Editorial Response: U.S. Food and Drug Administration Approval of AmBisome (Liposomal Amphotericin B) for Treatment of Visceral Leishmaniasis

The 11 August 1997 approval of AmBisome (liposomal amphotericin B; Nexstar, San Dimas, CA) by the U.S. Food and Drug Administration (FDA) for the treatment of visceral leishmaniasis (VL) constitutes the first licensing of an antileishmanial drug in the United States. This event is additionally significant as an example of the process by which antiparasitic drugs may generally be considered for approval by the FDA.

See article by Meyerhoff on pages 42–8.

Leishmaniasis occurs wherever the sandfly vector and suitable mammalian hosts are in close proximity. In mammals, *Leishmania* species are obligate intramacrophage microorganisms. Infection of the macrophages of the reticuloendothelial system (liver, spleen, bone marrow, and lymph nodes) results in VL that classically presents as fever, hepatosplenomegaly, and pancytopenia. There are ~500,000 cases per year [1] in South America (primarily Brazil), East Africa (primarily the Sudan), and Asia (primarily India); several hundreds of cases occur in the Mediterranean regions of southern Europe, and <10 cases are seen in the United States (although these are acquired elsewhere). Classic visceral disease is characteristically fatal because there is no effective immunity to *Leishmania* antigens. In contrast, cutaneous leishmaniasis (due to infection of skin macrophages) has a higher incidence of perhaps 1,500,000 cases worldwide [1], including 50–100 cases in the United States; however, immune mechanisms are eventually effective against cutaneous disease, and it is typically self-cured in 0.5 to 1.5 years.

Standard treatment of VL is with parenteral pentavalent antimonials—sodium stibogluconate (Pentostam; Burroughs Wellcome, Research Triangle Park, NC) and meglumine antimonate (Glucantime; Rhône-Poulenc, Antony Cedex, France)—that were introduced during World War II. To compensate for treatment failures, the dosage for visceral disease has recently been increased to the maximal tolerated amount (20 mg of antimony/[kg·d]) for a maximum convenient period of 4 weeks. At present, antimonials cure ~90% of cases of VL, except in some parts of India where the cure rate is much lower, but there are disadvantages of frequent mild-to-moderate adverse reactions (arthralgias and myalgias, ''chemical'' pancreatitis and hepatitis, gastrointestinal symptoms, and incidental T-wave changes on electrocardiograms) and the necessity for 28 daily injections [2]. One alternative, pentamidine, has the same problems of clinical resistance, side effects, and repeated injections [2]. A recently demonstrated alternative, paromomycin, has good efficacy [3]; however, its production under Good Manufacturing Procedures is not yet assured, and few patients have been treated so that the frequency of side effects and resistance is uncertain.

It may surprise the infectious diseases community that the mainstay of antifungal treatment, amphotericin B (deoxycholate), is also the most effective treatment for VL. Because *Leishmania* species as well as fungi contain ergosterol against which amphotericin B acts, rather than cholesterol as in mammalian cells, antileishmanial therapy with amphotericin B is biochemically rational. Furthermore, amphotericin B is made under Good Manufacturing Procedures; the drug still cures 100% of cases of VL in Indian patients [2], and the toxicity is well specified.

The primary disadvantage of amphotericin B therapy is that the toxic effects, although well specified, are also significant, including frequent infusion-related side effects (fever, chills, hypotension or hypertension) and delayed side effects (decreased renal function and levels of serum potassium). The need to develop less-toxic formulations of amphotericin B for the treatment of systemic mycoses has led to the manufacture and marketing of new clinical formulations in which deoxycholate has been replaced by other lipids: Abelcet (Liposome Company, Princeton, NJ), amphotericin B lipid complex; AmBisome, liposomal amphotericin B; and Amphotec (previously called Amphocil [amphotericin B cholesterol dispersion]; Sequus Pharmaceuticals, Menlo Park, CA), amphotericin B cholesteryl sulfate. In general, these new formulations are well taken up by the reticuloendothelial system, where *Leishmania* species reside, but are poorly taken up by the kidney, the major target of organ toxicity. Indeed, since *Leishmania* species reside solely in the reticuloendothelial system and other amphotericin B–susceptible microorganisms do not, the manufacturers of antifungal agents serendipitously have marketed new drugs for which VL should have the best therapeutic index.

The theoretical attractiveness of AmBisome therapy for VL led to clinical trials to determine the optimum regimen. As Meyerhoff [4] relates in this issue of *Clinical Infectious Diseases*, 100% of immunocompetent patients with VL (virtually all infected in Europe) were cured with three regimens containing total doses of >21 mg/kg: 1–1.4 mg/(kg·d) on days 1–21, 3 mg/(kg·d) on days 1–10, and 4 mg/(kg·d) on days 1–5 and 10 [5, 6]. In a larger study [6], there was a cure rate of 97% (32 of 33; SE, 0.03; lower limit of 95% CI, ~91%)

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Reprints or correspondence: Dr. Jonathan D. Berman, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C. 20307-5100.

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with a total dose of 18 mg/kg (3 mg/[kg · d] on days 1–5 and 10). Had the one patient not relapsed and all 33 been cured, the lower limit of the 95% confidence interval would still be ~91% (''rule of 3's''). These studies have been reported in the literature and were submitted to the FDA.

World Health Organization (WHO) trials in the three continents where VL is endemic have also been reported in the literature [7, 8], but the data were not submitted in the New Drug Application (NDA) to the FDA. In the WHO trials, cohorts generally contained 10 patients each. In India, a total dose of 6 mg/kg (2 mg/[kg · d] on days 1, 5, and 10) cured all patients [7, 8]. In Kenya, 14 mg/kg (2 mg/[kg · d] on days 1–6 and 10) was needed for a cure rate of 100% [8]. In Brazil, 20 mg/kg (2 mg/[kg · d] on days 1–10) cured 83% of patients [8]. Tolerance in almost all studies was excellent [5–8]. It should be noted that the drug cost is high: the U.S. ''hospital price'' is $157 for a 50-mg vial.

Given these data, what AmBisome regimen should the clinician choose? Drug regimens are evaluated on the basis of efficacy, toxicity, and practical issues such as the number of administrations and cost. For AmBisome, the large number of regimens and populations examined, the similar efficacy rates, and the relatively small number of adverse events per regimen make choosing among regimens difficult.

The FDA approval of AmBisome is valuable in this regard because it provides the FDA conclusion about appropriate AmBisome regimens, as well as making it possible for the drug to be used for an approved indication rather than ''off-label'' for an unapproved indication.

The review process for AmBisome is summarized by Meyerhoff. Comparison to an approved agent was not possible because there has not previously been an approved agent in the United States. Meyerhoff also indicates that if a concurrent active control had been used, an appropriate comparator might be the standard of care used in the geographic region under study. The NDA was aided by high-quality case reports available from European trials. Meyerhoff clearly indicates that data from countries other than the United States are acceptable to the FDA as long as scientific integrity and verifiability are maintained. The opposite also seems clear: that data from countries other than the United States (as well as data from the United States) that do not meet standards will be unacceptable.

The FDA review was also materially helped by the much larger safety database related to AmBisome's economically primary antifungal indication. My belief is that larger more expensive trials may be required when the only indication is treatment of the parasitic disease from which all safety data would have to derive. If so, the resource requirements will be significant for these diseases of limited economic return. AmBisome was granted an orphan drug designation for the treatment of VL in December 1996, and antiparasitic drugs may generally qualify for such status. It is important to recognize, however, that an orphan drug designation does not relate to clinical trial data and their standards. Rather, an orphan drug designation relates to business considerations and protects against competitive marketing of another formulation of the same drug.

The FDA-approved regimen for immunocompetent patients with VL (total dose of 21 mg/kg given on 7 days over a 21-day period) was specified by the AmBisome product insert of January 1998 to be 3 mg/(kg · d) on days 1–5, 14, and 21. This regimen is circumspect. The total dose is high; therefore, patients from all continents should be cured. There is no recommendation for patients with cutaneous and mucosal leishmaniasis, for whom there are almost no data.

On the other hand, the dosing regimen appears not to have been actually used for patients; the lack of correlation of dosage with geographic area means that all patients will be treated with the same dose despite previous reports [7, 8] suggesting that patients from Kenya and India need less total doses; larger doses spread over 21 days signify greater drug cost, requirement for medical care, and potential for toxicity.

Data from Kenya and India [7, 8] that were not submitted to the FDA suggest that there is a fundamental difference in the two ways that clinical trial results can be presented, evaluated, and influence therapy. Clinical trial results can be presented to regulatory authorities (the FDA) for approval, after which the drug sponsor can sell the drug for the recommended indication. Clinical trial results may also be presented for publication, after which clinicians may choose the recommended regimen in the practice of medicine. The judgment of FDA reviewers ultimately has legal standing, and in their evaluation, FDA reviewers emphasize data whose accuracy is verified because it was performed under Good Clinical Practices (GCP).

GCP are guidelines intended to ensure multiple negatives—i.e., none of the scores of study procedures are performed incorrectly. Some guidelines have been translated into legal requirements, and some may be implemented according to the investigator. Whether externally or personally specified, proving multiple negatives is expensive. For example, I interpreted GCP for liver function tests to require periodic calibration of the machine with authentic external controls, and the cost of a study performed according to this procedure and other GCP was four times that of a non-GCP study.

In comparison, the primary function of scientific journals is dissemination of peer-reviewed information. Peers assume that submitted data are, ipso facto, accurate data that do not need further verification. Note that accuracy and verifiability are not necessarily identical, and data presented in scientific journals may be just as accurate as GCP data that are accepted by the FDA. The aspartate transaminase level may truly be 84 U/L even if the machine was not recently calibrated.

My belief is that for immunocompetent patients with VL, AmBisome therapy should be administered on days 1–5 and 10 at the following dosages: 3–4 mg/(kg · d) if the disease was acquired in Europe or Brazil, 3 mg/(kg · d) if the disease was acquired in Africa, and 2–3 mg/(kg · d) if the disease was acquired in India. These recommendations take into account

information provided both in the NDA to the FDA and in the literature, and emphasize data from larger cohorts. Infusion-related side effects (hypotension or hypertension, dyspnea, generalized flushing, and fever) and nephrotoxicity (increased blood urea nitrogen level and hypokalemia) will occasionally be seen [9]. Drug cost should be about $150–$200 per 50-mg vial or $3,000–$4,000 for a 50-kg person receiving a total dose of 20 mg/kg.

The other choices available to U.S. practitioners are Pentostam, amphotericin B, and the other new lipid formulations of amphotericin B (Abelcet and Amphotec). In the United States, Pentostam must be obtained from the Centers for Disease Control and Prevention and used under the protocol of an Investigational New Drug; the other formulations of amphotericin B, licensed for the treatment of fungal diseases, must be used ''off-label'' for this indication, which is not listed in the *Physicians' Desk Reference*. My view is that compared with AmBisome, Pentostam is more toxic, less effective in some geographic regions, and, in spite of lower drug costs, probably as expensive when the total medical costs of the developed countries are considered. Both amphotericin B and Amphotec [10] are more likely to be toxic than AmBisome. Abelcet [11] may be competitive with AmBisome.

For immunosuppressed patients, the recommended regimen is 4 mg/(kg·d) on days 1–5, 10, 17, 24, 31, and 38. It is recognized that after initial cure, almost all patients will relapse without maintenance therapy.

In summary, AmBisome is the first drug approved by the FDA for the treatment of any form of leishmaniasis in the United States and in my mind is the treatment of choice for VL in this nation. The approval process summarized by Meyerhoff suggests that in certain circumstances, approval of antiparasitic drugs may be facilitated by the use of local comparators and safety data from other indications. Financial incentives for antiparasitic drugs may be aided by an orphan drug status. On the other hand, FDA standards will be maintained no matter what the indication or geographic region in which the study was performed, and some data that clinicians access might not be provided in the NDA or emphasized by the FDA.

Jonathan D. Berman
Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C.

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