should one interpret these data in the light of this change?

This study [8] certainly represents the rationale for future phase III, randomized clinical trials of both salvage and first-line therapy comparing a triazole that has documented clinical efficacy in IA (e.g., voriconazole) with the same triazole plus an echinocandin that has documented clinical efficacy in IA (e.g., caspofungin). These studies should be placebo-controlled, unless mortality is used as the main end point. It is not impossible for the existing research groups (Bacterial and Mycosis Study Group of the National Institute of Allergy and Infectious Disease Group of the European Organization for Research and Treatment of Cancer) to test the concept of combination therapy in randomized clinical trials. Meanwhile, great caution should be used before recommending combination therapy in the management of IA.

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References

2. Johnson MD, MacDougall C, Ostrosky-


