Rates of Treatment Discontinuation Due to Adverse Events for Echinocandins

In the June 2010 issue of *Antimicrobial Agents and Chemotherapy*, Wang et al. (8) reported a meta-analysis of the safety of systemic antifungals based on published study data. Among other aspects, the authors analyzed the rates of treatment discontinuation. This analysis appears to be biased by a methodological flaw.

In Table 3, the authors use the term “treatment discontinuation due to adverse effects,” implying a causal association of the underlying adverse event (AE) with the study medication. For anidulafungin, however, the table lists a value of 8.4%, which is roughly equivalent to the treatment discontinuation rate due to any AE independent of an association with the study medication in the original publication of the anidulafungin phase III trial on invasive candidiasis (IC) (6). Yet, in the supplementary appendix to this publication, Reboli et al. reported only one case of treatment discontinuation due to an AE related to anidulafungin (0.8%) (6). For the second cited anidulafungin study, no data on treatment discontinuations are published (2).

In contrast, for caspofungin and micafungin, Wang et al. used the numbers of treatment discontinuations due to AEs that were deemed to be related to the study medication. These are reported in the original papers as follows: 3.6% for caspofungin versus 2.8% for the two micafungin groups in a randomized comparative trial (RCT) for IC (5); 2.8% for caspofungin in an RCT versus amphotericin B for IC (4); 5% for caspofungin in an RCT versus liposomal amphotericin B as empirical therapy for neutropenic fever (7); 2% for both caspofungin groups in an RCT comparing two caspofungin dose levels for IC (1); and 4.9% for micafungin in an RCT versus liposomal amphotericin B for IC (3). These rates reflect the (rounded) values shown by Wang et al. for caspofungin and micafungin in their listing of clinical studies and are the basis for the estimated pooled rates of treatment discontinuations (caspofungin, 3.8%; micafungin, 3.6%) in Table 3.

Thus, the analysis used the total rates of treatment discontinuations due to any AEs for anidulafungin. Yet for caspofungin and micafungin, it used the rates of treatment discontinuations due to study drug-related AEs.

While the reliability of the assignment of an event as “drug related” in the studies may be debated, this methodological inconsistency still yields a safety comparison that is biased in disadvantage of anidulafungin. Consistent use of the values for treatment discontinuations reported as being due to drug-related AEs in the original publications yields a different pattern, with anidulafungin showing the lowest estimated discontinuation rate among the echinocandins (0.8% versus 3.8% and 3.6%).

Moreover, the general validity of the analysis approach used by Wang et al. is questionable, as it compares pooled safety data of trials with diverse characteristics. A rigorous investigation of quantitative differences in the safety of anidulafungin versus other echinocandins would require a comparative trial, which is not available.

As an aside, the discontinuation rate of fluconazole estimated by Wang et al. is the lowest rate of all antifungals (2.2% in Table 3). This result is somewhat astonishing from the clinician’s point of view and may relate to the fact that most of the underlying studies were performed before the echinocan-

dins, as a well-tolerated group of drugs, were introduced. So the investigators may have tended to continue study treatment in patients with adverse events for lack of a low-toxicity alternative.

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Authors’ Reply

Müller raised the issue of safety of the three licensed echinocandins, caspofungin, micafungin, and anidulafungin, concerning the difference between overall discontinuation and discontinuation due to drug-related adverse effects. But it is difficult to attribute discontinuation to study drug-related toxicity or to other reasons. Many of the trial reports did not state who made the attribution (e.g., investigators, participants, or sponsors). We used FDA data from the Web to demonstrate the profiles of adverse effects in patients with invasive candidiasis that received anidulafungin and caspofungin (2, 3). The rates of any discontinuation and discontinuation due to drug-related adverse effects in caspofungin in trials of invasive candidiasis ($n = 114$) were 26.3% and 2.6% (2), respectively. The rates of any discontinuation and discontinuation due to drug-related adverse effects in an anidulafungin trial of invasive candidiasis ($n = 131$) were 11.5% and 0.8% (3), respectively. In general, all three echinocandins are well tolerated. Caspofungin has been on the market much longer than both micafungin and anidulafungin, and it is difficult to make valid comparisons between available echinocandins based on such small numbers of adverse effects (1). Pitrou et al. mentioned that despite the publication of a CONSORT statement extension for harm-related data, the reporting of harm in randomized

controlled trials has remained inadequate in recent years (4, 5). Inconsistent reporting of safety data in randomized control studies may lead to confusion. Trial reports should specify who gave the reasons for discontinuation (e.g., participants or physicians) and whether the attribution was blinded (4).

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