

Safety and effectiveness of new treatment regimens for visceral leishmaniasis in Bangladesh and India

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Introduction

In 2010, WHO recommended changing national policy to prevent the emergence of resistance to monotherapy drugs in visceral leishmaniasis (VL), and specifically, to phase out miltefosine monotherapy. We planned a Phase III clinical trial in Bangladesh and a field implementation study in India to demonstrate the safety and effectiveness of liposomal amphotericin B (Ambisome) monotherapy and combination treatments.

Methods

In Bangladesh, we undertook a randomized open label clinical trial. The treatment regimens were: single-dose (5mg/kg) of liposomal amphotericin B (day 1) plus miltefosine (days 2-8); single-dose (5mg/kg) of liposomal amphotericin B (day 1) plus paromomycin (11mg/kg) on days 2-11; miltefosine plus paromomycin (days 1-10) and 5 mg/kg intravenous infusion of liposomal amphotericin B on days 1, 3, and 5 (total dose 15 mg/kg) as the standard treatment. 120 patients were recruited and treated as inpatients at Community Based Medical College, Bangladesh, Mymensingh (CBMC,B). 482 patients were recruited and treated in three Upazila Health Centers (Trishal, Bhaluka, and Gafargaon). The treatment outcome was assessed at completion of treatment and 6 months afterwards. In an implementation study in India, patients were treated with a single dose (10mg/kg) of liposomal amphotericin B at Hajipur District hospital; single-dose (5mg/kg) of liposomal amphotericin B (day 1) plus miltefosine (days 2-8) in Vaishali district; or miltefosine plus paromomycin (11mg/kg) on days 1-10 in Saran district. The outcome was assessed at the end of treatment, and at 6-month and 12-month follow-ups. The study was approved by ethics committees at Rajendra Memorial Research Institute of Medical Sciences Patna, MSF, London School of Hygiene and Tropical Medicine, International Centre for Diarrhoeal Disease Research (ICDDR,B), Dhaka, and the Bangladesh Medical Research Council.

Results

In Bangladesh, 602 patients were enrolled. Analysis was by intention-to-treat. The cure rates at 6 months were: liposomal amphotericin B, 98.1%; liposomal amphotericin B and paromomycin, 99.4%; liposomal amphotericin B and miltefosine, 94.4%; and miltefosine and paromomycin, 97.9%. 368 patients had adverse drug reactions, of which 60% patients were in liposomal amphotericin B; 61% in amphotericin B and paromomycin; 61% in amphotericin B and miltefosine; and 63% in miltefosine and paromomycin. In the implementation study in India, 1761 patients were enrolled. The final cure rates at 6 months were: 479 (94.7%; 95% CI 92.4-96.4) for amphotericin B; 265 (90.1%; 95% CI 86.7-93.5) for

liposomal amphotericin B and miltefosine; and 294 (97.4%; 95% CI 95.0-98.8) for miltefosine and paromomycin. The proportion of patients presenting adverse reactions was 120 (16.1%) for liposomal amphotericin B; 90 (27.4%) for liposomal amphotericin B and miltefosine; and 90 (22.4%) for miltefosine and paromomycin. Five serious adverse events occurred in the liposomal amphotericin B group; two seemed related to the drug (one allergic reaction, and one atrial ectopy), and three were unrelated (pneumonia, empyema, and urinary tract infection).

Conclusion

Liposomal Amphotericin B monotherapy and the combination therapies showed excellent safety and effectiveness in field trials, providing evidence to phase out miltefosine monotherapy as recommended by WHO. On the basis of these results, national programmes have revised the treatment policy where liposomal amphotericin B monotherapy has been recommended as the first option, and combination regimens as the second option.