Efnaconazole Topical Solution, 10%: The Benefits of Treating Onychomycosis Early

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ABSTRACT

Objective: To evaluate efficacy of efinaconazole topical solution, 10% in onychomycosis patients with early and long-standing disease.

Methods: An analysis of 1655 patients, aged 18-70 years, randomized to receive efinaconazole topical solution, 10% or vehicle from two identical multicenter, double-blind, vehicle-controlled 48-week studies evaluating safety and efficacy. The primary endpoint was complete cure rate (0% clinical involvement of target toenail, and both negative potassium hydroxide examination and fungal culture) at Week 52. Three groups were compared: those with early disease (<1 year), patients with a baseline disease of 1-5 years, and those with long-standing onychomycosis (>6 years).

Results: The majority of patients had long-standing disease; were older, male and white. While nail involvement of the target toenail did not differ noticeably amongst the three groups, the number of nails involved did increase progressively with disease duration. Differences were seen in terms of infecting pathogens in early disease that might have important treatment implications. Efinaconazole was more effective in treating early disease, however more than 40% of patients with long-standing disease were considered treatment successes.

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

Conclusions: Treatment of onychomycosis early to avoid disease progression to other toenails is important. Once daily efinaconazole topical solution, 10% is particularly effective in these patients.


INTRODUCTION

Onychomycosis is a progressive fungal infection of the nail bed, matrix or plate; it leads to destruction and deformity of the toenails and (less frequently) fingernails. It represents up to 50% of all nail disorders, and is nearly always associated with tinea pedis. Toenail onychomycosis frequently involves several nails and can be more challenging to treat because of the nail's slow growth rate.

Onychomycosis is caused by dermatophyte fungi (mainly Trichophyton rubrum) in up to 90% of cases, but can also be due to other fungi such as yeasts (mainly Candida albicans) or molds (mainly Scopulariopsis brevicaulis).

Onychomycosis is not self-healing and may be a source of more widespread fungal lesions, spreading to other digits, other sites (groin, skin, scalp), and even to family members if not treated and managed effectively.

Many onychomycosis patients suffer from onychomycosis that has been present for several years. Long-standing disease, the number of toenails involved and co-existing fingernail disease significantly influence its psychosocial effects. In a study of patients who had onychomycosis of over 10 years duration, 41% reported pain or discomfort, reflecting the continuing impact associated with this condition.

Early treatment before the disease progresses to total dystrophic onychomycosis can increase cure rate and may avoid the need for systemic treatments.

Two identical 52-week prospective, multicenter, randomized, double-blind studies in 1655 patients (18-70 years) assessed the safety and efficacy of efinaconazole topical solution, 10% in the treatment of onychomycosis. We provide an analysis of efficacy based on the duration of disease at baseline to provide important insights in the early treatment of the disease.

METHOD

Two multicenter, randomized, double-blind, vehicle-controlled studies designed to evaluate the efficacy, safety, and tolerability of efinaconazole topical solution, 10% relative to its vehicle in 1655 male and female patients aged 18 to 70 years with mild to moderate toenail onychomycosis.

Patients who presented with 20%-50% clinical involvement of the target toenail were randomized (3:1) to apply blinded study
TABLE 1. Baseline Demographics and Disease Duration

<table>
<thead>
<tr>
<th>Age (Mean/SD)</th>
<th>Baseline Disease Duration &lt;1 Year</th>
<th>Baseline Disease Duration 1-5 years</th>
<th>Baseline Disease Duration &gt;5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (Mean/SD)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>49.6 (10.3)</td>
<td>49.9 (12.6)</td>
<td>50.6 (11.4)</td>
</tr>
<tr>
<td>Female</td>
<td>34 (64.2%)</td>
<td>15 (71.4%)</td>
<td>388 (75.8%)</td>
</tr>
<tr>
<td>RACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34 (64.2%)</td>
<td>13 (61.9%)</td>
<td>429 (83.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (35.8%)</td>
<td>6 (28.6%)</td>
<td>124 (24.2%)</td>
</tr>
<tr>
<td>WEIGHT (Mean/SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84.1 (26.4)</td>
<td>79.1 (19.9)</td>
<td>87.9 (20.3)</td>
</tr>
</tbody>
</table>

TABLE 2. Subject Disposition at Baseline

<table>
<thead>
<tr>
<th>Percent Affected Nail (% Mean/SD)</th>
<th>Baseline Disease Duration &lt;1 Year</th>
<th>Baseline Disease Duration 1-5 years</th>
<th>Baseline Disease Duration &gt;5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Mean/SD</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>33.5 (10.2)</td>
<td>36.6 (12.5)</td>
<td>36.3 (10.8)</td>
<td>36.0 (10.6)</td>
</tr>
<tr>
<td>No. Affected non-target toenails (Mean/SD)</td>
<td>2.1 (1.7)</td>
<td>2.3 (1.7)</td>
<td>2.7 (1.6)</td>
</tr>
<tr>
<td>Diabetes Reported</td>
<td>4 (7.5%)</td>
<td>0 (0.0%)</td>
<td>38 (74%)</td>
</tr>
<tr>
<td>T. Pedis Reported</td>
<td>10 (18.9%)</td>
<td>4 (19.0%)</td>
<td>87 (17.0%)</td>
</tr>
</tbody>
</table>

**Efficacy Evaluation**

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. 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.

**RESULTS**

The majority of patients in the two studies had long-standing onychomycosis. Overall 74 patients (<5%) had suffered from onychomycosis for less than a year, compared with 682 patients with baseline disease duration of 1-5 years, and 770 patients who had suffered for more than 5 years (Table 1).

Patients with longer disease duration at baseline were older, predominantly male, white, and heavier (Table 1). At baseline, overall mean patient age was 49.7, 50.3, and 51.7 years, respectively. Patients were predominantly male (66.2%, 75.7%, and 82.1%, respectively), and white (63.5%, 82.3%, 83.2%). A substantial number of Asian patients were enrolled through participation of 33 Japanese sites. Most of these reported disease duration of <1 year. There was a tendency to both greater target toenail involvement and more affected non-target toenails with increased disease duration. The mean area of target toenail involvement increased from 34.4% to 37.1% with greater disease duration at baseline; the mean number of affected non-target toenails increased from 2.1 to 3.0 (individual data is shown in Table 2). More than two target toenails were affected in 39.2%, 55.0%, and 62.9% of cases, respectively, at baseline.

Co-existing diabetes or tinea pedis with onychomycosis is not uncommon. Interestingly, the incidence of co-existing tinea pedis appeared to decline with greater disease duration at baseline.
(from 18.9% to 12.1% of patients). The incidence of co-existing diabetes was lower and did not seem to be influenced by disease duration (individual data is shown in Table 2).

*Trichophyton rubrum* is the most common pathogen in onychomycosis. Interestingly in our study, the incidence of *T. rubrum* increased from 79.7% to 95.1% with increased disease duration at baseline. The incidence of *T. mentagrophytes* showed a corresponding decrease from 18.9% to 4.2%. Primary efficacy endpoints (OC)

Efinaconazole topical solution, 10% was more effective than vehicle irrespective of disease duration. It was possibly more effective with early disease and the diminishing vehicle effect might be indicative of a worsening condition of the toenails with disease duration.

At week 52, 42.6% of patients with a baseline disease duration of <1 year had a complete cure with efinaconazole compared to 16.7% on vehicle (Figure 1). In addition, 17.1% of patients with a baseline disease duration of 1-5 year had a complete cure with efinaconazole compared with 4.4% on vehicle (P<0.001, Figure 1). 16.2% of patients with baseline disease duration of >5 year had a complete cure on efinaconazole compared with 2.5% on vehicle (P<0.001, Figure 1).

At week 52, 28.3% of patients with no other toenails affected at baseline had a complete cure with efinaconazole compared to 23.7% on vehicle (Figure 2). In addition, 18.6% of patients with 1-2 non-target toenails affected at baseline had a complete cure with efinaconazole compared with 4.9% on vehicle (P<0.001, Figure 2). 16.5% of patients with more than two non-target toenails affected at baseline and had a complete cure on efinaconazole compared with 0.1% on vehicle (P<0.001, Figure 2).

Supportive and Secondary Efficacy Endpoints (OC)

At week 52, 66.0%, 59.0%, 53.8% of patients respectively achieved mycologic cure with efinaconazole compared with 27.8%, 14.7% and 14.4% on vehicle (last two P<0.001, Table 3). More patients also achieved a complete or almost complete cure with efinaconazole (48.9%, 28.3%, 24.4% respectively) compared to vehicle (22.2%, 7.4%, 5.0%), again with treatment benefits reducing with increased baseline disease duration (Table 3). At week 52, all of the patients with early disease (<1 year) who achieved mycologic cure were considered treatment successes (≤10% affected target

### Table 3.

<table>
<thead>
<tr>
<th>Secondary Endpoints at Week 52 (OC)</th>
<th>Baseline Disease Duration &lt;1 Year</th>
<th>Baseline Disease Duration 1-5 years</th>
<th>Baseline Disease Duration &gt;5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efinaconazole</td>
<td>Vehicle</td>
<td>Efinaconazole</td>
</tr>
<tr>
<td>Mycologic Cure (N/%)</td>
<td>31 (66.0%)</td>
<td>5 (27.8%)</td>
<td>252 (59.0%)</td>
</tr>
<tr>
<td>Complete/Almost Complete Cure (N/%)</td>
<td>23 (48.9%)</td>
<td>4 (22.2%)</td>
<td>120 (28.2%)</td>
</tr>
<tr>
<td>Treatment Success (N/%)</td>
<td>31 (66.0%)</td>
<td>5 (26.3%)</td>
<td>211 (48.8%)</td>
</tr>
</tbody>
</table>
toenail) irrespective of treatment (active or vehicle, Table 3).
By contrast, 83.7% of patients with a disease duration of 1-5 years and 78.5% with a disease duration >5 years, and who were mycologic cures were treatment successes at week 52, were considered treatment successes.

In patients who had no affected non-target toenails at baseline 8% of those treated with efinaconazole had 1-2 affected non-target toenails at week 52 compared to 12% of patients treated with vehicle (in one patient on vehicle the disease had spread to 4 non-target toenails). Spread of disease to other toenails was consistently greater in the vehicle group irrespective of the baseline affected non-target toenails.

DISCUSSION
The severity of onychomycosis may be associated with the length of time the individual has had the infection, so early intervention is advisable owing to the progressive nature of the fungal infection. If left untreated, toenails can become thick, causing pressure and irritation, and acting as a trigger for more severe complications.\(^1\)

It is known that the incidence of onychomycosis increases with age, and that it is more prevalent in males.\(^2\) Females tend to seek treatment earlier in the disease progression as they are more concerned about the appearance of their affected nails and report greater interference with their daily activities.\(^3\) Also in younger people appearance is of greater importance to them in establishing interpersonal relationships.\(^4\) In our study, patients with longer disease duration at baseline were older, and predominantly male. It might be expected that the majority of patients enrolling into a clinical trial would have suffered from onychomycosis for several years, however there may be cultural issues to consider as illustrated by the number of Japanese patients enrolling in our study with early onset disease.

"Co-existing diabetes or tinea pedis with onychomycosis is not uncommon."

Our data also support the view that disease severity may be associated with disease duration. Nail involvement (both the affected great toenail and other non-target toenails) was greater in those patients with longer standing disease.

The co-existence of diabetes\(^5\) or t.pedis\(^6\) in onychomycosis patients is commonplace, however it is not clear why the relative incidence of co-existing t.pedis seen in our study should decline with longer standing disease. There also appeared to be differences in the pathogenic profile and disease duration, which may have implications in treatment success, although T. rubrum remained the major pathogen.

It has been suggested that greater nail involvement could result in reduced treatment efficacy,\(^7\) however other workers have shown nail thickness, disease duration and number of non-target nails affected to be associated with a better prognosis.\(^8\) In our study, increased nail involvement correlated with longer disease duration. Overall, efinaconazole topical solution, 10% was shown to be more efficacious than vehicle irrespective of disease duration or number of nails affected. Efinaconazole was particularly effective in those patients with early-onset disease and with fewer non-target toenails affected, although total numbers of patients was smaller and this important group would warrant further study.

Mycological cure is a strong independent endpoint for evaluating topical anti-fungal agents as it signifies arrest of infection.\(^9\) It has been suggested it may be a more realistic and attainable clinical trial endpoint.\(^10,11\) It was a good predictor of treatment success in our study. Although less predictive with longer standing disease (perhaps indicative of more severe, widespread disease in these patients) approximately 80% of patients who were mycologic cures were deemed to be treatment successes.

The availability of an effective topical treatment for onychomycosis could encourage earlier treatment and prevent the progression of the disease, where it would become more difficult to treat successfully. In our study, spread of disease to other toenails was consistent greater in the vehicle group irrespective of the number of affected non-target toenails at baseline, indicative that treatment with efinaconazole may lead to less spreading of the disease. Spread of disease is an important aspect of onychomycosis treatment, very different to the cure data normally reported in clinical trials and is worthy of further study.

Treatment of onychomycosis early to avoid disease progression to other toenails is important. Once daily efinaconazole topical solution, 10% is a promising treatment in these patients.

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DISCLOSURES
Dr. Rich has served as paid consultant to Valeant Pharmaceuticals North America LLC and was a principle investigator in the pivotal trials with efinaconazole topical solution, 10%.

REFERENCES


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