EVALUATING AN ALTERNATIVE TREATMENT REGIMEN FOR FUNGAL MYCETOMA: A Phase II superiority trial to assess the safety and efficacy of two regimens of fosravuconazole compared to itraconazole

DNDi and the Mycetoma Research Centre, Khartoum conducted a Phase II clinical trial for fungal mycetoma patients in Sudan to assess the safety and efficacy of two different doses of once-weekly fosravuconazole for 12 months compared to the standard of care, daily itraconazole for 12 months, plus surgery for all at six months.

While the trial found that neither of the two fosravuconazole doses was superior to itraconazole, fosravuconazole was found to be an improvement because it can be administered weekly, rather than daily, for the 12-month treatment period and does not need to be taken with a meal, making it easier for patients to complete the course of treatment. The results of this study are now being used to support the registration of this medicine in Sudan so that mycetoma patients there can have access to this treatment option.

CONTEXT

Mycetoma is a highly neglected tropical disease, and we do not yet fully understand how it is spread or how many people are affected by it. It most commonly affects young adults living in remote and rural areas and is probably transmitted through thorn pricks, often to bare feet.

Mycetoma results in a painless lump that grows under the skin with multiple openings and discharge. It has two forms: one bacterial and the other fungal. Eumycetoma, the form of the disease caused by fungi, is a chronic, slow-growing infection that can eventually result in amputation. Since it so often occurs in the foot, it affects mobility.

Children affected by mycetoma may miss a lot of school or drop out entirely, and adults cannot work, leading to mental health consequences such as depression as well as negative economic impacts on the families of those affected. Most people affected by mycetoma are poor and cannot afford to travel long distances to seek diagnosis and treatment. As a result, the disease is often diagnosed at an advanced stage when it is more difficult to treat.

WHY WAS THIS CLINICAL TRIAL CONDUCTED?

Prior to this study, no randomized controlled trial had ever been conducted in patients with mycetoma.

People affected by mycetoma normally undergo surgery in addition to taking antifungal treatment before and after surgery for a total of 12 months. **Itraconazole**, which must be taken twice a day for a year, is the drug most commonly used, with reported cure rates of less than 40%. This low cure rate may be due to the fact that patients struggle to complete the lengthy, expensive treatment.

Fosravuconazole is an inexpensive treatment originally developed by Eisai Ltd, Japan to treat a fungal nail infection, onychomycosis. It has been shown to be effective in treating mycetoma too.

The trial was conducted to identify a weekly fosravuconazole dose that is safe, well tolerated, and effective for patients with small- to medium-sized mycetoma lesions who require surgery, and to demonstrate its superiority over the standard of care, twice-daily itraconazole. The trial was also designed to determine whether any of the treatment regimens were able to cure at least 70% of patients.

HOW AND WHERE WAS THIS TRIAL CONDUCTED?

The study began in 2017, conducted by DNDi and the Mycetoma Research Centre (MRC) with funding from the Global Health Innovative Technology Fund (GHIT) and others (see below). There were 104 participants in total, between 15 and 77 years old, who were treated at MRC in Khartoum, Sudan.

Study participants were randomly assigned to receive one of three treatments:

- 300 mg fosravuconazole daily for the first three days, followed by a weekly dose of 300 mg for a total duration of 12 months, or
- 200 mg fosravuconazole daily for the first three days, followed by a weekly dose of 200 mg for a total duration of 12 months, or
- 400 mg itraconazole daily for 12 months

All patients also underwent surgery after six months of treatment.

The main measure of success in this study was complete cure at the end of treatment at 12 months, defined as the absence of a mass, lesions, or discharge, with a normal ultrasound or MRI imaging of the original site of infection. If a mass was still present, then a sample taken from it was tested to see if it was still infected.

WHAT WERE THE RESULTS?

As usual for any clinical trial, the results were analysed in two different ways. The first analysis, the "intention to treat" analysis, included all of the patients enrolled in the study whether or not they actually completed the treatment. This kind of analysis is important to consider because it may better reflect treatment results in real life, where patients do not always strictly follow a course of treatment or may drop out of treatment. The second analysis, the "per protocol" analysis, looked only at the patients who completed the full course of treatment.

The **intention to treat analysis** (evaluating everyone who took at least one treatment dose and attended at least one follow-up visit) showed that surgery combined with fosravuconazole resulted in complete cure at 12 months in 50% of patients who received 300 mg of fosravuconazole and in 65% of those who received 200 mg, while 75% of patients treated with surgery and itraconazole were cured.

In the **per protocol analysis** (evaluating only patients who *completed* treatment), a complete cure was found in 85% of patients who received 200 mg fosravuconazole and 80% of those who received itraconazole, and 65% of patients that received 300 mg of fosravuconazole. The cure rate for itraconazole was much higher than seen previously, possibly because outside a clinical trial, the drop-out rate is much higher, due to the prohibitive cost of treatment and the heavy burden of taking treatment twice daily for a year. In a clinical trial, the medicines are free of charge and there is regular follow-up with patients to support them in taking their treatment.

All three regimens were well tolerated. There was no advantage to using the higher dose of fosravuconazole, and neither dose was superior to itraconazole. However, fosravuconazole only needs to be taken once a week, making it easier for patients to complete their treatment. Itraconazole needs to be taken every day. Fosravuconazole also has a low risk of interactions with other drugs, which is especially important given the long 12-month treatment period. In addition, fosravuconazole does not need to be taken with food, which is important for patients with fungal mycetoma, who often live in

extreme poverty and may not always have access to regular meals. The main disadvantages of fosravuconazole are the less-than-optimal cure rate and the long 12-month treatment duration.

This is the first randomized controlled double-blind trial ever conducted in patients with eumycetoma, so it can act as a benchmark for the future study of other antifungal medicines for eumycetoma, in combination with surgery. This is a major achievement, especially as it was run in a very challenging socio-economic context, including political instability in Sudan and during the COVID-19 pandemic.

WHAT ARE THE NEXT STEPS?

The patients in this trial who had been cured were enrolled in a subsequent observational study to see whether eumycetoma recurs after longer periods. Unfortunately, this trial had to be ended earlier than planned, due to the conflict in Sudan.

Despite the encouraging results of this study, we still need better treatments with a higher cure rate that can be taken over a shorter period of time and that are effective without surgery. The open-source drug discovery initiative **MycetOS** has reported some potentially interesting chemical compounds to evaluate, and there are new antifungal drugs in development for other diseases that could also be tested for mycetoma.

DNDi will work to ensure availability of fosravuconazole as a treatment for eumycetoma in Sudan with its pharmaceutical partner Eisai Ltd (Japan) and will continue efforts to find a cure for eumycetoma.

READ THE PUBLISHED STUDY

Fahal, Ahmed H et al. **Two dose levels of once-weekly fosravuconazole versus daily itraconazole, in combination with surgery, in patients with eumycetoma in Sudan: a randomised, double-blind, phase 2, proof-of-concept superiority trial.** *The Lancet Infectious Diseases,* Volume 24, Issue 11, 1254 – 1265. https://doi.org/10.1016/ S1473-3099(24)00404-3.

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