Correspondence

Lipid Formulations of Amphotericin B and Solid Organ Transplant Recipients with Central Nervous System Cryptococcosis

To the Editor—Sun and colleagues [1] report that lipid formulations of amphotericin B are independently associated with less mortality, compared with the mortality associated with amphotericin B deoxycholate, in solid organ transplant recipients with central nervous system cryptococcosis. We have reservations about the validity of this conclusion. First, the article does not demonstrate how a number of baseline characteristics are distributed between the treatment groups. Could Sun and colleagues [1] provide these baseline data? Second, the data concern patients who were treated in various centers in various countries. Treatment center may be an important confounder, because it may influence both the doctor’s choice for a certain treatment and the clinical outcome. This variable should be reported and corrected for in the final analysis. Third, the decision of whether a variable is a confounder that should be adjusted for by means of a multivariate model is based on statistical criteria (P < .2). Although it is common practice to correct for confounding in this way, this strategy may lead to bias from omission of important confounders or from inappropriate adjustment for nonconfounders [2]. For example, treatment with flucytosine, which is regarded as an important component of the treatment of central nervous system cryptococcosis, was not evenly distributed between the 2 groups: 67% of patients who received lipid formulations of amphotericin B were treated with flucytosine, compared with 40% of patients who received amphotericin B deoxycholate. Although treatment with flucytosine is not associated with the primary endpoint (ie, mortality) in a statistically significant way in this study, it is nonetheless a confounder that should be corrected for in the final analysis. The same argument holds for variables such as age, year of diagnosis, and treatment center. Many small confounders put together may cause a considerable degree of confounding. In fact, a substantial degree of residual confounding may also explain the lack of efficacy of flucytosine in this study. In conclusion, the reported difference in mortality between patients treated with lipid formulations of amphotericin B and those treated with amphotericin B deoxycholate may well be due to residual confounding.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Darius Soonawala,1 Gijs W. Landman,2 and J. W. van’t Wout1

1Department of Infectious Diseases, Leiden University Medical Centre, Leiden, 2Internal Medicine and Diabetes Centre, Isala Clinics, Zwolle, and 3Department of Internal Medicine, Bronovo Hospital, The Hague, The Netherlands

References


Reply to Soonawala et al

To the Editor—We thank Soonawala et al [1] for their interest in our work [2]. With regard to the baseline demographic and clinical characteristics of the study population, the patients receiving lipid formulations of amphotericin B (AmB) were older (P = .13) and more likely to receive a calcineurin-inhibitor agent (P < .001). There was no difference in the type of organ transplant, prednisone use or dose, renal dysfunction (serum creatinine >2 mg/dL), prior rejection, retransplantation, cytomegalovirus infection and disease, year of diagnosis of cryptococcal disease, fungemia, and serum and cerebrospinal fluid cryptococcal antigen titer >1: 512 (P > .05 for all factors). We agree that a causal knowledge is important for developing the most appropriate model to adjust for potential confounders. In selecting our variables, we included items that have been associated with poor outcome in cryptococcal disease as well as factors that we considered might contribute to the choice of treatment. The model that we presented in the article [2] was obtained from a backward stepwise inclusion and deletion of factors associated with poor outcome. However, when age, receipt of flucytosine, calcineurin-inhibitor agent use, and the year of diagnosis were forced into the model, the results were unchanged. Lipid formulations of AmB (odds ratio [OR], 5.2; P = .048), renal failure at baseline (OR, 0.19; P = .036), and fungemia (OR, 0.04; P < .01) were associated with 90-day survival, whereas no correlation could be shown between age (OR, 1.02; P = .58), flucytosine use (OR, 1.578; P = .57), or the year of diagnosis (OR, 1.13; P = .47) and survival. In this model, each site was considered a cluster, and the standard error was adjust-