Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies

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Background: Onychomycosis is a common nail infection, often resulting in nail plate damage and deformity. Topical lacquer treatments have negligible efficacy. Oral treatments, although more efficacious, are limited by drug interactions and potential hepatotoxicity.

Objective: We investigated the safety and efficacy of efinaconazole 10% solution (efinaconazole), the first triazole antifungal developed for distal lateral subungual onychomycosis.

Methods: Two identical, multicenter, randomized, double-blind, vehicle-controlled studies were conducted in patients with toenail distal lateral subungual onychomycosis (20%-50% clinical involvement [study 1: N = 870, study 2: N = 785]). Patients were randomized (3:1) to efinaconazole or vehicle, once daily for 48 weeks, with 4-week posttreatment follow-up. Debridement was not performed. The primary end point was complete cure rate (0% clinical involvement of target toenail, and both negative potassium hydroxide examination and fungal culture) at week 52.

Results: Mycologic cure rates were significantly greater with efinaconazole (study 1: 55.2%, study 2: 53.4%) compared with vehicle (P < .001). The primary end point, complete cure, was also significantly greater for efinaconazole (study 1: 17.8% vs 3.3%, study 2: 15.2% vs 5.5%, P < .001). Treatment success (percent affected target toenail [0%-≤ 10%]) for efinaconazole ranged from 21.3% to 44.8% in study 1 and from 17.9% to 40.2% in study 2, compared with 5.6% to 16.8% and 7.0% to 15.4%, respectively, with vehicle. Adverse events associated with efinaconazole were local site reactions (2%) and clinically similar to vehicle.

Limitations: A period of 52 weeks may be too brief to evaluate a clinical cure in onychomycosis.

Conclusions: Once daily topical efinaconazole appears to be a viable alternative to oral treatment options for onychomycosis. (J Am Acad Dermatol 2013;68:600-8.)

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Distal lateral subungual onychomycosis (DLSO) is a common and progressive fungal infection of the nail bed, which may extend into the matrix or plate, leading to destruction and deformity of toenails and, less frequently, fingernails.\(^1\)\(^,\)\(^2\) Prevalence increases with age\(^3\)\(^-\)\(^5\) and it is associated with patient distress, disability, and pain.\(^6\)\(^-\)\(^10\) Onychomycosis is challenging to treat because of slow nail growth and difficulties delivering treatment to the infection site.\(^3\)\(^,\)\(^11\)

Phase III studies of oral itraconazole and terbinafine report complete cure rates of 14% and 38% and mycologic cure rates of 54% and 70%, respectively.\(^12\)\(^,\)\(^13\) Subsequent studies report lower complete cure rates.\(^14\)\(^-\)\(^17\) Oral treatment is limited by drug interactions and risk of acute liver injury (requiring laboratory monitoring), which is relevant to elderly patients.\(^18\)\(^,\)\(^19\)

Patients may prefer an efficacious topical treatment if there are minimal systemic side effects and no laboratory monitoring. However, ciclopirox lacquer has a complete cure rate of 5.5% to 8.5%,\(^12\) and mycologic cure rates of 34%.\(^20\) It requires frequent nail debridement and residual lacquer removal.\(^21\)

Thus, we investigated the safety and efficacy of efinaconazole 10% (wt/wt) solution (IDP-108), the first triazole antifungal developed specifically for the topical treatment of DLSO.

**METHODS**

**Study design**

In 2 identical, multicenter, randomized, parallel-group, double-blind, vehicle-controlled studies, patients with mild to moderate toenail DLSO (defined as 20%-50% clinical involvement of the target toenail, without dermatophytomas or matrix [lunula] involvement) were randomized to receive efinaconazole 10% solution or vehicle. Eligibility criteria included: 18 to 70 years of age, clinical diagnosis of DLSO affecting at least 1 great toenail, target toenail uninfected length 3 mm or more (from the proximal nailfold), thickness 3 mm or less, evidence of toenail growth, positive potassium hydroxide microscopy result, and culture of dermatophyte or mixed dermatophyte/\textit{Candida} less than or equal to 42 days before baseline. Women of childbearing age were required to use birth control.

Exclusion criteria included: history of immunosuppression and/or clinical signs indicative of possible immunosuppression, known HIV infection, uncontrolled diabetes mellitus, presence of toenail infection other than dermatophytes, severe moccasin tinea pedis at screening/baseline, any disease/condition that might have caused toenail abnormalities or interfered with the evaluation, and previous target toenail surgery. Patients were not excluded for concomitant drugs that inhibit cytochrome P450 3A4.

Enrolled patients were randomized to receive efinaconazole or vehicle (3:1 ratio) self-applied once daily for 48 weeks without debridement, followed by a treatment-free 4-week follow-up. Treatment was applied to the clean, dry nail plate surface, lateral and proximal nailfolds, hyponychium, and undersurface of the nail plate. Patients were assessed for efficacy and safety at baseline, 12-week intervals postbaseline (ie, weeks 12, 24, 36, and 48), and final visit (week 52).

**Randomization and masking**

Study drugs were provided in a kit containing identical masked bottles with a randomization number determined by a computer-generated randomization schedule. Access to the randomization schedule was permitted after both the database was locked and the study unblinded. The investigators, sponsor, investigational center staff, clinical monitors, patients, and all other study personnel were unaware of study drug assignment to individual patients. In case of a medical emergency where it became necessary to know treatment assignment, the identity was made available to the investigator. If the treatment code was broken, the patient was discontinued.
Study assessment

The primary efficacy end point was the proportion of patients achieving complete cure at week 52 (4-week posttreatment visit) defined as 0% clinical involvement of the target toenail and mycologic cure (negative potassium hydroxide examination, and negative fungal culture of the target toenail sample). Secondary end points were: mycologic cure, treatment success (<10% clinical involvement of the target toenail), complete or almost complete cure (≤5% clinical involvement and mycologic cure), and unaffected toenail growth (change from baseline). All secondary end points were assessed at week 52.

Supportive efficacy end points included treatment success (0%–≤10% clinical involvement of the target toenail), change in the number of affected nontarget toenails, change in quality of life, and target toenail growth. A study investigator assessed the outcomes at each visit.

Safety assessments included monitoring and recording of adverse events (AEs) until week 52.

Study oversight

The studies were conducted in accordance with the ethical principles specified in the Declaration of Helsinki and in compliance with requirements of local regulatory committees. All patients provided written informed consent.

Statistical analysis

Data from each trial were analyzed separately using software (SAS, SAS Institute Inc, Cary, NC). The intent-to-treat population included all patients randomized and dispensed study drug. The safety population included all patients who received at least 1 dose of study drug, and 1 postbaseline assessment.

Efficacy end points were compared using Cochran-Mantel-Haenszel tests (stratified by analysis center) at a 5% significance level. Unaffected new toenail growth was analyzed using a 2-way variance analysis. Missing efficacy data were imputed using the last observation carried forward method; no imputations for missing safety data were performed.

All AEs were recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA version 12.1). A Fisher exact test was used to compare the incidences of treatment-emergent AEs and treatment-related AEs occurring with frequencies 1% or higher.

RESULTS

Patients

There were 1655 patients with DLSO randomized (study 1: 870, study 2: 785) at 118 sites: United States (study 1: 34, study 2: 36), Canada (study 1: 7, study 2: 8), and Japan (study 1: 33). Studies were conducted from December 2009 to September 2011 (study 1: DPSI-IDP-108-P3-01) and October 2011 (study 2: DPSI-IDP-108-P3-02) (ClinicalTrials.gov numbers NCT01008033 and NCT01007708). Patients were randomized to efinaconazole 10% solution (study 1: 656, study 2: 583) or vehicle (study 1: 214, study 2: 202) (Fig 1).

At baseline, patient mean age was 52.3 and 50.6 years (studies 1 and 2, respectively). Patients were
predominantly male (74.4% and 80.4%, respectively). The majority of patients were white (64.9% and 87.8%, respectively), although a substantial number of Asian patients were in study 1 from participation of 33 Japanese sites (Table I).

The mean area of target toenail involvement was 36.7% and 36.3% (studies 1 and 2, respectively) and the mean number of affected nontarget toenails was 2.8 in each study. There were no significant or clinically meaningful differences between treatment groups for demographics or baseline characteristics (Table I).

Overall, 1436 (86.8%) patients completed the 48-week treatment and 1420 (85.8%) patients completed the 4-week follow-up. A total of 235 (14.2%) patients discontinued early because of patient request (98, 41.7%), lost to follow-up (78, 33.2%), AEs (33, 14.0%), protocol violation (7, 3.0%), other (17, 7.2%), worsening condition (1, 0.5%), and pregnancy (1, 0.5%) (Fig 1).

### Efficacy

**Primary efficacy end point.** At week 52, 17.8% (study 1) and 15.2% (study 2) of patients had a complete cure on efinaconazole compared with 3.3% and 5.5%, respectively, of patients on vehicle (both P < .001) (Fig 2).

**Secondary and supportive efficacy end points.** At week 52, 55.2% (study 1) and 53.4% (study 2) of patients achieved mycologic cure on efinaconazole compared with 16.8% (study 1) and 16.9% (study 2) on vehicle (both P < .001) (Fig 3). More patients treated with efinaconazole (study 1: 26.4% and study 2: 23.4%) achieved a complete or almost complete cure compared with vehicle (study 1: 7.0% and study 2: 7.5%; both P < .001). At week 52, 35.7% (study 1) and 31.0% (study 2) of patients on efinaconazole had treatment success (<10% clinical involvement) compared with 11.7% (study 1) and 11.9% (study 2) on vehicle (P < .001). The proportion of patients who had treatment success increased, based on defining clinical involvement as less than or equal to 10%, less than or equal to 5%, and less than or equal to 0% (Fig 4). Mean unaffected new toenail growth (study 1: 5.0 mm, study 2: 3.8 mm) was greater for efinaconazole than vehicle (study 1: 1.6 mm, study 2: 0.9 mm; P < .001).

Fig 5 shows successful treatment in 2 patients. These patients had 40% to 45% involvement at baseline. One patient was assessed as complete cure (0%) at week 52, the other as almost complete cure (≤5% clinical involvement).

### Safety

Efinaconazole AE rates were similar to vehicle (study 1: 66% vs 61%, study 2: 64.5% vs 58.5%) (Table II). They were generally mild (study 1: 45.5% vs 44.3%, study 2: 61.0% vs 60.6%) or moderate (study 1: 50.0% vs 53.8%, study 2: 35.1% vs 37.3%) in

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**Table I. Study demographics and baseline characteristics (intent-to-treat population)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efinaconazole</td>
<td>Vehicle</td>
<td></td>
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<tr>
<td></td>
<td>Mean, median</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52.4, 54.0</td>
<td>20.0-71.0</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male 489 (74.5%)</td>
<td>Female 167 (25.5%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic/Latino 71 (10.8%)</td>
<td>Non-Hispanic/Latino 585 (89.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White 425 (64.8%)</td>
<td>Black/African American 36 (5.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>American Indian/Alaskan Native 1 (0.2%)</td>
<td>Asian (including Japanese 189 (28.8%)</td>
<td></td>
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<tr>
<td></td>
<td>Native Hawaiian/Pacific Islander 1 (0.2%)</td>
<td>Other 4 (0.6%)</td>
<td></td>
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<tr>
<td></td>
<td>Percent of affected toenail Mean, median 36.7, 40.0</td>
<td>Range 20.0-50.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of affected nontarget toenails Mean, median 2.8, 3.0</td>
<td>Range 0.0-5.0</td>
<td></td>
</tr>
</tbody>
</table>

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severity, not related to study drug (study 1: 91.8% vs 98.6%, study 2: 92.7% vs 96.9%), and resolved without sequelae (study 1: 83.6% vs 83.8%, study 2: 80.3% vs 80.5%).

The rate of discontinuations as a result of AEs was low for efinaconazole while higher than vehicle (study 1: 3.2% vs 0.5%, study 2: 1.9% vs 0%). The most common AEs leading to study discontinuation were treatment related and associated with the application site (application site dermatitis and vesicles).

Yet, efinaconazole was not associated with redness, swelling, burning, itching, or vesiculation, and localized skin reactions were similar to vehicle. Thus,
although more patients on efinaconazole discontinued treatment as a result of application site dermatitis and vesicles, the overall AE rates did not differ from vehicle. There were no clinically meaningful changes from baseline in laboratory or vital sign measurements for either treatment group.

Fig 4. Treatment success (percent affected toenail area) at week 52 efinaconazole versus vehicle (intent-to-treat population).

Fig 5. Representative clinical photographs from 2 patients with moderate (40%-45% involvement) distal lateral subungual onychomycosis at baseline treated with efinaconazole for 48 weeks shown, at baseline, week 24, and week 52 (complete cure [subject A] and almost complete cure [subject B] at week 52).
DISCUSSION

Although oral treatment of onychomycosis is standard of care, drug interactions and risk of acute liver injury limit their use. Yet, the development of effective topical antifungals has been challenging. Apart from laser treatment to improve the nail’s appearance, no new onychomycosis treatments have been introduced for over 10 years. Difficulties in formulating topical treatments to penetrate the nail and reach the site of infection in the nail bed may have hampered their development.22-24 Poor nail penetration may be a function of physiochemical properties, including lipophilicity and keratin binding, and formulation.25-28

In 2 studies, efinaconazole 10% solution was significantly more effective than vehicle in treating DLSO, without requiring debridement. The results were 2- to 3-fold greater than in studies of other topical antifungals. Complete cure rates were within the range of oral itraconazole and mycologic cure rates were within range of both oral therapies.12,13 When efficacy was defined as complete or almost complete cure (≤ 5% clinical involvement), response rates increased by a factor of 48% to 54%. Minimal visible difference was noted between nails rated as almost complete or complete cures (Fig 5).

The safety and tolerability profile of efinaconazole was similar to vehicle, with the most common AEs being mild, considered unrelated to treatment, and resolvable. A small proportion of patients receiving efinaconazole (2%-3%) were more likely to discontinue than those receiving vehicle (0%-0.5%), mainly as a result of application site events.

We speculate that complete cure rates (a regulatory standard) may underestimate the clinical value of efinaconazole, given that toenails require up to 78 weeks to grow cleanly, whereas our studies were 52 weeks.29,30 Treatment success rates of 40% to 45% (≤ 10% clinical involvement), along with the upward slope of complete cure rates both suggest that a substantial proportion of patients were heading toward a complete cure. An alternative predictor may be mycologic cure, assuming that once it is achieved clinical cure follows.31

The onychomycosis recurrence rates of 33.7% and 11.9% reported for itraconazole and terbinafine, respectively,32 suggest potential for efinaconazole maintenance treatment, although the risk-benefit profile is unknown. Being a topical solution, systemic absorption is low, reducing the likelihood of drug interactions and acute liver injury (Jo et al and Crean et al, unpublished data, October 2012).

Generalizability of these studies may be limited from using carefully selected patients and controlled methods. Participants were older, with mild or moderate disease, seen over a fixed duration.

Table II. Analysis of treatment-emergent adverse events reported by more than 2% of patients in at least 1 study (safety patients)

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
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<tbody>
<tr>
<td></td>
<td>Efinaconazole (N = 653)</td>
<td>Efinaconazole (N = 574)</td>
</tr>
<tr>
<td></td>
<td>Vehicle (N = 213)</td>
<td>Vehicle (N = 200)</td>
</tr>
<tr>
<td>No. of patients who reported at least 1 TEAE</td>
<td>431 (66.0%)</td>
<td>370 (64.5%)</td>
</tr>
<tr>
<td>Individual TEAEs reported by &gt;2% of patients in at least 1 study</td>
<td>130 (61.0%)</td>
<td>117 (58.5%)</td>
</tr>
<tr>
<td>Application site dermatitis</td>
<td>23 (3.5%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Application site vesicles</td>
<td>13 (2.0%)</td>
<td>18 (3.1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (2.0%)</td>
<td>19 (3.3%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>16 (2.5%)</td>
<td>19 (3.3%)</td>
</tr>
<tr>
<td>Blood creatinine phosphokinase increased</td>
<td>-</td>
<td>11 (1.9%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8 (1.2%)</td>
<td>14 (2.4%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>19 (2.9%)</td>
<td>8 (1.4%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>22 (3.4%)</td>
<td>5 (0.8%)</td>
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<tr>
<td>Folliculitis</td>
<td>5 (0.8%)</td>
<td>5 (2.3%)</td>
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<tr>
<td>Headache</td>
<td>15 (2.3%)</td>
<td>25 (4.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (2.6%)</td>
<td>11 (1.9%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>16 (2.5%)</td>
<td>10 (1.7%)</td>
</tr>
<tr>
<td>Ingrowing nail</td>
<td>17 (2.6%)</td>
<td>11 (1.9%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>78 (11.9%)</td>
<td>63 (11.0%)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>10 (1.5%)</td>
<td>6 (1.0%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>30 (4.6%)</td>
<td>17 (3.0%)</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>7 (1.1%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>38 (5.8%)</td>
<td>35 (6.1%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (1.8%)</td>
<td>12 (2.1%)</td>
</tr>
</tbody>
</table>

TEAE, Treatment-emergent adverse event.
These studies do not provide data in children, or those with severe disease. It is unknown whether continued improvement would occur with either longer treatment or follow-up. Nor has efinaconazole been studied in combination with oral antifungal treatments.

Overall, in 2 well-controlled studies, efinaconazole 10% solution, the first triazole antifungal developed for DLSO, provided an effective and well-tolerated treatment. It may be the first topical treatment for DLSO that can be considered a viable alternative to oral treatments.

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**REFERENCES**


