Paromomycin in Cryptosporidiosis

Sir—Hewitt and colleagues should be commended for publishing the findings of their placebo-controlled trial of paromomycin for the treatment of cryptosporidiosis [1]. Their results are similar to those noted in a previous placebo-controlled trial and in other open-label treatment studies [2, 3]. However, several weaknesses in the trial design and analysis may have led the authors to incorrect conclusions.

The planned analysis was intent-to-treat, but the data that were presented excluded information on individuals who dropped out during the study. Importantly, patients who dropped out were all in the placebo arm of the study, and all dropped out because of poor clinical response. Therefore, these patients who dropped out should have been included in the analysis as having failed treatment.

Including patients who dropped out or died as having failed treatment, and defining “response to treatment” as either partial or complete response, we recalculated the results of the study as follows: at week 3, 8 (84%) of 17 patients in the paromomycin arm had responded to treatment, and 5 (28%) of 18 patients in the placebo arm had responded ($P = .23$; $\chi^2$ test); at week 6, 10 (59%) of 17 patients in the paromomycin arm had responded to treatment, and 8 (44%) of 18 patients in the placebo arm (who received placebo during the first 3-week period and paromomycin during the second 3-week period) had responded ($P = .40$; $\chi^2$ test).

Thus, in this modified analysis, the difference in the response rates between the arms of the study approaches the difference anticipated in the trial design, with a trend favoring paromomycin treatment over administration of placebo. However, the power of this study to achieve statistical significance was limited by the small sample size. On the basis of this difference between groups, a sample size of 108 subjects per study arm would be needed to have an 80% power of achieving significance with this level of difference (in contrast to the 17 and 18 subjects per study arm in this trial).

Although stool frequency is an important clinical endpoint, important confounding factors need to be considered. The poor correlation of parasitologic and clinical responses suggests that cryptosporidiosis was not always the cause of treatment failure. In previous short-term studies of patients with AIDS and cryptosporidiosis, we found high rates of coinfection with other opportunistic infections. Infections with mycobacteria, cytomegalovirus (CMV), or microsporidia were frequent causes of relapse, failure to respond to treatment, and/or death [2–4]. {Clostridium difficile} superinfection is also a concern. The high frequency of an elevated alkaline phosphatase level that was noted by Hewitt and colleagues [1] likely reflects either biliary tract involvement with Cryptosporidium species or coinfection with mycobacteria or CMV (in the biliary tract). Since paromomycin does not enter the biliary tract, patients with biliary disease may not be ideal candidates for assessing the drug’s efficacy.

These issues raise several questions. Were those patients who had either treatment failure or relapse or those who died examined for concomitant infection using biliary tract imaging, blood culture to detect mycobacteria, endoscopy for CMV infection, and stool studies? Did resolution in the patients in the placebo arm of the study correlate with a higher CD4 cell count or with a short duration of illness? The drugs used for prophylaxis and treatment of mycobacteria have some activity against Cryptosporidium species [4, 5]. Were patients in the placebo arm treated with macrolides or rifabutin? We have noted significant changes in oocyst excretion ($\approx 1$ log reduction in the number of oocysts excreted) after changing a single nucleoside in a patient’s antiviral regimen. Was antiviral therapy modified for any of the patients? If so, did changes correlate with the response rate?

Given these concerns, we feel that the title of the article by Hewitt and colleagues [1] may be somewhat misleading. However, important conclusions can be drawn. First, the antiparasitic drugs that are currently available are, at best, modestly effective. Therefore, their efficacy will not likely be established by small placebo-controlled trials. As an alternative approach, treatment with combinations of drugs should be examined [4, 6]. A factorial design might allow for the evaluation of the efficacy of individual agents. Second, the disease and response rates are variable, and carefully controlled trials are needed to establish what regimens are effective. It is essential that these trials account for confounding variables, such as antiretroviral therapies and concomitant infections, by incorporating quantitative parasitologic end points into the trial design [4, 6].

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Reply

Str—We thank Dr. White and colleagues for their interest in our article about paromomycin and the treatment of AIDS-related cryptosporidiosis [1]. We decided to present the as-treated analysis because, according to our interpretation of the data, there was no trend favoring treatment with paromomycin over administration of placebo. A P value of 0.23 from an intent-to-treat analysis represents an approximately 1 in 4 chance that a difference in efficacy does not actually exist. We did not consider this P value to be low enough to call it a trend.

The comments made by Dr. White and colleagues clearly point out the difficulty of conducting clinical research with enteric pathogens in immunocompromised hosts. Because coinfection with other pathogens is likely when AIDS-related cryptosporidiosis is present, our exclusion criteria included known coinfection at the time of enrollment with any of the following organisms: active cytomegalovirus (CMV colitis), Mycobacterium avium complex, Clostridium difficile, and Microsporidium species. Subsequent to enrollment, there were 3 patients in each arm of the study who had Microsporidium species detected in their stool. Evaluation of treatment failure encouraged investigation for coinfection but did not require it.

Biliary tract involvement is common in cases of cryptosporidiosis. Therefore, it would be quite difficult to exclude patients with biliary tract involvement in clinical trials of possible treatments. In addition, because biliary tract involvement is common, an agent deemed effective for AIDS-related cryptosporidiosis should be effective against all of the manifestations of the disease in the gastrointestinal tract.

Concurrent treatment with rifabutin, which might possibly prevent AIDS-related cryptosporidiosis, as has been recently shown [2], was allowed during the study, but treatment with macrolides was not allowed within 14 days of study entry or during the period when paromomycin was being administered. Changes to antiretroviral therapy were allowed but seldom occurred. In addition, CD4 cell count showed no discernible effect on the outcome of treatment, because entry criteria required a CD4 cell count of <150 cells/mm³. In fact, the median CD4 count was <30 cells/mm³ for both the paromomycin and the placebo groups.

In reviewing our experience with AIDS-related cryptosporidiosis, what we found most interesting is the wide clinical variability of the disease in HIV-infected persons. The ability of the disease to resolve or improve without intervention in patients who were given placebo was remarkable and, in a study with no placebo control, could easily lead to the conclusion that a particular intervention did appear to be effective. We agree that there is still need for well-designed, placebo-controlled studies of any potential antimicrobial agent(s).

As Dr. White and colleagues imply, the best treatment for cryptosporidiosis in HIV-infected persons is highly active antiretroviral therapy [3]. Restoration of lost immune response has improved outcomes for a number of opportunistic infections, including cryptosporidiosis.

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Testing of Urinary Escherichia coli Isolates for Shiga Toxin Production

Str—We read with interest the recent letter by Wilson et al. [1] on the prevalence of Shiga toxin–producing Escherichia coli (STEC) among isolates from urine samples. Wilson et al. concluded that routine screening of E. coli isolates from urine

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