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# Randomized Double-blind Comparison of Short-term Itraconazole and Terbinafine Therapy for Toenail Onychomycosis

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**Previous studies evaluating short-term itraconazole and terbinafine therapy for onychomycosis have varied in protocol and size; this double-blind study enabled a large-scale, standardized, direct comparison. Patients with toenail onychomycosis were randomized to itraconazole 200 mg daily ($n=146$) or terbinafine 250 mg daily ($n=146$) for 12 weeks, with a 36-week follow-up. Mycological cure rates at the follow-up end-point were significantly equivalent (61% with itraconazole vs. 67% with terbinafine). A similar proportion of patients in each group experienced adverse events during treatment (itraconazole, 22%; terbinafine, 23%). More patients receiving terbinafine stopped treatment permanently because of treatment-related adverse events (8% vs. 1%).** ***Keywords: antifungal agents; dermatophytosis; efficacy; safety; tolerability.***

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Onychomycosis is a recalcitrant nail condition caused most frequently by infection with dermatophytes and less often by infection with yeasts or moulds. Although onychomycosis is notoriously difficult to treat, two of the more recently developed systemic antifungal agents, the triazole derivative itraconazole and the allylamine derivative terbinafine, have given cause for renewed optimism.

Itraconazole and terbinafine have different chemical structures and modes of action (1, 2) but their pharmacokinetic behaviour is similar; both agents enter the nail plate via the nail matrix and the nail bed within approximately 7 days of the start of therapy and remain in the nail plate for several months after treatment has stopped (3–7). These pharmacokinetic features mean that itraconazole and terbinafine need to be administered continuously for only a short time to ensure effective treatment of onychomycosis (5, 8–12).

Previous studies of the effectiveness of short-term continuous itraconazole and terbinafine regimens in the treatment of onychomycosis have varied widely in protocol and size. The present clinical trial was performed to facilitate a large-scale standardized direct comparison of the efficacy and safety of itraconazole 200 mg daily and terbinafine 250 mg daily, administered for a short term of 12 weeks, in the treatment of onychomycosis of the toenails.

## MATERIALS AND METHODS

This multicentre, randomized, double-blind, parallel-group trial involved men and women aged 18–65 years with clinically suspected and microscopically and culturally proven onychomycosis of the toenail. Patients, who gave written informed consent to participate, were randomized to 12 weeks' treatment with itraconazole 200 mg daily or terbinafine 250 mg daily. No study medication was taken during a 36-week follow-up period.

Patients were eligible for inclusion if the onychomycosis was caused by a dermatophyte, if they had no evidence of a superimposed *Candida* infection and if more than 50% of the surface of at least one nail was affected, including a possible destroyed and missing part of the nail plate (or, if the lunula was involved, if at least 25% of the surface of at least one nail was affected). Distal subungual infection of the toe, additional onychomycosis of the fingernail or a fungal lesion of the pilose or glabrous skin did not prevent patients from entering the trial.

Patients were ineligible if they had received systemic antifungal therapy during the 3 months before the start of the trial or topical antifungal therapy during 1 month before the start of the trial. Other exclusion criteria included abnormal liver function tests at the start of the trial, (possible) pregnancy or lactation, psoriasis, concurrent use of rifampicin, phenytoin, digoxin, oral anticoagulants or $H_2$-receptor antagonists, serious disease that could prevent completion of the trial and previous hypersensitivity to azole or allylamine antifungal agents. In addition, systemic or topical antimicrobial agents, topical treatment of the dermatophyte-infected tissue, local corticosteroids, antacids and agents metabolized by oxidation (e.g. cyclosporine) were prohibited during the trial.

### *Study assessments*

At the first visit, the patient's history, previous treatment and disease characteristics were recorded and baseline assessments were performed. Patients were to return for efficacy and safety assessments at weeks 4, 8 and 12 of treatment and at weeks 12, 24 and 36 of follow-up.

A mycological examination (microscopy and culture) was performed at each visit, using material collected from the area of the most severely affected toenail (the target toenail) that was closest to the healthy area. Mycological cure was defined as microscopy (KOH-preparation) and culture negative. The primary efficacy variable was the mycological cure rate at the end of follow-up. Secondary efficacy variables were investigator's global clinical evaluation of response to treatment, performed at the end of treatment and at each visit during follow-up; clinical response, defined as an investigator's global clinical evaluation of "cured" or "markedly improved" ($\geq$50% clinical improvement); nail assessments, including percentage total affected area and total number of infected nails, performed at each visit; and assessment of the target toenail for signs and symptoms of onycholysis, hyperkeratosis, paronychial inflammation and discoloration, performed at each visit, using a 4-point scale: 0, absent; 1, mild; 2, moderate; 3, severe.

At the end of treatment, investigators and patients rated the overall tolerability of the trial medication as "very good", "good", "moderate", "poor" and "not tolerated". Blood samples for routine haematology and biochemistry were taken at the start of the trial, at week 4 and at the end of treatment. If laboratory abnormalities occurred during treatment, additional assessments were performed at week 8 of treatment and at week 12 of follow-up. Treatment was stopped in any patient showing significant liver function test abnormalities (i.e. liver transaminases more than 3 times the upper normal limit).

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*Statistical analyses*

Two populations were defined for the statistical analyses: an evaluable-patients population, comprising all randomized patients with at least 1 drug intake and positive microscopy or culture at baseline (and at least 1 of the 2 tests performed); and an intention-to-treat population, comprising all randomized patients, regardless of compliance, unless they had received no treatment at all. The evaluable-patients observed-case analysis was the primary analysis for efficacy. An intention-to-treat worst-case analysis was also performed for the primary efficacy variable, in which missing values were imputed with the worst possible score. The intention-to-treat worst-case analysis was the primary analysis for safety.

The Mann-Whitney U test and the Fisher exact probability test were used to detect differences in demographic data and baseline disease characteristics. The one-sided Blackwelder test was used to test equivalence in efficacy between the two groups (13). In line with criteria used in previous trials (14), a 15% difference was considered to be clinically acceptable; however, equivalence testing was also performed for a maximum allowable difference of 10%.

## RESULTS

*Patient disposition and characteristics*

A total of 299 patients were recruited into the trial, of whom 297 were randomized to treatment. The intention-to-treat population comprised 292 patients, 146 in each group; 289 patients were considered evaluable for efficacy, 145 in the itraconazole group and 144 in the terbinafine group. During treatment, 11 patients receiving itraconazole and 23 receiving terbinafine withdrew from the trial, because of adverse events (itraconazole, $n=2$; terbinafine, $n=11$), ineligibility (itraconazole, $n=1$; terbinafine, $n=1$), loss to follow-up (itraconazole, $n=7$; terbinafine, $n=6$) and treatment deviation (itraconazole, $n=1$; terbinafine, $n=5$). As a result, 135 patients in the itraconazole group and 123 patients in the terbinafine group started the follow-up period, during which 15 patients on itraconazole and 14 on terbinafine withdrew from the trial; none of these withdrawals was attributable to adverse events.

No significant differences were found between groups for sex, age and weight. The median duration of current onychomycosis was 3 years in both groups. *Trichophyton rubrum* was detected in 85% and *T. mentagrophytes* in 13% of patients in whom a pathogen was identified. Fifteen percent of patients in the itraconazole group and 17% in the terbinafine group had received previous treatment with systemic antimycotic agents; 29% and 23%, respectively, had received previous topical treatment.

Concurrent diseases were noted in 43% of patients receiving itraconazole and in 47% receiving terbinafine: tinea pedis was noted in 32% and 35%, respectively; tinea manus and diabetes each occurred in 1 patient in each group. Concurrent medication was taken by 24% of patients receiving itraconazole and by 18% receiving terbinafine.

*Efficacy*

The number of patients who were mycologically cured was similar in the 2 groups (itraconazole, $n=78$; terbinafine, $n=79$). However, more patients withdrew from the terbinafine group, so the mycological cure rate was slightly lower in the itraconazole group. In the intention-to-treat worst-case analysis, the mycological cure rates at the end-point of follow-up, 54% with itraconazole and 56% with terbinafine, were statistically significantly equivalent (maximum allowable difference 10%). In the evaluable-patients observed-case analysis, the rates were 28% with itraconazole and 33% with terbinafine at the end-point of treatment and 61% and 67%, respectively, at the end-point of follow-up. These results were significantly equivalent with a maximum allowable difference of 15% and tended to be equivalent with a maximum allowable difference of 10%.

Negative direct microscopy results were achieved in 61% of itraconazole-treated patients and 63% of terbinafine-treated patients by the end-point of follow-up; at the same point, negative cultures were achieved in 66% and 65%, respectively.

Results of the investigators' global clinical evaluation are presented in Table I. Clinical response rates were significantly equivalent (maximum allowable difference 10%) at the treatment and follow-up end-points. Complete clinical cure rates were similar in both groups.

At baseline, the mean percentage affected area per nail was 53% in the itraconazole group and 44% in the terbinafine group and the mean number of affected nails was 5.3 and 5.2, respectively. At the end of treatment, the mean total affected area per nail had decreased to 33% in the itraconazole group and 27% in the terbinafine group and the mean number of affected nails was 4.6 and 4.3, respectively. At the end-point of follow-up, the mean percentage affected area per nail had fallen to 13% in the itraconazole group (representing a shift of −43% from baseline) and to 9% in the terbinafine group (representing a shift of −38% from baseline) and the mean number of affected nails was 1.7 and 1.3, respectively.

Signs and symptoms improved by a comparable extent in the two groups. Overall, from baseline to the end-point of follow-up, the mean severity score for discoloration, hyperkeratosis and onycholysis decreased by 65–80%; the greatest improvement was in onycholysis (around 80% improvement in each group). For paronychial inflammation, the mean severity scores were less than 1 (mild) in both groups throughout the study.

*Safety*

At the end-point of the treatment period, the investigators rated the tolerability of the trial medication as "very good" or

Table I. *Investigators' global clinical evaluation*

| Evaluation | Patients (%) | |
|---|---|---|
| | Itraconazole | Terbinafine |
| Cure | | |
| End-point of treatment | 6.2 | 3.5 |
| Week 24 of follow-up | 30.3 | 27.1 |
| End-point of follow-up | 42.8 | 38.9 |
| Marked improvement | | |
| End-point of treatment | 43.4 | 38.9 |
| Week 24 of follow-up | 42.1 | 36.1 |
| End-point of follow-up | 33.1 | 34.0 |
| Clinical response | | |
| End-point of treatment | 52.6[a] | 48.0 |
| Week 24 of follow-up | 87.5[a] | 85.0 |
| End-point of follow-up | 82.1[a] | 86.8 |

[a] Test for equivalence between groups significant: one-sided $p$-value (terbinafine > itraconazole) $<0.1$.

"good" in 97% of patients in the itraconazole group and in 92% of patients in the terbinafine group. Similar statements were given by the patients.

During treatment, adverse events were noted in 32 patients receiving itraconazole and in 34 receiving terbinafine. In this period, 2 patients from the itraconazole group and 11 from the terbinafine group stopped treatment permanently because of adverse events considered to be possibly or definitely related to study medication, including 1 patient in the terbinafine group with abnormal liver function tests. During follow-up, adverse events were reported in 8 patients in the itraconazole group and 4 in the terbinafine group.

The most frequently reported adverse events were abdominal pain (itraconazole, $n=4$; terbinafine, $n=5$), dyspepsia ($n=3$ in each group), headache (itraconazole, $n=1$; terbinafine, $n=5$), viral infection (itraconazole, $n=3$; terbinafine, $n=2$), nausea (itraconazole, $n=2$; terbinafine, $n=3$) and taste perversion (terbinafine, $n=3$).

No serious adverse events considered to be related to study medication were reported in either group. During treatment, severe adverse events considered to be possibly or definitely related to study medication were noted in 2 patients receiving itraconazole (constipation; abdominal pain) and in 7 patients receiving terbinafine (nausea; taste loss and taste perversion; taste loss alone; abdominal pain ($n=2$); joint pain; fatigue).

No consistent, clinically relevant changes were found in biochemistry or haematology, although a tendency towards a decrease in total cholesterol was seen in the itraconazole group.

## DISCUSSION

The equivalent effectiveness of itraconazole and terbinafine observed in the present study is in agreement with the findings of a previous study comparing itraconazole and terbinafine in the treatment of onychomycosis (15); by contrast, higher cure rates for terbinafine than for itraconazole have been reported in 2 other studies (16, 17). In all 4 studies, dosage regimens and treatment durations were identical; however, our study involved patients with only severe toenail onychomycosis (i.e. involvement of $>50\%$ of the surface of the target nail or, if the lunula was involved, $>25\%$ of the surface). The higher cure rates reported for terbinafine (16, 17) may be attributable to a primarily fungicidal mode of action. However, terbinafine has shown fungicidal activity in selected *in vitro* tests only (18), whereas antifungal activities of itraconazole and terbinafine were found to be comparable in an *ex vivo* model and the closest manifestation of complete fungicidicity occurred with itraconazole 200 mg twice daily against *T. mentagrophytes* (19).

Experience to date suggests that both itraconazole and terbinafine are safe and well tolerated, with gastrointestinal-related symptoms reported most frequently (20, 21). However, treatment-related severe adverse events were noted in fewer patients receiving itraconazole than in patients receiving terbinafine and more patients on terbinafine stopped treatment permanently because of treatment-related adverse events.

In conclusion, the results of the present trial indicate that short-term (12-week) regimens of itraconazole 200 mg daily and terbinafine 250 mg daily are equally effective and safe in the treatment of onychomycosis.

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