

## SHORT COMMUNICATION

## Efficacy of Fluconazole at a 400 mg Weekly Dose for the Treatment of Onychomycosis

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Onychomycosis currently accounts for a third of the total superficial fungal infections worldwide (1). Although many antifungal drugs exist, nail infections represent an increasing therapeutic challenge. Topical treatment fails to produce acceptable clinical response and systemic treatment often does not bring the desired success either (2).

Numerous clinical trials have confirmed the efficacy of fluconazole (FLZ) in the treatment of onychomycosis. It accumulates in the stratum corneum, hair and nails, and is present in the therapeutic concentration at 4 or even 6 months post-treatment. Additionally, FLZ is a relatively safe drug with well-described interactions and side effects (3–6).

The aim of this study was to assess the efficacy of onychomycosis treatment with FLZ pulse therapy administered in patients with foot onychomycosis for a maximum of 12 months at a 400 mg dose once weekly.

## MATERIAL AND METHODS

The study included 50 patients (32 males, 18 females; aged 18–70 years; median age, 53 years), diagnosed with foot onychomycosis during a 4-year period (July 7, 2007–July 12, 2011). For every patient, dermatophyte infection was determined with mycological examination, including direct microscopy (KOH) and culture. Nail samples yielded *Trichophyton rubrum* in 41 patients (82%) (Fig. 1), *T. mentagrophytes* in 7 patients (14%), and *T. tonsurans* in one patient. A mixed infection of *T. rubrum* and *T. mentagrophytes* was demonstrated in one patient. The

number of affected nail plates ranged from 1–10, with a mean of 3 plates. The big toenail plate was infected in all patients. In 2 patients with massive fungal infection of the toenail, onychomycosis involved also the fingernails. Forty-one patients (82%) had distal subungual lateral onychomycosis (DSLO). In 6 patients (12%), DLSO was accompanied by total dystrophic onychomycosis (TDO) and in 2 patients (4%) proximal subungual onychomycosis (PSO) was observed in addition to DLSO. One patient presented with TDO only. All patients met the inclusion criterion of having lesions spread over at least 20% of the plate surface of the big toe, and having at least 2 mm of healthy nail from the eponychium to the proximal border of the lesion.

The exclusion criteria for this study included chronic conditions that may cause changes within the nail plates, such as psoriasis, lichen planus, immunocompromised conditions, not well-controlled diabetes, azole hypersensitivity, systemic diseases that may alter blood chemistry test results, and treatment with corticosteroid or antifungal drugs received topically or orally within 2 weeks or 6 months, respectively, prior to the trial.

During the trial, all patients received FLZ (Teva Pharmaceuticals, Kraków, Poland) at a dose of 400 mg once weekly to achieve clinical cure, with a maximum time of up to 12 months. Patients were taking 2 tablets of 200 mg FLZ at once, always on the same day of the week. Patients were informed about the need for proper care that was removal of the affected part of the nail plate by cutting and sawing. In the course of therapy, at every 2 months and 2 months post-treatment, levels of liver transaminases (ALT, AST) and bilirubin were controlled, clinical condition of the nails was assessed and mycological (KOH and culture) evaluation was performed. Patients who experienced in the course of treatment an increase in transaminase levels of over 2 times upper limit of normal were excluded from the trial. Complete healing or significant

improvement of the clinical status (i.e. when the lesions covered 1–20% of the nail plate surface) was assumed as the clinical cure. Negative results in microscopy (KOH) and culture were used as a proxy for mycological cure. After completion of treatment, patients were advised to carry out disinfection of their footwear using cotton wool soaked with 10% formaldehyde solution, placed inside shoes and kept in a plastic bag for 48 h.

All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the Wrocław Medical University.

## RESULTS

Of the 50 patients, 33 (66%) completed the trial with a full 2-month follow-up period. Eleven (22%) patients withdrew from the trial (4 because of the lack of



Fig. 1. Toe-nail onychomycosis induced by *T. rubrum* in 2 selected patients (I and II) before (a) and after (b) a 12-month therapy with FLZ (400 mg/week).

therapeutic effect, and 7 without giving any reason), while 6 (12%) patients were excluded from the trial due to side effects of the drug. These included transient gastrointestinal disorders, transient increase in liver enzymes and lichen planus-like skin lesions. The evaluation of treatment efficacy was based on a group of 33 patients who completed treatment and follow-up. Among these patients, 22 (66.7%) achieved a complete clinical and mycological cure. Seven patients (21.2%) achieved mycological eradication, yet no clinical cure was obtained. Four patients (12.1%) showed mycological and clinical failure. Patients who failed mycologically were positive for dermatophytes in both KOH and culture. The fungi were identified as *T. rubrum* and *T. mentagrophytes* in 3 and one cases, respectively. Among the 22 patients for whom both clinical and mycological cure was obtained, 6 (27.3%) were treated with FLZ for 12 months (Fig. 1), 5 (22.7%) for 10 months, and another 5 (22.7%) for 8 months. Three patients (13.6%) were cured after 6 months, one after 5 months, and 2 (9.1%) after 4 months of treatment. The median treatment duration in patients with full recovery was 9 months. Patients who had a favourable clinical response after only 4 months of treatment had suffered from onychomycosis for 1.5 or 2 years; in both such patients only one toenail was affected, with the lesions occupying less than 50% of the nail plate surface. Patients who required a 12-month therapy had been suffering from onychomycosis for 2–25 years and had a mean of 4 toenail plates affected, with the lesions spread over around 75% of the nail surface on average.

Four patients (12.1%) with no therapeutic effect achieved in the study, presented at the onset of the trial dystrophic onychomycosis with lesions spread over 75% of the nail plate. One patient (4.6%) experienced recurrence 2 months after the end of treatment.

## DISCUSSION

A large body of literature have described good therapeutic effects of the FLZ pulse method in the treatment of foot onychomycosis. Patients were receiving the drug at 150 mg, 300 mg, or 450 mg doses once a week for several months (up to 12 months). Such therapy was well tolerated and serious side effects were rare and comparable to placebo. Fortunately, FLZ remained in the fingernails and toenails for up to 6 months after treatment cessation; low rates of relapse and further improvement, even after therapy interruption, were observed (6–10).

This study provides the results of the treatment trial for onychomycosis with FLZ at a dose of 400 mg weekly. The overall clinical and mycological cure

was demonstrated in 22 (66.7%) of the patients. The relapse rate was very low as only one patient (4.6%) experienced recurrence 2 months after the end of treatment. According to the present study, longer treatment (6 months or more) was required in patients who had a longer history of the condition and in whom the number of the affected nail plates and proportion of the lesioned area were significantly higher. The adverse effects occurred in 6 (12%) patients. This is in line with previous reports where the percentage of patients with side effects from the treatment with FLZ ranged from 1% to 10% (5, 8, 9).

In conclusion, this study demonstrated high efficacy of FLZ at a 400 mg/week dose in the treatment of dermatophytic onychomycosis. A high rate of clinical response and low recurrence rate, along with good tolerance and low therapy costs compared with other antimycotic agents underscore the usefulness of FLZ in the treatment of onychomycosis.

*The authors declare no conflict of interests.*

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