134

Safety and efficacy data from a phase 2 randomized trial of a miltefosine/thermotherapy combination in uncomplicated New World cutaneous leishmaniasis

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Introduction

Cutaneous leishmaniasis (CL) causes disfiguring skin lesions, resulting in scarring. Current standard of care comprises antimonials, either meglumine antimoniate or sodium stibogluconate, which have serious drawbacks, including their safety, efficacy, drug resistance, treatment duration, and availability. A combination of treatments could potentially improve efficacy and safety, and reduce treatment duration. We aimed to compare treatment efficacy and safety with thermotherapy versus thermotherapy plus a short course of miltefosine.

Methods

We randomized participants in an open-label superiority trial, enrolling patients aged 18-60 years with non-complicated CL (≤four lesions ≤4cm in diameter, not located on face or joints). Parasites involved included *Leishmania panamensis, L. braziliensis*, and *L. peruviana*. 130 subjects were recruited in Colombia and Peru, and randomly allocated to either one application of thermotherapy (50°C for 30mins; TT group) or TT plus 2.5mg/kg/day miltefosine for 21 days (TT+MLT group). Patients were followed up for 24 hours after thermotherapy for safety and on Days 7, 14, 21, 45, 63, 90 and 180 for safety and efficacy. Primary efficacy endpoint, initial cure, was re-epithelialization of ulcerated lesions or flattening, and no signs of induration of non-ulcerated lesions on day 90.

Ethics

This study was approved by the ethics committees of the Programa de Estudios y Control de Enfermedades Tropicales, Colombia, and the Instituto de Medicina Alexander Von Humboldt, Peru. ClinicalTrials.gov registry number, NCT02687971.

Results

64 and 66 patients were allocated to TT and TT+MLT arms respectively, with five lost to follow-up; three in TT; two in TT+MLT. In intention-to-treat analysis, initial cure rates were 80.3% (53/66) in TT+MLT and 57.8% (37/64) in TT groups (difference, 22.49%, 95%CI=5.51-39.47; p=0.005). In per-protocol analysis, initial cure was seen in 53/62 (85.5%) in TT+MLT and 37/56 (66.1%) in TT group (difference, 19.4%,95%CI=2.52-36.28; p=0.011). 125 subjects

experienced adverse events (AE's; 59 in TT; 66 in TT+M). Most thermotherapy-related AEs were at the application site, including pain (n=12), erythema (n=37), local oedema (n=38), and vesicles (n=107). Subjects taking miltefosine reported gastrointestinal AE's, including nausea (n=17), vomiting (n=22), diarrhoea (n=5), and mild or transient elevations in aspartate transaminase and or alanine transaminase (n=19). Most AE's were mild or moderate but three serious AE's, unrelated to study interventions, were reported.

Conclusion
TT+MLT treatment resulted in improved cure, as compared to TT alone, for treatment of uncomplicated CL in Colombia and Peru. Although most patients reported at least one AE, most were mild or moderate and resolved by end of treatment. A phase III trial in Latin America will now compare combination treatment against meglumine antimoniate and miltefosine monotherapy. Additional studies in areas where other species of *Leishmania* are prevalent are also required to determine if the combination of TT+MLT could be used widely.

Conflicts of Interest
None declared.

word count 448 final

final version author approval (BA via email/28Feb)