Towards an arsenic-free oral treatment for human African trypanosomiasis due to *Trypanosoma brucei rhodesiense*: a new tool for disease elimination

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Introduction

Trypanosoma brucei rhodesiense human African trypanosomiasis (r-HAT), the zoonotic, acute form of sleeping sickness in eastern Africa, is lethal if untreated. Today, only one arsenic-based, neurotoxic drug, melarsoprol, is available for treatment of the advanced meningo-encephalitic stage. A new oral treatment would simplify HAT elimination as proposed by WHO. Fexinidazole was recommended by the European Medicines Agency (EMA) in 2018 as the first oral treatment for *Trypanosoma brucei gambiense* HAT, but it was not yet evaluated for r-HAT.

Methods

This single-arm clinical trial, sponsored by DNDi, began in October 2019 and tested fexinidazole treatment in patients with r-HAT as an alternative to existing treatment in Malawi and Uganda. Patients (aged ≥6 years) with both stages of the disease were recruited up to the target of 34 patients with stage 2 disease evaluable at the end of hospitalization. Patients were hospitalised during the 10 days of treatment and followed up to 12 months after hospital discharge. The primary outcome was r-HAT-related or treatment-related fatality at the end of hospitalisation in patients with stage 2 disease and was compared with an unacceptable fatality rate of 8.5%, a threshold defined according to results from a previous clinical trial with melarsoprol. This trial is registered with ClinicalTrials.gov, NCT03974178.

Ethics

The protocol and amendments were approved by the National Health Science Research Committee in Malawi, by the Independent Ethics Committee, the Vector Control Division–Research and Ethics Review Committee in Uganda and by the Commission Cantonale d'Ethique de la Recherche (Geneva, Switzerland).

Results

45 patients received treatment between 1 October 2019 and 28 November 2021 (35 [78%] had stage 2 disease and ten [22%] stage 1, 31 [69%] were male and 14 [31%] female, with median age of 24 years). The primary efficacy result of the clinical trial, analysed among the 34 evaluable patients, was achieved, with no r-HAT-related or treatment-related deaths during hospitalisation (0.0%, 95% CI 0.0–8.4), compared with a benchmark of 8.5% lethality attributable to melarsoprol. Safety was acceptable, with no severe adverse events related to fexinidazole; and one patient relapsed.

Conclusions

Fexinidazole, an oral treatment, was shown to be a good alternative to existing injectable and toxic drugs. Results were submitted for EMA regulatory review in preparation for use in endemic countries, and a positive scientific opinion was received in December 2023 to extend the indication of fexinidazole for the treatment of r-HAT. Fexinidazole is expected to be deployed in 2024 as a new r-HAT therapeutic.

Conflicts of interest

All authors declare no competing interests.