Salvage Therapy for Aspergillosis

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Participants at the John E. Bennett Forum on Design of Clinical Trials for Fungal Infections suggested guidelines for the regulatory approval of drugs solely on the basis of salvage therapy—that is, the use of an unlicensed drug to treat patients who have experienced failure with or who have been intolerant of an approved drug. The topics covered included requirements for study design (i.e., the design allows the comparison of comparable items), entry criteria (in particular, the duration of therapy before salvage therapy is introduced), and outcome criteria that determine whether or not the treatment was successful.

The initial approval for marketing of caspofungin by the US Food and Drug Administration was based only on a salvage trial involving patients with invasive aspergillosis; the event appears to have ushered in a new era of development of antifungal drugs. The approval waived the requirement for a randomized trial in which a new drug was compared with a drug of proven efficacy for the initial treatment of a mycosis. Instead, patients were entered into this open, nonrandomized study after failure of or intolerance to prior therapy and were compared with a historical group [1]. In consideration of the absence of precedents for registering a drug on the basis of on salvage therapy, participants at the John E. Bennett Forum on Design of Clinical Trials for Fungal Infections set about to offer suggestions for the conduct of future salvage trials involving aspergillosis. The session was chaired by John Wingard.

REQUIREMENT FOR STUDY DESIGN

The regimen chosen for salvage therapy must have a strong rationale, because patients experiencing failure of conventional therapy for invasive aspergillosis have a very poor prognosis [2]. Salvage regimens can and should be compared with randomized controls. Historical controls, even if contemporary, are never the same population that is entered into a clinical trial.

If patients are experiencing rapid failure, randomization should be between the new drug and another drug already licensed for either initial or salvage therapy. Unlike trials for primary therapy, the comparator would not have to be licensed for initial therapy. For example, if the patient were experiencing failure of voriconazole, which is licensed for initial therapy, the comparators for a new drug could be liposomal amphotericin B (AmBisome), amphotericin B lipid complex, itraconazole, or caspofungin, all of which are licensed for salvage therapy. Either a superiority or a noninferiority trial design could be used. As discussed in detail in a previous forum [3], most antifungal drugs have been licensed on the basis of demonstration that they were not inferior to a drug licensed for that indication. Although rarely used, a superiority trial asks whether the new drug provides a significantly better outcome than does a licensed drug.

If patients being entered into the trial have stable or slowly progressive disease, the interesting possibility arises of continuing the original regimen as 1 arm of the study. The single drug chosen for study would have to be popular enough to enroll a sufficient number of patients and instill sufficient confidence that investigators would be willing to continue the drug despite inadequate response in some patients. The other arm could be the original drug plus a single new drug used in combination, provided that the trial was a superiority trial. With this trial design, one could ask whether adding a second drug was better than continuing the orig-

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inal regimen alone, which is a very useful question. The other kind of trial, a noninferiority trial, could show, at best, that the addition of a single new drug was not worse than continuing the old drug alone, which is not a useful conclusion. The only way to use the usual noninferiority trial design would be to compare continuing the old drug with switching to an entirely different drug and asking if the outcome was at least no worse than that associated with the new drug. Either design allows assessment of the common practice of changing drugs for a patient who is not responding well to the initial therapy. In either case, patients in 1 arm of the study would continue with the existing therapy. The design would be successful only if the patients randomized to continue initial therapy were sufficiently stable to continue the initial regimen for a long enough period to determine efficacy.

Patients with different underlying diseases or conditions, such as solid-organ transplantation, AIDS, and stem-cell transplantation, have different outcomes. Either these different groups should be entered into different trials or the randomization and outcome should be stratified by groups of underlying disease with similar outcomes.

ENTRY CRITERIA FOR SALVAGE THERAPY

Patients who are entered into a salvage therapy trial either are intolerant of or have experienced failure of initial therapy. These 2 groups require separate trial designs and should have separate trials. The majority of the discussion at the forum was centered on trials of patients who have experienced failure of, rather than been intolerant of, conventional therapy. The problem of drug intolerance in treating invasive aspergillosis has been mitigated by the favorable safety and efficacy profile of voriconazole [4].

Minimum and maximum times should be established for the duration of initial therapy before the patient is judged to have experienced treatment failure. Patients considered to have had treatment failure because of radiological progression should have the following characteristics:

- First, they should have received therapy for >1 week. Radiological progression may be seen during the first week of treatment in patients who later respond. Also, patients who are extremely ill may die during the first week and may be too ill to respond to any new regimen.
- Second, they should have radiological images by the same technique available for external review. CT should be compared with CT, chest radiography with chest radiography, and MRI with MRI.
- Finally, they should show progression of infiltrates or appearance of new infiltrates in order to document progression. Radiological findings must be accompanied by clinical signs of active infection.

Patients enrolled because of inadequate response should have clinical signs of continuing infection, such as fever. Failure to document improvement by radiology alone is not adequate evidence of failure, because results seen on imaging may improve very slowly.

OUTCOME CRITERIA IN SALVAGE THERAPY

Death from any cause should be considered as failure. Patients with invasive aspergillosis have serious comorbidities. Trying to discern the role that aspergillosis played in the patient's death is too often open to question. Patients entered into the trial because of stable disease cannot be judged as having treatment success if disease remains stable.

The necessity of switching to a new agent or addition of a new agent should be considered as a treatment failure. The case report form should capture as much detail as possible about the change in regimen so that failures due to toxicity may be distinguished from failures due to inefficacy. Every effort should be made to limit the number of patients whose regimens are changed. Serum galactomannan testing is not currently documented to be a reliable marker of success or failure.

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