Double-Blind Active-Control Trials: Beware the Comparator You Keep

Mark J. DiNubile
Merck Research Laboratories, West Point, Pennsylvania

The indirect impact of the known comparator drug in double-blind comparative clinical trials of novel agents is underappreciated, despite its potentially pernicious effects. This hypothesis-generating analysis illustrates potential spillover effects of a comparator (amphotericin) in the evaluation of the first member (caspofungin) of a novel class (echinocandins) of antifungal drugs. Reported rates of drug-related fever in the first 3 studies of caspofungin for the treatment of mucosal candidiasis in patients with advanced human immunodeficiency virus infection were retrospectively analyzed. We compared patients who received 50 mg of caspofungin per day in a double-blind trial that used fluconazole as the comparator with patients who received the corresponding dosage in 2 similar earlier studies that used amphotericin as the comparator. With respect to the incidence of drug-related fever, the difference between the concurrent caspofungin and fluconazole groups was less than the difference between caspofungin groups from studies that used different comparators. In phase II/III blinded, active-control trials, the reporting of adverse experiences attributed to a first-in-class drug might be confounded to a variable degree by expectations regarding a well-known comparator.

In drug development, comparative trials with an active control group serve to place the new kid on the block in the context of established therapy. However, standards—whether gold or bronze—come with their own baggage. Adverse events may be attributed to a novel agent with a frequency that is, in some part, modulated by the reputation of the comparator drug, especially during initial assessment of unconventional compounds in double-blind studies. Consequently, untoward events typically associated with the known comparator may be reflexively reported to the sponsor by site investigators as possibly drug related.

This brief hypothesis-generating analysis illustrates the potential spillover effect of a comparator in the evaluation of the first member (caspofungin; formerly MK-0991) of a novel class (echinocandins) of cell wall–active antifungal drugs subsequently approved by the US Food and Drug Administration. Adverse events were strictly defined in the phase II/III program as “any unfavorable and unintended change in the structure, function, or chemistry of the body temporarily associated with the use of the study drug, whether or not determined to be related to that drug.” In accordance with customary practice at Merck, adverse events considered by the investigator to be “definitely, probably, or possibly related to the study drug” were tabulated as drug related. All patients who received at least 1 dose of study drug were included in the safety analyses. Adverse events were usually monitored for at least 14 days after receipt of the last dose of study drug. This conservative approach could theoretically inflate the reported frequencies of adverse events for both caspofungin and the comparator agents.

In the first 2 double-blind, dose-ranging studies of caspofungin versus amphotericin B deoxycholate for mucosal candidiasis, the reported incidence of amphotericin-related fever (as defined on the basis of the aforementioned criteria) ranged from 12% to 40% for different dose groups. The frequency of drug-related fever did not appear to be consistently dose dependent for doses of caspofungin of 35–70 mg administered once per day. In the study of oropharyngeal and esophageal candidiasis with 3 caspofungin dosing arms, drug-related fever was reported more often at the lowest dosage (35 mg per day; 21%) than at either the 50- or 70-mg/day dosages (12% and 16%, respectively). Thus far, fever has not been recognized as a common problem with regard to the small (but accumulating) experience with subjects who are given 100 mg of caspofungin as either a one-time...
dose or in multiple daily doses [5]. Could the reporting of caspofungin-related fever in the early double-blind, comparative trials have been misleadingly inflated to some extent by the notorious side-effect profile of conventional amphotericin B, including its anticipated temporal association with spiking fevers and intense rigors [2]?

To investigate this question, I retrospectively compared the frequency of drug-related fever in patients who received 50 mg of caspofungin per day in a third double-blind trial that compared caspofungin with intravenous fluconazole for the same indication with the frequency of drug-related fever in patients who received the corresponding dosage in the 2 earlier studies that used amphotericin B in the control arm [6]. All 3 protocols had similar designs and were concerned with the safety and efficacy of caspofungin for treatment of mucosal candidiasis in largely HIV-infected populations with low CD4 cell counts [3, 4, 6, 7]. I subsequently examined the frequency of drug-related fever in a noncomparative, open-label study of caspofungin as salvage therapy for documented invasive aspergillosis in severely immunocompromised patients [8]. As dictated by this last protocol, patients with invasive aspergillosis that was unresponsive or refractory to treatment with antifungal drugs licensed at the time initially received a loading dose of 70 mg of caspofungin before treatment was maintained indefinitely at 50 mg per day.

The studies selected for the present analysis of fever represented the first 4 clinical trials of caspofungin [3, 4, 6, 8]. Composite rates of drug-related fever across studies, by treatment assignment, were 12%, 70%, and 1% of recipients of caspofungin (50 mg per day), amphotericin B deoxycholate (0.5 mg/kg per day), and fluconazole (200 mg per day), respectively. However, the reported incidence of fever associated with caspofungin differed markedly by protocol and appeared to mirror the frequency of fever associated with the corresponding comparator (figure 1). In the later head-to-head comparison with fluconazole 200 mg given intravenously once per day, caspofungin-related fevers occurred in <4% of treated patients [6]. Although the 3 comparative trials that examined mucosal candidiasis involved almost identical study designs and populations, the reported rates of drug-related fever in the concurrent caspofungin and fluconazole groups were more similar than were the rates in the caspofungin groups in studies using different (albeit standard) comparator agents [3, 4, 6].

Which of these estimates of the incidence of fever more accurately quantified the actual incidence of caspofungin-related fever in clinical practice? Is the rate derived from the amphotericin B comparisons too high? On the other hand, might the incidence with fluconazole as the comparator be artificially low, because fluconazole is viewed as safe and well tolerated? To help resolve this issue, we examined an ongoing open-label study involving patients with invasive aspergillosis that did not have a control group [8] (figure 2). Patients whose infections were refractory to or intolerant of conventional therapies available at the time of the study had their regimens switched to caspofungin at the discretion of the site investigator. For the most part, these patients were seriously ill and profoundly immunosuppressed, necessitating longer courses of caspofungin than those given in the aforementioned 3 studies of mucosal candidiasis. In addition, surveillance for adverse events may be less compulsive in an open-label, noncomparative “salvage” study than in blind, controlled trials. Nonetheless, when the current analysis of fever was undertaken, caspofungin-related fever was noted in only 2 (3%) of the 69 patients enrolled in the noncomparative, open-label study—an incidence that almost exactly matched the incidence observed in the double-blind trial of caspofungin versus fluconazole. At the end of the study, 2 (2%) of the total 90 patients had experienced drug-related fever.

Curiously, the impressive differences in the incidence of fever among these 4 studies were largely confined to the reported frequencies of caspofungin-related fever. The absolute incidence of fevers judged to be “definitely or probably unrelated to study drug” was nearly constant across studies. This counterintuitive finding may partially derive from the obfuscating effect of disease-related fever, which almost invariably complicates the subjective attribution of causality in therapeutic trials involving febrile infectious diseases, particularly when fever resolution is part of the efficacy end point [9, 10]. One might have predicted a priori that the

Figure 1. Reported incidence of drug-related fever in double-blind, active-control trials of caspofungin for treatment of mucosal candidiasis. The frequencies of fever attributed to caspofungin and to the comparator agent were much lower in the 1 trial that used fluconazole [6] than in the combined 2 trials that used amphotericin B deoxycholate [3, 4] as the comparator.
higher number of febrile episodes attributed to caspofungin in the amphotericin B studies would have been offset by a corresponding decrease in the reported frequency for non–drug-related fevers. The total incidence of fever would have then remained essentially unchanged, despite the comparator—at least for the 3 studies [3, 4, 6] of a similar condition (mucosal candidiasis) in comparable populations (patients with advanced HIV infection). Expectations regarding drug toxicities could heighten sensitivity to possible drug reactions, some of which might not otherwise have been reported at all, by lowering the threshold for the investigator to react to treatment-coincident adverse events.

In the last head-to-head, double-blind comparison of caspofungin with conventional amphotericin B for patients with invasive candidiasis [10], drug-related fever was reported in 7% of caspofungin recipients and 23% of amphotericin B recipients. The somewhat-lower incidence of fever attributed to caspofungin in this study, compared with the incidence in the earlier trials of mucosal candidiasis with amphotericin B as the comparator, might indicate that caspofungin was acquiring its own identity as a relatively well-tolerated drug; alternatively or additionally, the fact that invasive candidiasis has a greater propensity to cause fever than does mucosal candidiasis may have inhibited the reporting of fever as a drug-related adverse event. It is also psychologically plausible that spillover effects may influence the reported frequency of laboratory adverse events. Accordingly, I reviewed the incidence of drug-related hypokalemia in the invasive candidiasis study as a possible example, because a common adverse effect of amphotericin B use is renal potassium wasting. The reported incidence of caspofungin-related hypokalemia approached 10%, compared with a 23% rate for the amphotericin B group, with each frequency exceeding the 4% rate observed in both treatment arms of the study of caspofungin versus fluconazole treatment for mucosal candidiasis [6].

There is an attractive and parsimonious explanation that may reconcile the observed discrepancy in the incidence of caspofungin-related fever between both of the studies that used conventional amphotericin B as the comparator (∼21%) and the other 2 studies (3%–4%): attribution of an adverse event to either study drug can be influenced by the known properties of an established comparator drug. Consistent with this hypothesis, febrile reactions to caspofungin were not observed in healthy subjects in the phase I studies. Despite the relatively high incidence of fever attributed to caspofungin in the amphotericin B studies, fever has not proven to be a troublesome complication of treatment with caspofungin (or other echinocandins) in more recent phase III trials, postlicensure studies, or clinical practice [11–15].

Estimates of the incidence of adverse experiences related to a first-in-class drug from active-control trials might be confounded, to a variable degree, by expectations regarding the comparator in double-blind studies. The requisite factors for exposing or exacerbating this phenomenon include (1) relatively little experience with the new drug or class of drugs being studied; (2) an established comparator associated with a well-recognized, readily apparent, and clinically relevant toxicity; and (3) a double-blind study design in which the possible treatment assignments are known to the investigator, but the actual treatment allocation remains concealed. Attribution of causality for adverse events may be influenced by awareness of the specific allocation schedule, being maximal with equal randomization to the control arm (so that any adverse event is as likely, a priori, to have developed in a subject receiving the comparator agent as in a subject receiving the new agent). The acute development of fever and chills during infusions of amphotericin B may create the perfect storm for the spillover phenomenon [2]. On the other hand, telltale signs associated with the comparator drug that implicitly “unblind” the investigator [16] could serve to counter transference between treatment groups, especially after the distinguishing safety profile of the new drug has been established. Spillover effects
could also occur from an active treatment arm into a placebo group, if the comparator drug being tested has a widely known propensity to cause a certain obvious clinical adverse event that is also a prominent feature of the underlying disease under study. The magnitude of effect would probably be less if the investigational drug comes from an already established class, the reputation of the comparator with regard to the adverse effect in question is not well known in advance, or the adverse event itself occurs infrequently and/or is not clinically important or easily recognizable. Lastly, but very importantly, these theoretical limitations in no way diminish the critical and otherwise unobtainable data gleaned from randomized, double-blind, active-controlled studies of emerging therapies [17].

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