

# Evaluation of Gender as a Clinically Relevant Outcome Variable in the Treatment of Onychomycosis With Efinaconazole Topical Solution 10%

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## PRACTICE POINTS

- Men, particularly as they age, are more likely to develop onychomycosis.
- Treatment adherence may be a bigger issue among male patients.
- Onychomycosis in males may be more difficult to treat for a variety of reasons.

*Although there are limited data available on gender as an outcome variable in the treatment of onychomycosis, differences in disease prevalence and impact in males versus females have been observed. This article provides a gender subgroup analysis based on results from recent studies evaluating the efficacy, safety, and tolerability of efinaconazole topical solution 10% in the treatment of onychomycosis. Data were collected from two 52-week, prospective, multicenter, randomized, double-blind studies of patients (age range, 18–70 years) randomized to receive either efinaconazole topical solution 10% or vehicle for treatment of onychomycosis. Results from this analysis indicated that once-daily application of efinaconazole topical solution 10% may provide a useful topical option for treatment of mild to moderate toenail onychomycosis, especially in female patients.*

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Onychomycosis is the most common nail disease in adults, representing up to 50% of all nail disorders, and is nearly always associated with tinea pedis.<sup>1,2</sup> Moreover, toenail onychomycosis frequently involves several nails<sup>3</sup> and can be more challenging to treat because of the slow growth rate of nails and the difficult delivery of antifungal agents to the nail bed.<sup>3,4</sup>

The most prevalent predisposing risk factor for developing onychomycosis is advanced age, with a reported prevalence of 18.2% in patients aged 60 to 79 years compared to 0.7% in patients younger than 19 years.<sup>2</sup> Men are up to 3 times more likely to develop onychomycosis than women, though the reasons for this gender difference are less clear.<sup>2,5</sup> It has been hypothesized that occupational factors may play a role,<sup>2</sup> with increased use of occlusive footwear and more frequent nail injuries contributing to a higher incidence of onychomycosis in males.<sup>6</sup>

Differences in hormone levels associated with gender also may result in different capacities to inhibit the growth of dermatophytes.<sup>2</sup> The risk for developing onychomycosis increases with age at a similar rate in both genders.<sup>7</sup>

Although onychomycosis is more common in men, the disease has been shown to have a greater impact on quality of life (QOL) in women. Studies have shown that onychomycosis was more likely to cause embarrassment in women than in men (83% vs 71%; N=258), and women with onychomycosis felt severely embarrassed more often than

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men (44% vs 26%; N=258).<sup>8,9</sup> Additionally, one study (N=43,593) showed statistically significant differences associated with gender among onychomycosis patients who reported experiencing pain (33.7% of women vs 26.7% of men;  $P<.001$ ), discomfort in walking (43.1% vs 36.4%;  $P<.001$ ), and embarrassment (28.8% vs 25.1%;  $P<.001$ ).<sup>10</sup> Severe cases of onychomycosis even appear to have a negative impact on patients' intimate relationships, and lower self-esteem has been reported in female patients due to unsightly and contagious-looking nail plates.<sup>11,12</sup> Socks and stockings frequently may be damaged due to the constant friction from diseased nails that are sharp and dystrophic.<sup>13,14</sup> In one study, treatment satisfaction was related to improvement in nail condition; however, males tended to be more satisfied with the improvement than females. Females were significantly less satisfied than males based on QOL scores for discomfort in wearing shoes (61.5 vs 86.3;  $P=.001$ ), restrictions in shoe options (59.0 vs 82.8;  $P=.001$ ), and the need to conceal toenails (73.3 vs 89.3;  $P<.01$ ).<sup>15</sup>

Numerous studies have assessed the effectiveness of antifungal drugs in treating onychomycosis; however, there are limited data available on the impact of gender on outcome variables. Results from 2 identical 52-week, prospective, multicenter, randomized, double-blind studies of a total of 1655 participants (age range, 18–70 years) assessing the safety and efficacy of efinaconazole topical solution 10% in the treatment of onychomycosis were reported in 2013.<sup>16</sup> Here, a gender subgroup analysis for male and female participants with mild to moderate onychomycosis is presented.

## Methods

Two 52-week, prospective, multicenter, randomized, double-blind, vehicle-controlled studies were designed to evaluate the efficacy, safety, and tolerability of efinaconazole topical solution 10% versus vehicle in 1655 participants aged 18 to 70 years with mild to moderate toenail onychomycosis. Participants who presented with 20% to 50% clinical involvement of the target toenail were randomized (3:1 ratio) to once-daily application of a blinded study drug on the toenails for 48 weeks, followed by a 4-week follow-up period.<sup>16</sup>

**Efficacy Evaluation**—The primary efficacy end point was complete cure, defined as 0% clinical involvement of target toenail and mycologic cure based on negative potassium hydroxide examination and negative fungal culture at week 52.<sup>16</sup> Secondary and supportive efficacy end points included mycologic cure, treatment success (<10% clinical involvement of the target toenail), complete or almost complete cure ( $\leq 5\%$  clinical involvement and mycologic cure), and change in QOL based on a self-administered

QOL questionnaire. All secondary end points were assessed at week 52.<sup>16</sup> All items in the QOL questionnaire were transferred to a 0 to 100 scale, with higher scores indicating better functioning.<sup>17</sup>

In both studies, treatment compliance was assessed through participant diaries that detailed all drug applications as well as the weight of returned product bottles. Participants were considered non-compliant if they missed more than 14 cumulative applications of the study drug in the 28 days leading up to the visit at week 48, if they missed more than 20% of the total number of expected study drug applications during the treatment period, and/or if they missed 28 or more consecutive applications of the study drug during the total treatment period.

**Safety Evaluation**—Safety assessments included monitoring and recording adverse events (AEs) until week 52.<sup>16</sup>

## Results

The 2 studies included a total of 1275 (77.2%) male and 376 (22.8%) female participants with mild to moderate onychomycosis (intention-to-treat population). Pooled results are provided in this analysis.

At baseline, the mean area of target toenail involvement among male and female participants in the efinaconazole treatment group was 36.7% and 35.6%, respectively, compared to 36.4% and 37.9%, respectively, in the vehicle group. The mean number of affected nontarget toenails was 2.8 and 2.7 among male and female participants, respectively, in the efinaconazole group compared to 2.9 and 2.4, respectively, in the vehicle group (Table 1).

Female participants tended to be somewhat more compliant with treatment than male participants at study end. At week 52, 93.0% and 93.4% of female participants in the efinaconazole and vehicle groups, respectively, were considered compliant with treatment compared to 91.1% and 88.6% of male participants, respectively (Table 1).

**Primary Efficacy End Point (Observed Case)**—At week 52, 15.8% of male and 27.1% of female participants in the efinaconazole treatment group had a complete cure compared to 4.2% and 6.3%, respectively, of those in the vehicle group (both  $P<.001$ ). Efinaconazole topical solution 10% was significantly more effective than vehicle from week 48 ( $P<.001$  male and  $P=.004$  female).

The differences in complete cure rates reported for male (15.8%) and female (27.1%) participants treated with efinaconazole topical solution 10% were significant at week 52 ( $P=.001$ ) (Figure 1).

**Secondary and Supportive Efficacy End Points (Observed Case)**—At week 52, 53.7% of male participants and 64.8% of female participants in the efinaconazole group achieved mycologic cure

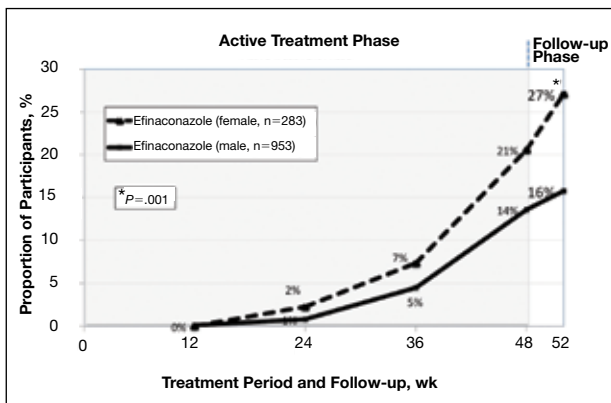
Table 1.

**Nail Involvement and Treatment Compliance by Treatment Group (Pooled Data; Intention-to-Treat Population)**

Variable	Treatment Group			
	Efinaconazole Topical Solution 10%		Vehicle	
	Male (n=953)	Female (n=283)	Male (n=322)	Female (n=93)
Nail involvement affected target toenail, %				
Mean (SD)	36.7 (10.4)	35.6 (11.0)	36.4 (10.4)	37.9 (11.0)
Median	40.0	35.0	40.0	40.0
Range	20.0–60.0	20.0–50.0	20.0–50.0	20.0–50.0
No. of affected nontarget toenails, n				
Mean (SD)	2.8 (1.6)	2.7 (1.7)	2.9 (1.6)	2.4 (1.7)
Median	3.0	3.0	3.0	2.0
Range	0.0–5.0	0.0–5.0	0.0–5.0	0.0–5.0
Compliant with treatment, n (%) <sup>a</sup>				
Yes	828 (91.1)	254 (93.0)	264 (88.6)	85 (93.4)
No	81 (8.9)	19 (7.0)	34 (11.4)	6 (6.6)
Unknown	44	10	24	2

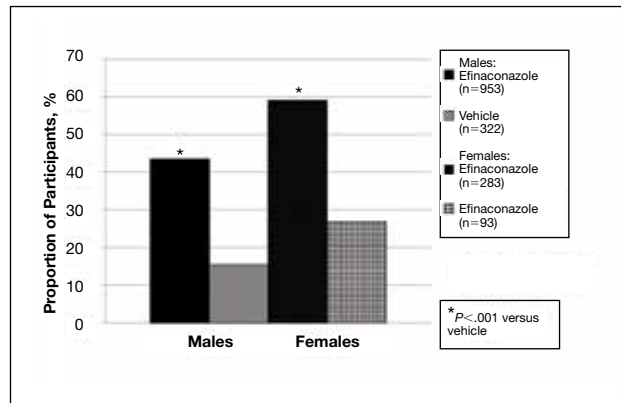
Abbreviation: SD, standard deviation.

<sup>a</sup>Participants were not dosing compliant if they missed more than 14 cumulative doses in the 28 days leading up to the week 48 visit, missed more than 20% of the total number of expected doses during the treatment period, and/or missed 28 or more consecutive doses during the treatment period. Those participants where data are unknown are excluded from the percentage calculations.



**Figure 1.** Proportion of male and female participants treated with once-daily application of efinaconazole topical solution 10% who achieved complete cure from weeks 12 to 52 (observed case; intention-to-treat population; pooled data).

compared to 14.8% and 22.5%, respectively, of those in the vehicle group (both  $P < .001$ ). Mycologic cure in the efinaconazole group versus the vehicle group became statistically significant at week 12 in male participants ( $P = .002$ ) and at week 24 in female participants ( $P < .001$ ).



**Figure 2.** Treatment success (defined as  $\leq 10\%$  clinical involvement of the target toenail) at week 52. Comparison of results with efinaconazole topical solution 10% and vehicle (observed case; intention-to-treat population; pooled data).

At week 52, more male and female participants in the efinaconazole group (24.9% and 36.8%, respectively) achieved complete or almost complete cure compared to those in the vehicle group (6.8% and 11.3%, respectively), and 43.5% and 59.1% of male and female participants, respectively, were considered

treatment successes ( $\leq 10\%$  clinical involvement of the target toenail) compared to 15.5% and 26.8%, respectively, in the vehicle group (all  $P < .001$ ) (Figure 2).

Treatment satisfaction scores were higher among female participants. At week 52, the mean QOL assessment score among female participants in the efinaconazole group was 77.2 compared to 70.3 among male participants in the same group (43.0 and 41.2, respectively, in the vehicle group). All QOL assessment scores were lower (ie, worse) in female onychomycosis participants at baseline. Improvements in all QOL scores were much greater in female participants at week 52 (Table 2).

The total number of efinaconazole applications was similar among male and female participants (315.1 vs 316.7). The mean amount of efinaconazole applied was greater in male participants (50.4 g vs 45.6 g), and overall compliance rates, though similar, were slightly higher in females compared to males (efinaconazole only) (93.0% vs 91.1%).

**Safety**—Overall, AE rates for efinaconazole were similar to those reported for vehicle (65.3% vs 59.8%).<sup>16</sup> Slightly more female participants reported 1 or more AE than males (71.3% vs 63.5%). Adverse events were generally mild (50.0% in females; 53.7% in males) or moderate (46.7% in females; 41.8% in males) in severity, were not related to the study drug (89.9% in females; 93.1% in males), and resolved without sequelae. The rate of discontinuation from AEs was low (2.8% in females; 2.5% in males).

## Comment

Efinaconazole topical solution 10% was significantly more effective than vehicle in both male and female participants with mild to moderate onychomycosis. It appears to be especially effective in female participants, with more than 27% of female participants achieving complete cure at week 52, and nearly 37% of female participants achieving complete or almost complete cure at week 52.

Mycologic cure is the only consistently defined efficacy parameter reported in toenail onychomycosis studies.<sup>18</sup> It often is considered the main treatment goal, with complete cure occurring somewhat later as the nails grow out.<sup>19</sup> Indeed, in this subgroup analysis the differences seen between the active and vehicle groups correlated well with the cure rates seen at week 52. Interestingly, significantly better mycologic cure rates ( $P = .002$ , active vs vehicle) were seen as early as week 12 in the male subgroup.

The current analysis suggests that male onychomycosis patients may be more difficult to treat, a finding noted by other investigators, though the reason is not clear.<sup>20</sup> It is known that the prevalence of onychomycosis is higher in males,<sup>2,5</sup> but data comparing cure rates by gender is lacking. It has been suggested that men more frequently undergo nail trauma and tend to seek help for more advanced disease.<sup>20</sup> Treatment compliance also may be an issue. In our study, mean nail involvement was similar among male and female participants treated with efinaconazole (36.7% and 35.6%, respectively). Treatment compliance was higher among females compared to males

Table 2.

### Onychomycosis Quality-of-Life Assessment Scores at Baseline and Week 52 (Pooled Data; Efinaconazole-Treated Participants; Intention-to-Treat Population)<sup>a</sup>

Questionnaire Item	Mean Baseline Score, n		Change From Baseline (Week 52), n	
	Male	Female	Male	Female
Symptom frequency	56.3	50.8	25.9	29.4
Symptom bothersomeness	71.6	61.9	16.7	22.4
Physical activities problems	69.9	58.2	16.4	22.0
Appearance problems	62.0	49.2	21.3	28.1
Overall problem	50.1	32.0	26.1	36.0
Stigma	72.0	64.9	8.4	12.7

<sup>a</sup>Range 0 to 100; higher scores indicate better functioning.

(93.0% vs 91.1%), with the lowest compliance rates seen in males in the vehicle group (where complete cure rates also were the lowest). The amount of study drug used was greater in males, possibly due to larger toenails, though toenail surface area was not measured. Although there is no evidence to suggest that male toenails grow quicker, as many factors can impact nail growth, they tend to be thicker. Patients with thick toenails may be less likely to achieve complete cure.<sup>20</sup> It also is possible that male toenails take longer to grow out fully, and they may require a longer treatment course. The 52-week duration of these studies may not have allowed for full regrowth of the nails, despite mycologic cure. Indeed, continued improvement in cure rates in onychomycosis patients with longer treatment courses have been noted by other investigators.<sup>21</sup>

The current analysis revealed much lower baseline QOL scores in female onychomycosis patients compared to male patients. Given that target nail involvement at baseline was similar across both groups, this finding may be indicative of greater concern about their condition among females, supporting other views that onychomycosis has a greater impact on QOL in female patients. Similar scores reported across genders at week 52 likely reflects the greater efficacy seen in females.

## Conclusion

Based on this subgroup analysis, once-daily application of efinaconazole topical solution 10% may provide a useful option in the treatment of mild to moderate onychomycosis, particularly in female patients. The greater improvement in nail condition concomitantly among females translates to higher overall treatment satisfaction.

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