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Efficacy and safety of 14-day treatment with paromomycin and miltefosine for primary visceral leishmaniasis in eastern Africa: non-inferiority trial

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Introduction

The parasitic disease visceral leishmaniasis (VL) is most commonly caused by *Leishmania donovani* in eastern Africa, currently the region with highest burden worldwide. Current treatment for VL comprises the combination of sodium stibogluconate and paromomycin, SSG/PM; this is toxic, painful, and requires hospitalisation and daily injections. Treatments are urgently needed that are safe, effective, and appropriate for use in remote areas.

Methods

We conducted a phase III open-label randomised non-inferiority trial in Ethiopia, Kenya, Sudan, and Uganda. The trial used a parallel-arm design with two arms, comparing the combination regimen of 20 mg/kg/day paromomycin and allometric miltefosine (MF) for 14 days with the current 17-day standard of care, 20 mg/kg/day SSG and 15 mg/kg/day PM. We enrolled adults and children aged 4-50 years with primary VL, without HIV or severe concomitant disease co-infection. The primary endpoint was definitive cure at 6 months' follow-up.

Ethics

This study was approved by the MSF Ethics Review Board and by ethics committees at the Institute of Endemic Diseases, Khartoum, Sudan; Kenya Medical Research Institute, Nairobi, Kenya; Makerere University, Uganda; and the University of Gondar, Ethiopia. Clinicaltrials.gov registry number, NCT03129646.

Results

439 predominantly male (80%) patients aged 4 to 50 years were recruited over a period of 29 months. A similar proportion of patients in the PM/MF and the SSG/PM arms achieved definitive cure at 6-month follow-up in primary efficacy analysis using modified intention-to-treat; mITT; 91.2% cure for PM/MF (97.5% confidence interval, CI, 85-98.6) and 91.8% for SSG/PM (97.5% CI, 85.6-99.2). Non-inferiority was not demonstrated in the mITT population, with the upper limit of the 97.5% CI, 7.4%, slightly exceeding the non-inferiority margin of 7%. However, the per-protocol analysis did show non-inferiority, with 92% (97.5% CI, 85-98.5) cure in the PM/MF arm, as compared to 91.7% (97.5% CI, 84.7-98.2) in the SSG/PM arm. Most adverse drug reactions (ADR's) were mild to moderate. The most common expected ADR's were MF-related vomiting, and PM-related injection site pain and hypoacusis. ADR's suggesting SSG-related cardiac toxicity were reported in 6.5% (11/170) of patients in the SSG/PM arm. Eighteen serious adverse events were reported in 13 patients, four of which were considered related to study drugs. Fatality rate in the trial was 0.9% (4/439), with one death judged due to SSG-related cardiotoxicity.

Conclusion

The results of this study demonstrate that the 14-day PM/MF regimen achieved a clinically meaningful rate of cure with very similar efficacy to the standard of care, SSG/PM. It was generally well tolerated, with ADR's as expected, based on the known safety profiles of study drugs. The PM/MF regimen has one fewer painful injection per day, a 3-day shorter treatment duration, and with no risk of SSG-associated life threating cardiotoxicity, as compared to SSG/PM. This regimen may therefore provide a more patient-friendly alternative for adults and children with VL in eastern Africa.

Conflicts of interest

None declared.