Reply to Ojha et al.

To the Editor—Our article in Clinical Infectious Diseases [1] has generated a critical commentary from Ojha et al. [2]. The basis of these criticisms centers around perceived bias in the assignment of patients to the 2 treatment groups in the context of the small sample size in our study; the authors claim that the antimony group was older, included more men, and had longer duration of symptoms. Then, Ojha and colleagues link this potential unequal distribution to the statement, “Previous studies have reported that older age, male sex, longer duration of symptoms, and previous cutaneous leishmaniasis may be related to risk of mucosal leishmaniasis [ML], disease severity, and time to cure [3, 4]” [2, p. 1104].

We disagree with these claims by Ojha et al. [2]. First, neither age, sex, nor longer duration of disease in the group who received antimony plus pentoxifylline, compared with the group who received antimony plus placebo, was statistically significantly different. In our trial [1], we could not identify major issues that make us believe that our randomization failed. This was partially supported by our randomization process and the reasonable balance observed in patients’ characteristics between the 2 treatment arms.

Second, the studies cited by Ojha et al. [2–4] did not examine or report differences in severity of mucosal disease or response to therapy as variables that were influenced by age, sex, or prolonged disease. Specifically, the study by Castelucci et al. [3] (L. Castelucci is from our group) was a retrospective cohort study that evaluated genetic influences in the development of ML. This study showed a familial aggregation of ML, with no data regarding the severity of ML in these patients. In the study by Machado-Coelho et al. [4], older age, male sex, and longer duration of cutaneous leishmaniasis were found to be risk factors for development of ML. This study did not report any information about the severity of ML or treatment outcome, and it certainly did not link these with age, sex, and duration of cutaneous leishmaniasis. Therefore, neither study cited by Ojha et al. [2] provide support for their claims that these risk factors may impact therapeutic outcome, which suggests that the claims lack scientific merit and are erroneous.

In addition to the absence of differences in these variables between the 2 groups, there was also no difference between groups in terms of the severity of mucosal disease (assessed by an otorhinological examination). Although the severity of ML lesions may vary widely [5], only patients with deep ulcers and nasal septum involvement were enrolled in our study [1]. It is important to note that the randomization of severe forms of ML did not differ between the 2 treatment groups.

We agree that large trials are important and achieve higher statistical power and more quantitative documentation regarding the effects of treatment than do small trials. However, ML is a rare disease predominantly associated with Leishmania braziliensis infection, which only occurs in 3% of the patients who develop cutaneous leishmaniasis [6]. Despite the high incidence of disease in our study region in Corte de Pedra, Brazil, we see only ~20 new cases of ML per year, and the majority of the patients have an early stage of disease. Therefore, a larger randomized clinical trial of severe ML would require a multicenter study. Ojha et al. [2] should acknowledge that, despite the issues and problems associated with small studies, they are sometimes the only feasible initial approach to the study of diseases that occur with low frequency in difficult-to-access populations. Thus, the tremendous value of small studies should not be minimized.

Lastly, we agree that more robust statistical tests are necessary for analyzing small studies in which large sample theory is violated, and parametric assumptions are not tenable in general. Therefore, in our original article [1], we used nonparametric methods, recognizing that we were working with a small sample size. There are several methods that can be used as robust statistical techniques for small trials [7]. However, we do not believe that these alternatives would be helpful for statistical estimation and inference in studies involving small sample sizes, although different methods may handle different aspects of the problem better than others.

In our article [1], we were cautious in our recommendations. Given our current comments in response to Ojha et al. [2], our interpretation of the observations and conclusions remain unchanged: “pentoxifylline combined with Sbv [antimony] is, therefore, a therapeutic choice for patients with mucosal leishmaniasis who have advanced forms of the disease” [1, p. 792]. We do not claim that a larger study is not needed; indeed, it is our hope to inspire a larger study through our novel and intriguing findings.

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References

Comparison of 2 Studies of Treatment of Invasive Aspergillosis

To the Editor—Congratulations to Cornely et al. [1] for completing another important randomized study of invasive aspergillosis (IA). This is the second largest completed such study, and enrollment occurred remarkably fast, being completed in 18 months. At face value, it would be easy to make 2 conclusions from this study with respect to the treatment of IA: (1) the efficacy of 3 mg/kg of liposomal amphotericin B is essentially equivalent to that of 10 mg/kg liposomal amphotericin B (although the latter is slightly more toxic), and (2) liposomal amphotericin B has the same efficacy as voriconazole. Although the first conclusion is probably valid, the second needs further analysis and should be questioned.

I, as well as others, have demonstrated very different response rates among different patient groups with IA [2, 3], and these response rates depended on how early the diagnosis was achieved [4, 5]. Other factors that are important for a successful outcome include the dose of corticosteroids once the diagnosis has been made [6]. For example, it has been known for many years that patients with IA after allogeneic hematopoietic stem cell transplantation (HSCT) generally experience a poor outcome, with an associated mortality rate that is typically >75%, whereas patients with acute leukemia whose neutropenia resolves have a mortality rate that is generally <50% and, in some series, <30%. These differing outcomes are critically important in interpreting therapeutic trials of IA, because different trials enroll different proportions of at-risk patients. This is particularly germane to a comparison of the study by Cornely et al. [1] with the randomized study by Herbrecht et al. [7], in which voriconazole is compared with standard amphotericin B.

Many clinicians would argue that patients with acute leukemia are “at high risk” and, therefore, should be considered to be in the same risk group as those who have received an allogeneic HSCT, but a critical distinction needs to be made between the high risk of acquisition of IA and a high risk of dying of IA. These risks differ markedly between patients with acute leukemia (who have a moderate to low risk of death if treated) and patients with allogeneic HSCT (who, even if treated, have high risk of death), as they do between patients with HIV infection and patients with AIDS, in whom the risk of acquisition of IA is low (2%–4%), but the risk of dying of IA exceeds 80% [8, 9]. A similar contrast applies between risks of IA acquisition and IA-related death in liver transplant recipients [9].

In table 1, the different underlying conditions, enrollment characteristics, and outcomes from the 2 trials [1, 7] are summarized. For both trials, modified intent-to-treat populations are shown. This table shows considerable differences between the studies. For example, in the study by Cornely et al. [1], >90% of the patients had hematological malignancy (including autologous HSCT), whereas <60% of the patients in the study by Herbrecht et al. [7] had hematological malignancy, with a higher proportion of allogeneic HSCT recipients and patients with AIDS, (P<.001). However, the biggest contrast between the studies was with respect to the confirmation of disease. Two-thirds of the patients in the study by Herbrecht et al. [7] had microbiologically confirmed disease, whereas <40% of the patients in the study by Cornely et al. [1] had microbiologically confirmed disease (P<.001). Antigen testing was not performed as a direct part of the study by Herbrecht et al. [7]; therefore, all microbiological confirmation related to histological examination, culture, and microscopic examination findings. Furthermore, >20% of the cases in the study by Cornely et al. [1] were confirmed by antigen testing only (usually an early diagnostic feature), and ~15% of cases were otherwise microbiologically confirmed by other methods. This major difference is accounted for by the use of halo signs (an early sign of infection [5, 10]), which were used at enrollment for approximately one-third of the patients in the study by Herbrecht et al. [7], compared with nearly 60% of the patients in the study by Cornely et al. [1] (P<.001). In accordance with this, the proportion of patients with proven IA, usually achieved later during the course of disease, was much lower in the study by Cornely et al. [1] (9% vs. 39%; P<.001). Thus, the study by Cornely et al. [1] enrolled many more patients with early disease and a higher proportion of patients with a “good prognosis,” compared with the study by Herbrecht et al. [7].

In the study by Herbrecht et al. [7], all evaluations were performed at 12 weeks, regardless of how long the patients had received the initially assigned therapy, although a secondary analysis examined responses at the completion of assigned therapy. In the study by Cornely et al. [1], responses were evaluated at the end of treatment, which had a median duration of 14–15 days but ranged from 1 day to 60 days. Eighty-four–day (12-week) responses were not reported in the study by Cornely et al. [1], although survival was reported. In the study by Herbrecht et al. [7], major efforts were made by the Data Review Committee to distinguish patients who experienced partial responses, who had to have at least 50% improvement in their radiologic abnormalities, from those who experienced less improvement, who were categorized as having a stable response. Such efforts included clearly defined a priori criteria, duplicate assessments, and clinician input into the final