Amphotericin B: Is a Lipid-Formulation Gold Standard Feasible?

Str—We read with interest the article by Ostrosky-Zeichner et al. [1] proposing that lipid-based formulations of amphotericin B (LFABs) replace amphotericin B deoxycholate (AmBD) as the gold standard for treatment of most invasive mycoses. On the basis of a review of comparative efficacy, toxicity, and cost, we believe AmBD remains a viable first-line agent.

Although the benefits of LFABs have been described in relation to secondary, microbiological end points in clinical trials [2, 3], primary end points have not demonstrated the superior efficacy of LFABs versus AmBD. In a randomized study of patients with histoplasmosis and AIDS, only 1 of 3 primary end points showed an apparent benefit of treatment with liposomal amphotericin rather than with AmBD [4]. The only outcome measurement that demonstrated the superiority of treatment with liposomal amphotericin was “clinical success,” which was a composite end point that included the requirement that the patient be afebrile for 3 days. If any fever occurred during that time, including during drug infusion, the treatment was considered a clinical failure. The apparent difference in the efficacy LFABs and AmBD may therefore have been caused by a difference in infusion-related adverse events, rather than by a true difference in efficacy.

Moreover, AmBD-induced toxicities are usually treatable (e.g., infusion reactions) or reversible (e.g., anemia and azotemia) if treatment with the drug is discontinued in a timely manner [5–7]. Patients who develop toxicities can be given an LFAB, limiting the global impact of toxicity caused by the deoxycholate formulation.

Finally, the cost of LFABs is prohibitive. In the year 2000, sales of LFABs in the United States were $180 million, versus $3.3 million for AmBD (table 1). Indeed, despite strictly enforced limitations on their use at our institution, LFABs have been the number one pharmacy cost for each of the previous 5 years. Of the ~1650 drugs administered to patients at Harbor-UCLA Medical Center in 2001, LFABs accounted for 5% of all pharmacy costs.

If LFABs became the new gold standard, the financial impact would be enormous. For example, if 75% of the doses of AmBD administered in the United States in the year 2000 had been administered as LFABs, the additional cost incurred would have been approximately $240 million (75% of 550,000 doses × $580 in additional cost per dose). Although some of the cost differential might be mitigated by savings that result from a decrease in

| Table 1.  Data on sales of amphotericin B (AmB) formulations in the United States, 2000. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Type of AmB, brand name         | Quantity per vial, mg           | Cost per vial, a US$            | Daily dose, b mg                | Estimated no. of vials per daily dose | No. of vials distributed c      | No. of doses administered d     | Estimated sales, e US$          | Estimated cost per dose, f US$ |
| LFAbs                           |                                 |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| Ambisome (liposomal)            | 50                              | 157                             | 350                             | 7                               | 808,000                         | 115,000                         | ...                             | ...                             |
| Abelcet (lipid-complex)         | 100                             | 85                              | 350                             | 4                               | 739,000                         | 185,000                         | ...                             | ...                             |
| Amphotec (colloidal dispersion) | 50                              | NA                              | 350                             | 7                               | 22,200                          | 3,000                           | ...                             | ...                             |
| Total                           |                                 |                                 |                                 |                                 | 1,566,500                       | 307,000                         | 180,000,000                    | 585                             |
| AmBD                            |                                 |                                 |                                 |                                 |                                 |                                 |                                 |                                 |
| Fungizone                       | 50                              | 4.50                            | 35                              | 0.7                             | 345,500                         | 500,000                         | ...                             | ...                             |
| Amphotericin B                  | 50                              | 4.50                            | 35                              | 0.7                             | 200,600                         | 290,000                         | ...                             | ...                             |
| Amphocin                        | 50                              | 4.50                            | 35                              | 0.7                             | 6,500                           | 10,000                          | ...                             | ...                             |
| Total                           |                                 |                                 |                                 |                                 | 552,000                         | 800,000                         | 3,300,000                      | 4.50                            |

NOTE. AmBD, amphotericin B deoxycholate; LFAbs, lipid formulations of amphotericin B; NA, not available.

a Data on cost per vial provided by Jennifer Yi of Harbor-University of California Los Angeles Medical Center.
b Data assumes a mean body mass of 70 kg and a daily dose of 0.5 mg/kg per day, for AmBD, and 5 mg/kg per day, for LFABs.
c Data on no. of vials distributed and estimated sales provided by IMS Health (Fairfield, Connecticut).
d No. of doses administered is calculated by dividing the number of vials distributed by the estimated number of vials used per daily dose.


Reprints or correspondence: Dr. Markus Schneemann, Dept. of Medicine, Medical Clinic B, Ramistrasse 100, Zurich CH-8091, Switzerland (markus.schneemann@usz.ch).
Clinical Infectious Diseases 2004;38:302–4 © 2003 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2004/3802-0021$15.00

Amphocin 50 4.50 35 0.7 6,500 10,000 … … … …
Fungizone 50 4.50 35 0.7 345,500 500,000 … … … …
Amphotec (colloidal dispersion) 100 NA 350 4 14,500 3,500 … … … …
Abelcet (lipid-complex) 100 85 350 4 739,000 185,000 … … … …
Ambisome (liposomal) 50 157 350 7 22,200 3,000 … … … …
ciden ces of toxicity, it is doubtful that the entire sum would be recouped. On the contrary, Cagnoni et al. [8] estimated that the use of LFABs in a randomized study added approximately $5800 to the average cost of hospitalization. This cost likely underestimates the true financial burden in typical clinical practice, as the doses of LFABs utilized in the study were modest (most patients received 3 mg/kg per day).

Hence, although LFABs have been proven equally efficacious as and less toxic than AmBd, we believe that the economic impact of a global switch away from AmBd would be difficult to justify. Rather, both AmBd and LFABs should be considered alternative gold standards. At hospitals with limited resources, such as ours, it would be financially impossible to replace AmBd with LFABs.

Brad Spellberg,1 Mallory D. Witt,1,2 and C. Keith Beck1,2
1Divisions of Infectious Diseases and HIV Services, Department of Medicine, Harbor–University of California at Los Angeles (UCLA) Medical Center, Torrance, and 2The David Geffen School of Medicine at UCLA, Los Angeles, California

References

Clinical Infectious Diseases 2004;38:304–5
© 2003 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2004/3802-0022$15.00

Lipid Amphotericin B Formulations as Comparators in Clinical Trials

Sir—We would like to thank Ostrosky-Zeichner et al. [1] for their compilation of data on lipid formulations of amphotericin B (LFABs). Two years ago, we outlined options for use of a non-US Food and Drug Administration (FDA)–approved comparator in active-controlled trials [2]. One of these options was to supply evidence from the literature and elsewhere regarding the safety and efficacy of the unapproved comparator. Ostrosky-Zeichner et al. [1] have taken the first step toward compiling this evidence for LFABs. However, they also point out that individual LFABs have important differences in pharmacokinetics and safety profiles. Therefore, one cannot view these drugs as interchangeable [3]. These differences may be important in a clinical trial in which one is specifically attempting to measure differences in safety and efficacy between drugs. The current absence of evidence of differences between individual LFABs cannot be interpreted as evidence of the absence of true differences, because these drugs have rarely been compared directly. Drug sponsors who wish to use an LFAB as a comparator in a clinical trial for a disease for which the formulation is not FDA-approved should compile evidence on that specific LFAB and on the selected dose for the specific disease under study. However, is the question of whether conventional or lipid formulations of amphotericin B should be the gold standard now a moot point? One usually chooses non-FDA–approved comparators in a clinical trial because of lack of other treatment options for the disease under study. In the case of LFABs, the issue was the potential safety benefit of LFABs compared with conventional amphotericin B (C-Amb) in treating diseases for which there were no other available therapies. However, since the previous discussion of alternative trial designs for antifungal drugs, the FDA has approved voriconazole for the primary treatment of invasive aspergillosis [4] and caspofungin for the primary treatment of candidemia and invasive candidiasis [5]. Voriconazole was statistically superior to C-Amb plus other licensed therapy, which included LFABs, in the treatment of invasive aspergillosis. Caspofungin had comparable efficacy to C-Amb in treating candidemia and had a more advantageous safety profile. Fluconazole is also FDA-approved for the treatment of invasive candidiasis and candidemia [6] and has a more favorable adverse event profile than does C-Amb. Although some LFABs may have safety advantages over C-Amb, the toxicities of LFABs are not inconsiderable, as Ostrosky-Zeichner et al. [1] point out. The Declaration of Helsinki, an international document that describes ethical considerations in clinical investigations, states that, "In any medical study, every patient—including those in the control group, if any—should be assured of the best proven diagnostic and therapeutic method" (p. 926) [7]. One could assert, then, that using comparators in clinical trials with known safety disadvantages compared with other FDA-approved therapies with similar efficacy for the disease under study would not meet this standard. Although LFABs give clinicians an important option in the treatment of fungal disease, the question remains: should any amphotericin product be the gold standard for use as a comparator in clinical trials of invasive aspergillosis and candida...