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The debate: A case for randomized controls in invasive aspergillosis

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Randomized trials in invasive aspergillosis have evolved over the past decade. Definitions of disease now include specifics of the underlying disease and how this affects interpretation of certain tests, including high resolution computed tomography and smears or cultures of sputum and bronchoalveolar lavage. Study hypotheses have changed from underpowered superiority trials to adequately powered noninferioirty trials. Consensus building between Europe and North America has allowed trials to be conducted with the same protocol in both regions, thereby increasing study enrollment. In aggregate, the following outcomes can be drawn from randomized trials: (i) Liposomal amphotericin B is possibly superior to conventional amphotericin B at 14 days and less toxic. Whether the dose of liposomal amphotericin is 1 or 4 mg/kg daily is not as important as other factors in determining outcome of possible aspergillosis; (ii) amphotericin B colloidal dispersion is less nephrotoxic but has more acute infusion-related reactions than conventional amphotericin B; (iii) starting treatment with voriconazole is superior to starting with conventional amphotericin B. In an era of increasing cost containment, it will be the randomized trials that provide the clinician with the information needed to avoid inappropriate use of expensive drugs and drug combinations.

Keywords Aspergillosis, trials, antifungal

The usual advantages of randomized clinical trials have been enumerated elsewhere but additional advantages in this trial design have accrued for invasive aspergillosis (IA). First, the trials disabused the idea that such trials could not be done. At the time when the US Food and Drug Administration (FDA) approved itraconazole and caspofungin based on open, non-randomized trials, one of the arguments made by industry and advisory committees was that randomized trials were impossible because inadequate numbers of patients were available. Second, the trials proved that sufficient numbers of investigators could agree about entry criteria. In the not-so-distant past, patients with chronic lung disease who had *Aspergillus* in their sputum were considered to have aspergillosis, with no distinction between hyphae growing in ectatic bronchi and hyphae growing within bronchial walls or alveoli. Introduction of the term 'invasive aspergillosis' helped focus on the difference between infection and colonization. Fungus ball of the lung or of the paranasal sinus and allergic bronchopulmonary aspergillosis became recognized as distinct entities which were not infections, meaning that the fungus was growing in previously existing air spaces, not proliferating within viable tissues of the host. Third, entry criteria for studies benefited by creation of a category of 'probable' IA, using diagnostic criteria that are only suggestive of the diagnosis when the patient is in a highly vulnerable population [1]. The category of 'probable' IA allowed patients to be enrolled earlier in the infection, a time when drugs were more likely to be effective. Definition of 'probable' IA is still being refined and will change as

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newer laboratory tests and immunosuppressive regimens evolve. Ideally, a reliable noninvasive diagnostic test for early infection will someday eliminate the need for a category of 'probable' IA.

The limitations of randomized trials are at least well known as their advantages. Patients enrolled in studies generally differ from the population of patients with the disease, requiring extrapolation of the randomized study results to patients not enrolled in the studies. With IA, the extrapolation has often extended to patients who are not likely to have the infection. These patients have a much different risk–benefit ratio, and are potentially subject to adverse drug effects without benefit of treating the correct disease. Another extrapolation is to consider that patients who might benefit from a single active drug are even more likely to benefit from adding one or more active drugs, increasing toxicity and cost without a known added increase in efficacy.

It is easy to find fault with the published randomized trials of IA. Under the general principle that it is 'better to light a candle than to curse the darkness', this paper will examine what has been learned about treatment of IA from randomized trials. The analysis will show that we have learned not only about treating IA but also how to study it. The first of these trials was conducted in Nijmegen, The Netherlands, by Verweij *et al.* in 1988–1991 [2]. Although the study included both candidiasis and aspergillosis, 18 of the 28 patients had aspergillosis. The definition of IA might not be acceptable today, based in large part on a sputum containing at least 50 *Aspergillus* colonies per ml in a neutropenic acute leukemic patient with pneumonia not responding to antibacterial therapy. The study was seriously underpowered for conclusions about aspergillosis, with only nine aspergillosis patients per arm. This trial tested whether addition of intravenous flucytosine to amphotericin B would be superior to amphotericin B alone, using survival as an endpoint. With only one patient surviving treatment in the amphotericin B arm and two in the combination arm, the study proved that amphotericin B at doses of 0.5–1.0 mg/kg, with or without flucytosine, was associated with a dreadful outcome in this patient population.

The Nijmegen study added rationale to a study conducted during 1992–1996 in several centers in the Netherlands and in Strasbourg, France [3]. This study enrolled neutropenic patients with deep mycoses, with 55 having IA, defined as unresponsive pneumonia with hyphae or a positive culture of *Aspergillus* in lung, sputum or bronchoalveolar lavage. The study was designed to test whether liposomal amphotericin B 5 mg/kg was at least 40% superior to conventional amphotericin B 1 mg/kg on day 14 of therapy. Although it might seem that expecting such a great difference over such a short time interval was a lot to ask, a 40% difference (delta) allowed a small sample size and was plausible based on the prior miserable results with amphotericin B. The outcome was that eight of 29 (27%) patients treated with conventional amphotericin B responded, compared to 13 of 26 (50%) treated with liposomal amphotericin B. The result was a failed superiority trial but nevertheless encouraged further study of liposomal amphotericin B.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a nearly simultaneous study during 1993–1996 [4]. This international study was the first randomized trial confined to IA. The diagnostic criteria included many patients with only a clinical suspicion of the disease. Almost all patients had been treated with up to 500 mg of conventional amphotericin B before enrollment. The study was designed to test whether liposomal amphotericin B 4 mg/kg was superior at the end of treatment compared to the same drug at 1 mg/kg. Unlike the usual design of superiority trials, the percentage by which the higher dose was hoped to be superior was not specified, supplanting this with a simple test for a difference at $p \leq 0.05$ for each of two endpoints, one being clinical improvement and the other radiological improvement, including a stable image as an improvement. No specified time for censoring the data for success was included in the design. Surprisingly, the lower dose provided superior results by both clinical and radiologic criteria. Although this study failed to show that 4 mg/kg was superior to 1 mg/kg, the study provided food for thought about subsequent study designs.

A different amphotericin B formulation, a colloidal dispersion (ABCD), was studied during 1993–1997 but only published in 2002 [5]. The double blinded randomized study, largely done in the United States and Canada, was a noninferiority trial with a stated delta of 15%. Conventional amphotericin B 1–1.5 mg/kg was compared to ABCD 6 mg/kg. Invasive aspergillosis was defined as positive cultures from lung, bronchoalveolar lavage or two sputums or visualization of hyphae in lung or bronchoalveolar lavage in a patient with pneumonia. The specified underlying diseases included a broad range of immunosuppressive conditions and chronic lung diseases. This is the only randomized trial to include patients with chronic obstructive pulmonary disease, cystic fibrosis and diabetes mellitus as underlying diseases. A third party, blinded to the treatment arm, reviewed the data. One hundred and three (59%) of 174 enrolled patients were included in the primary

efficacy analysis. Inclusion required absence of protocol violations and receipt of at least seven days of therapy. Patients who died in the first week or switched to other drugs were excluded from the primary efficacy analysis. A therapeutic response occurred in 52% of 52 ABCD recipients and 51% of 53 conventional amphotericin B recipients. Because of the small sample size, the 95% confidence intervals were broad, permitting the possibility that ABCD might be 18% worse or 20% better than conventional amphotericin B. This was a failed noninferiority trial as primary therapy. Consequently the drug was licensed for salvage therapy of aspergillosis, not primary therapy. In an analysis of all 174 patients, 35% of ABCD and 35% of conventional amphotericin B recipients responded, with the 61% of the 61 favorable responses being stable disease, not a complete or partial response. Nephrotoxicity of ABCD was less than conventional amphotericin B but drug related chills and fever were more common with ABCD.

The largest randomized study of IA was conducted in 1997–2000 to compare voriconazole with conventional amphotericin B, the only drug licensed for the primary treatment of IA [6]. This open, noninferiority trial tested whether voriconazole efficacy was within 20% of amphotericin B. To allow for the expected early termination of conventional amphotericin B due to toxicity, the study allowed patients in either arm to be changed to any other drug licensed for salvage therapy in aspergillosis. The licensed drugs used as salvage therapy at the time were itraconazole, amphotericin B lipid complex and liposomal amphotericin B. Diagnostic criteria were set by an international committee and centered around the Mycoses Study Group/European Organization for Research and Treatment of Cancer (MSG/EORTC) consensus criteria, with the additional use of computerized tomograms (CT) [1]. Patients with a hematopoietic stem cell transplant or neutropenia due to hematologic disease and who had a halo or crescent sign on CT not attributable to another infection were considered as having probable IA. Of the total of 155 patients enrolled because of this criterion, 60 were excluded by the radiology review committee because they could not confirm the presence of a halo or crescent sign. The remaining 95 patients enrolled because of this finding constituted 34% of all enrolled patients. Unlike the ABCD study, stable radiology at the primary endpoint of 12 weeks was considered a failure. Serum galactomannan was not available at enough centers to be considered for addition to the enrollment criteria. Entry criteria and therapeutic response were reviewed and confirmed or rejected by a panel of experts blinded to the study drug. The primary efficacy analysis found a 53% response in the voriconazole arm and 32% in the amphotericin B arm. With confidence intervals showing that voriconazole was between 10% and 33% superior to the amphotericin B arm, the former regimen was considered superior to the latter. In a secondary analysis, crude survival was also superior in the voriconazole arm. A valid criticism of this study is that the median duration of conventional amphotericin B was only 10 days compared to 77 days for voriconazole. A subsequent analysis found that patients switched from conventional to a lipid formulation of amphotericin B had only a 30% response rate (14 of 47), this number being a composite of a 38% response in those switched for toxicity and 19% in those switched for failure [7]. A reasonable conclusion of the study is that starting with conventional amphotericin B for IA was inferior to voriconazole and that changing to a lipid formulation later did not result in significantly improved efficacy. The study does not allow a conclusion as to how starting with a lipid formulation would compare with initial voriconazole. The physician's individual decision will have to be informed by matters of cost, oral use, and drug interactions.

No other randomized trial has been conducted on IA since the voriconazole study was published in 2002. This regrettable fact lies in the reticence of companies to spend money that they may not recoup in sales. Studies using caspofungin, micafungin and posaconazole have been open salvage trials that offer at best qualitative statements about efficacy of these drugs. The lack of clear definitions for entry into salvage trials has made these reports even less informative than they might be [8]. The medical community is in serious need of quantitative data about newer drugs alone and in combination for IA. The methodology is not perfect but has sufficient consensus to be usable [9]. Relying solely on opinion of experts is to abandon all that has been learned in the last two decades.

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