Comment on: Unresponsiveness to AmBisome in some Sudanese patients with kala-azar

The excellent paper by Mueller et al. (2007) gives us an idea of how difficult it is to perform clinical research in field conditions, however I believe that their final recommendation for the use of combined antileishmanial therapy could not be drawn from their study.

They have seen that a group of failing patients to AmBisome—after a previous relapse with antimonials—do respond to a second course of antimonials. They therefore recommend combined or sequential therapy with both drugs in relapse cases.

HIV co-infected patients tend to have a higher parasite burden, lower positive serology rates, frequent relapses and a protracted course, despite different and multiple antileishmanial therapies (Alvar et al., 1997). Very immunocompromised HIV patients with visceral leishmaniasis have amastigotes in their bone marrow, skin and other tissues, even when they do not have clinically overt kala-azar. For these cases, addition of effective antiretroviral therapy is pivotal for immune restoration and parasite clearance (Russo et al., 2003). It is very likely that most of the failing patients to AmBisome in Mueller et al.’s study were co-infected with HIV: they had a higher parasite burden, lower positive serology rates, had a relapse and showed a protracted course. Unfortunately, HIV testing could not be performed in six of the patients owing to the extremely difficult field conditions.

To the best of my knowledge, combined antileishmanial therapy with AmBisome and antimonials has not been tested in randomised clinical trials. Sequential therapy has been used in many HIV co-infected patients without significant success. Combination therapy might prevent the development of Leishmania resistance, but again clinical and pre-clinical data are lacking. In addition, if failing patients responded to a second course of antimonials the possibility of resistance to this drug is very unlikely, although it is possible that AmBisome significantly lowered the parasite burden, facilitating clinical success of the second antimonial course.

I believe that relapsing cases should be HIV tested and, if positive, the treatment approach should include secondary prophylaxis until antiretroviral therapy is available and effective. If this is not possible, a second course of antimonials compared with AmBisome therapy or even the use of oral miltefosine for refractory cases could be a better approach instead of recommending combined therapy, until more pre-clinical and clinical data are available.

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References


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Reply to comment on: Unresponsiveness to AmBisome in some Sudanese patients with kala-azar

We would like to thank Dr Górgolas for a thought-provoking response. Visceral leishmaniasis (VL) in Sudan is due to Leishmania donovani and has a primarily important human reservoir (Zijlstra and El-Hassan, 2001). The potential for development of resistance is thus unlike L. infantum, which is a zoonosis of dogs (Gramiccia and Gradoni, 2005). Leishmania donovani is a serious public health burden without HIV co-infection. This has considerable implications when considering the choice of second-line treatment.

Dr Górgolas points out that HIV co-infection is an important issue. The six patients he mentions not tested for HIV were aged 1, 2, 4, 6, 7 and 8 years. Except for their relapse, none showed signs of having HIV at any time. Furthermore, initial lymph node aspirate readings of these six untested patients were 2+ (two patients), 3+ (one patient) and 5+ (one patient), with two others diagnosed serologically. We therefore do not support Dr Górgolas’ assertion that most of these patients were HIV co-infected.

Dr Górgolas correctly states that the combination of AmBisome plus antimonials has not been tested in clinical trials and that data are lacking to show that combination therapy prevents the development of resistance. We would welcome the engagement of academics to perform clinical trials on combination chemotherapy for VL, but to date only one trial (sodium stibogluconate and paromomycin) is in progress in East Africa and it is largely focusing on the registration of paromomycin. Large-scale trials of monotherapy or combination drug therapy in Sudanese VL are lacking, although a few studies, including several field evaluations of
treatment, have been published. However, the knowledge that humans are the important reservoir of *L. donovani*, as well as our recent experience (Mueller et al., 2007), indicates to us that we expect VL in Sudan could behave similarly to VL in India, where resistance has made antimonials useless (Jha, 2006). Indeed, the policy of adherence to monotherapy in VL reminds us of the tragic histories of therapy in malaria, tuberculosis, HIV and many bacterial infections where resistance developed following widespread use of monotherapies.

Dr Górgolas suggests a repeat course of sodium stibogluconate or miltefosine instead of combination therapy. We have used the former approach for years and find that 40–60-day courses of this toxic drug are needed. Unlike AmBisome, miltefosine is not used or licensed in Sudan—the only data from Africa for this drug derive from treatment centres in Ethiopia (Ritmeijer et al., 2006).

Therefore, for VL in Africa and India, we consider that current evidence and, importantly, the experience supports combination therapies for relapses as appropriate choices, specifically antimonials plus AmBisome or antimonials plus paromomycin.

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References


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