

Managing Assessments and Expectations: Patient Responses Following Therapy With Efinaconazole Topical Solution, 10%

Neal Bhatia MD
Therapeutics Clinical Research, San Diego, CA

ABSTRACT

Introduction: Successful treatment of onychomycosis is both a clinical and therapeutic challenge. Effective patient education and reassurance are critical. This post hoc analysis aims to provide some guidance to physicians based on initial disease severity and influencing factors.

Methods: A post hoc analysis of two multicenter, randomized, double-blind, vehicle-controlled studies evaluating the efficacy and safety of efinaconazole topical solution, 10% in mild to moderate onychomycosis. Outcomes were assessed based on baseline severity (20%-29%, 30%-39%, 40%-49%, and ≥50% affected target toenail).

Results: Overall, the mean percent affected toenail following efinaconazole treatment decreased from 36.4% to 20.6% (a 43% reduction). The percent reduction in mean percent affected toenail (range, 43.6% to 59.8%) with efinaconazole was similar irrespective of baseline severity. Improvement was only seen in the very mildest patients with vehicle and not before week 36. Improvement was influenced by gender (females did better) and disease duration (long standing disease responding less well).

Conclusions: Our onychomycosis patients treated with efinaconazole might expect a 50% improvement in their disease within a year, and this will be seen as significant by many, especially those who have suffered for many years. Many will do better, but they will need to be reminded of the slow growth of the toenail.

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Onychomycosis remains a major clinical and therapeutic challenge for dermatologists, podiatrists, and other healthcare professionals. The disease is difficult to treat effectively and is extremely recalcitrant, but the approach has to start with confirming the diagnosis. A progressive disease that starts by affecting only one or two toenails, onychomycosis often spreads to other toenails, and carries increased risk of secondary infection.[1] In addition, with relapse or re-infection common occurrences a long-term management strategy is needed if the potential impact of the disease is going to be successfully addressed.[2-5]

It is not uncommon for patients to struggle with onychomycosis for several years; waiting until it has advanced to a more severe, sometimes debilitating stage, where increased pain and discomfort can lead to difficulty in walking or performing daily activities, before seeking treatment.[6,7] Yet many onychomycosis patients will find the prospect of long-term treatment somewhat daunting without effective patient education and ongoing reassurance. In healthy young adults, toenails grow at a rate of 1.62mm per month, therefore a new nail could take over a year to grow fully.[8] This rate of growth is often decreased in the presence of peripheral vascular disease, onychomycosis, and in the elderly and patients need to be reminded that the nail does not grow at the same pace as the skin.

While generally accepted that they may demonstrate poor compliance as a result, there are limited data within the scientific literature.[9-11] Ultimately, patients seek a normal-looking nail and even with mild onychomycosis they can experience negative social or emotional effects and reduced quality of life due to the aesthetic appearance of their affected toenails.[6,12-14] The premature perception by patients that an improvement in their condition is associated with cure impacts compliance,[9] when a physician's long-term goal is to eradicate the causative fungus and prevent relapse.

Our study is a post hoc analysis of two large multicenter studies of the treatment of mild to moderate onychomycosis with topical therapy that aims to provide insights into patient outcomes based on initial disease severity and influencing factors.

METHODS

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.[15] Patients who presented with 20%-50% clinical involvement of the target toenail were randomized (3:1) to apply blinded study drug once daily to the toenails for 48 weeks.

In this post hoc analysis, patients were categorized based on their baseline disease severity. Four groups were assessed – those with 20%-29%, 30%-39%, 40%-49%, and ≥50% affected

TABLE 1.

Subject Demographics: Percent Affected Nail at Baseline (Efinaconazole treated patients, pooled data, ITT population)				
Percent Affected Target Toenail (%, N-values)	20%-29% (N=317)	30%-39% (N=279)	40%-49% (N=354)	≥50% (N=286)
Age, y (SD)				
Mean	50.6 (11.9)	51.2 (11.0)	51.9 (11.1)	52.4 (11.4)
Median	52.0	52.0	53.0	52.0
Range	18.0-70.0	20.0-71.0	20.0-71.0	22.0-71.0
Sex				
Male	234 (73.8%)	215 (77.1%)	285 (80.5%)	219 (76.6%)
Female	83 (26.2%)	64 (22.9%)	69 (19.5%)	67 (23.4%)
Ethnicity				
Hispanic/Latino	53 (16.7%)	52 (18.7%)	51 (14.4%)	37 (12.9%)
Non-Hispanic/Latino	264 (83.3%)	226 (81.3%)	303 (85.6%)	249 (87.1%)
Race				
White	241 (76.0%)	209 (74.9%)	264 (74.6%)	233 (81.5%)
Black/African American	23 (7.3%)	18 (6.5%)	15 (4.2%)	14 (4.9%)
American Indian/Alaskan Native	1 (0.3%)	1 (0.4%)	1 (0.3%)	0 (0.0%)
Asian	47 (14.8%)	49 (17.6%)	68 (19.2%)	36 (12.6%)
Native Hawaiian/Pacific Islander	1 (0.3%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Other	4 (1.3%)	1 (0.4%)	6 (1.7%)	3 (1.0%)

target toenail. Data are presented for the pooled Intent-to-Treat (ITT) population.

RESULTS

Subject demographics are summarized in Table 1. The numbers of patients in each group assessed were comparable (range, 279-354). There were no obvious differences in terms of demographics.

Overall, the mean percent affected target toenail at baseline was comparable between efinaconazole and vehicle (36.4% and 36.7% respectively). Over the duration of the 48-week study, and 4-week follow-up the mean percent affected target toenail changed very little with vehicle (only a 1% reduction from baseline to study end). In contrast, the mean percent affected target toenail following efinaconazole treatment was 20.6% at week 52, a 43% reduction (Figure 1).

Improvement in affected target toenail with efinaconazole at week 52 was greater in females, although the trajectory for the male cohort was similar. Both genders showed significant improvement (active versus vehicle) from week 12 (P=.001 [males] and P=.034 [females] and both P<.001 from week 24). At week 52, mean percent affected target toenail was 14.4% (females) and 20.6% (males), a 60% and 44% reduction respectively, see Figure 2A. Differences were less marked with respect to age. Younger patients (<45 years old) tended to do slightly better, with a mean percent affected target toenail of 16.0% following efinaconazole treatment, compared with 20.2% in the older cohort (P=.185 [<45 years] and P<.001 [≥45 years] active versus vehicle at week 12; and both P<.001 active versus vehicle from week 24, see Figure 2B). Similar findings are observed in the assessment of patients with diabetes. Those patients where co-existing diabetes was recorded at

FIGURE 1. Mean percent affected target toenail (baseline to week 52). Comparison of efinaconazole and vehicle. Pooled ITT data.

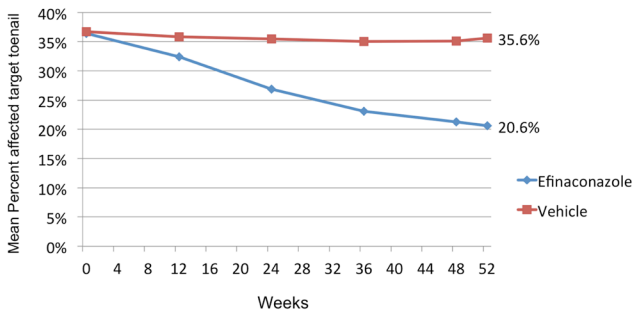


FIGURE 2. Mean percent affected toenail (baseline to week 52): influence of A: gender (females sold lines, males dashed lines); B: age (<45-year solid lines, ≥45 year dashed lines); C: co-existing diabetes (diabetes reported solid lines, no diabetes reported dashed lines); D: disease duration (1, ≥1 ≤5 years, and >5 years. Pooled ITT data (observed case).

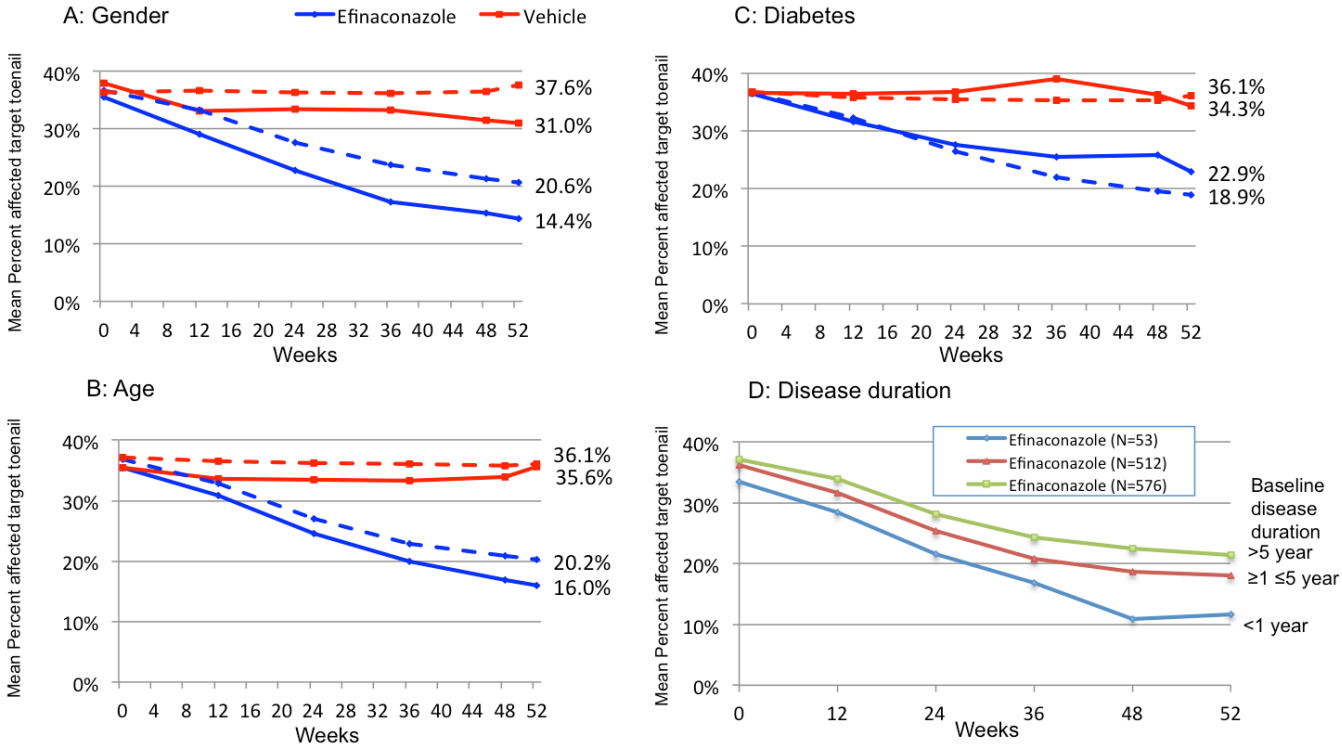
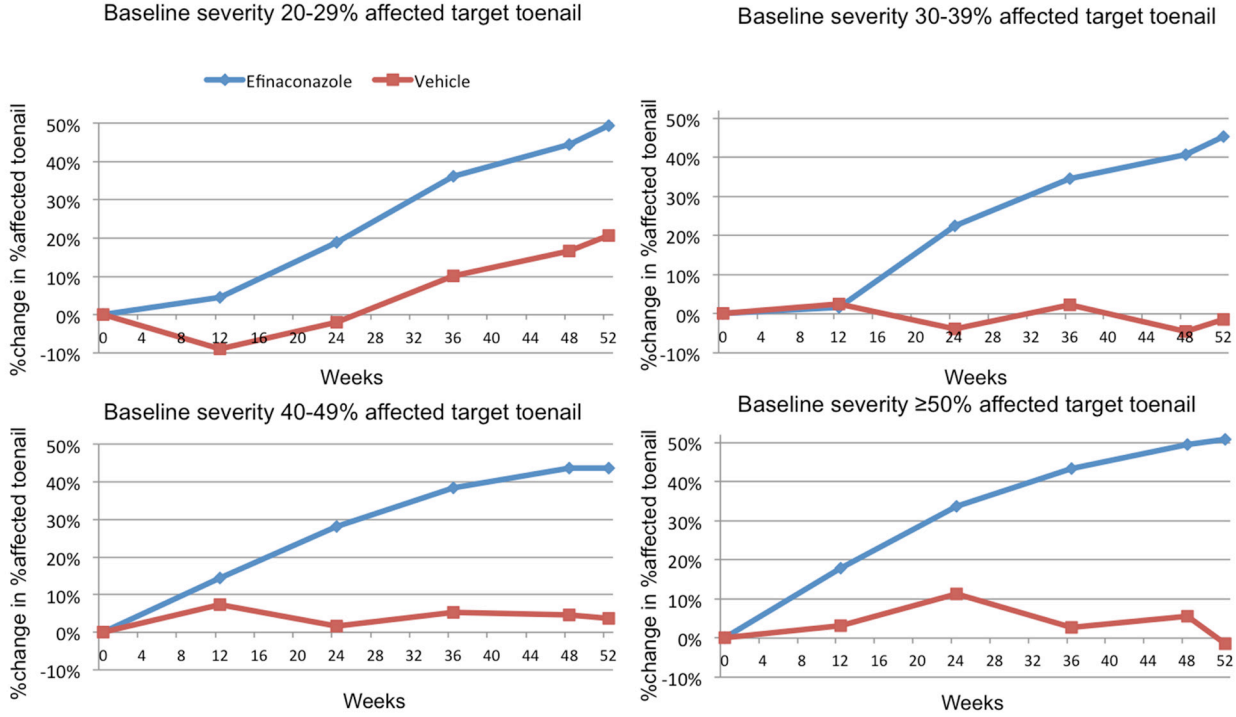


FIGURE 3. Percent change in percent affected target toenail based on baseline disease severity (baseline to week 52, pooled data, observed case).



baseline tended to do slightly better (*P*<.001 active versus vehicle from week 24 [non-diabetic population only] see Figure 2C). Disease duration seemed to have more of an impact on treatment success. Those patients with more recent onychomycosis faired better than those with long-standing disease of more than 5 years (*P*<.001 active versus vehicle of patients with disease duration one year or more, see Figure 2D). Figures 3 show the percent change in percent affected toenail from baseline to week 52 by baseline severity. The percent change in percent-affected toenail was similar following efinaconazole, irrespective of baseline severity. Percent change ranged from 43.6% to 50.8% by week 52. In contrast, with vehicle, there was no appreciable improvement with a mean target toenail involvement of 30% or greater at baseline. Only in patients with less than 30% target toenail involvement at baseline was some improvement seen with vehicle, although not apparent before week 36.

DISCUSSION

Patients suffering from onychomycosis can often face many weeks of treatment before noticeable improvement in their toenails is seen. Being able to provide patients with both reassurance and realistic expectations in the early weeks of treatment are important if we are to ensure longer-term success.

Clinical trial data can provide the dermatologists with guidance in terms of which treatments are likely to be the more successful, but efficacy outcomes based on complete cure are felt by some to be unrealistic and not so helpful in the real world.[16,17]

In this study we assessed the degree of improvement over time and aimed to identify factors that might influence the appearance of the toenail. Our study suggests that patients might expect a 50% improvement in their affected target toenail within one year irrespective of baseline severity. Clinical data suggests almost 1 in 5 patients (18.5%) will be recognized as complete cures.[18] Over the duration of the studies, treatment with efinaconazole led to a 43% mean improvement of the target toenail, which will be seen as significant by many patients. In contrast, the mean percent involvement of the target toenail treated with vehicle did not change, apart from in the group of patients with relatively mild disease (less than 30% target toenail involvement) where there was some small improvement from week 36. Mean data suggest that the degree of improvement was not influenced by baseline severity; with almost half of the affected nail growing out at the end of the study in patients treated with efinaconazole.

Improvement in the appearance of the nail did seem to be influenced by gender and disease duration, so it is likely that female patients and those with more recent disease will see improvement much quicker. The greater efficacy of efinaconazole in females has already been reported, although the reasons are less clear.[18] Male patients may be more difficult to treat, or are more likely to present with more severe disease. They may also be less compliant. It may be that their toenails just take longer to grow out and therefore require longer therapy as suggested by the trajectories in our analysis. Although the benefit seen in females by week 52 is greater, the net benefit (active minus vehicle) is similar to that seen in males.

"Being able to provide patients with both reassurance and realistic expectations in the early weeks of treatment are important if we are to ensure longer-term success."

The importance of treating early onychomycosis (when it may be less severe) has been highlighted by other workers.[19] Our analysis showed greatest benefit with efinaconazole in those patients who had suffered from onychomycosis for less than a year. Although baseline severity was similar to that of patients with long-standing disease (mean % nail involvement of 33.5% compared to 37.2%), it is recognized that patients with long-standing disease had more non-target toenails affected.[19]

So what guidance can we provide our onychomycosis patients being treated with a topical antifungal such as efinaconazole topical solution, 10%? Firstly, it is important to emphasize that it is a long-term solution, aiming to reverse a disease process that has been progressively worse for several years. While it could take many months for the diseased nail to grow out completely, improvements are likely to be noticed as early as 12 weeks, especially in females and those with more recent disease. In addition, patients must be aware of the concomitant management strategies essential to keep the disease under control. Aside from the confirmation of the diagnosis, this includes proper nail care, treatment of recurrent tinea pedis and eradication of the nail reservoir of dermatophytes, use of nail polish and potential issues with therapies, and the potential for recurrence with non-adherence to the extent of the treatment course.

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DISCLOSURES

Dr. Bhatia is a consultant and/or speaker for Actavis, Allergan, Aqua, Bayer, Dusa, Exeltis, Ferndale, Galderma, Leo, Nerium, Novartis, PharmaDerm, Promius, and Valeant.

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AUTHOR CORRESPONDENCE

Neal Bhatia MD

E-mail:..... bhatiaharbor@gmail.com