



Once-weekly repurposed fosravuconazole versus daily itraconazole, with surgery, in patients with eumycetoma in Sudan: a randomised, double-blind, phase 2, proof-of-concept superiority trial

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Introduction

Treatment options for the highly neglected fungal tropical disease eumycetoma are limited and poorly adapted to patients' contexts, with surgery often required. The first-line treatment, itraconazole, thought to be 40% effective, must be taken twice daily for ≥ 12 months with food, making adherence difficult. An effective, affordable, context-appropriate treatment is urgently needed. The Drugs for Neglected Diseases Initiative (DNDi) repurposed the broad-spectrum antifungal agent fosravuconazole, developed by Eisai Ltd for onychomycosis. We aimed to compare two different doses of weekly fosravuconazole with standard-of-care daily itraconazole in patients with eumycetoma.

Methods

This phase 2, randomised, double-blind, active-controlled, superiority trial was done at the Mycetoma Research Centre, Soba University Hospital, Sudan. Patients aged ≥ 15 years with a small-to-medium lesion (≥ 2 to < 16 cm) caused by *M. mycetomatis* requiring surgery were randomly assigned (1:1:1) to receive either 300 mg fosravuconazole weekly (group 1), 200 mg fosravuconazole weekly (group 2), or 400 mg itraconazole daily (group 3), for 12 months, together with surgery at 6 months in all groups. The primary efficacy endpoint, assessed in all patients receiving at least one dose of study drug (modified intention to treat), was complete cure at 12 months (absence of eumycetoma mass and sinuses and discharge with normal imaging; or a negative fungal culture if mass present). Safety was assessed in patients who received at least one dose of study drug. This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03086226) (NCT03086226).

Ethics

This study was approved by the National Medicines and Poisons Board and the Soba University Hospital Ethics Committee.

Results

Between 9 May, 2017, and 10 June, 2021, 104 patients were randomised (34 to group 1, 34 to group 2, and 36 to group 3). Median age was 29.0 (IQR 22.0–33.0), 23.0 (20.0–29.0) and 24.5 (19.5–33.0) years for Groups 1, 2, and 3 respectively. Complete cure rates at end of treatment were 50.0% (95% CI 32.4–67.6), 64.7% (46.5–80.3), and 75.0% (57.8–87.9) with Groups 1, 2 and 3, respectively, showing no superiority of fosravuconazole over the standard-of-care ($p=0.030$ for Group 2 vs Group 3; and $p=0.347$ for Group 1 vs Group 3; with significance level set at 0.022). Treatment-emergent adverse drug reactions were reported in one (3%) of 34 patients in group 2 (nausea or vomiting) and three (8%) of 36 patients in group 3 (cortisol decreased, QT prolonged).

Conclusion

Although not superior, fosravuconazole 200 mg seemed to have similar efficacy to itraconazole, coupled with advantages such as a weekly, not daily, administration, no food effect, and low risk for drug-drug interactions. An early access programme is under review by authorities in Sudan and a regulatory dossier and global access plan are under preparation.

Conflicts of interest

All authors declare no competing interests.