

Short Research Article

Efinaconazole 10% topical solution: treatment of mild to moderate toenail onychomycosis in Japanese subjects

Running Head: Efinaconazole in Japanese Patients with Onychomycosis

ABSTRACT

Objective: To evaluate efficacy, safety, and tolerability of efinaconazole topical solution, 10% in a cohort of Japanese patients with mild to moderate toenail onychomycosis.

Methods: A subgroup analysis of patients, aged 22-70 years, randomized to receive efinaconazole topical solution, 10% or vehicle from a multicenter, double-blind, vehicle-controlled 48-week study evaluating safety and efficacy. 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: The primary end point, complete cure, was achieved in 30.6% of patients treated with efinaconazole compared to 12.3% with vehicle (Observed case, $P=.006$), and was significantly better than that seen in the non-Japanese patients ($P<.001$). Treatment success (percent affected target toenail $\leq 10\%$ at week 52) for efinaconazole was 60.6% compared to 33.3% with vehicle ($P<.001$). The majority of adverse events (AEs) were mild (16.6%) or moderate (81.1%) and few (7.8%) associated with efinaconazole. Eleven patients (6.0%) treated with efinaconazole discontinued the study due to AEs.

Conclusions: Once daily efinaconazole topical solution, 10% may provide a useful topical option in the treatment of mild to moderate onychomycosis among ethnic Japanese patients.

Introduction

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*.^{1,2} Epidemiology data indicate a prevalence of 13.8% in the US,³ with a number of factors contributing to an increasing incidence.

Epidemiology studies on onychomycosis and tinea pedis have been performed across Europe and East Asia. The prevalence of onychomycosis has been estimated as more than 10% in Japan, although direct, reliable epidemiological data are lacking.⁴ A randomized survey of outpatients who visited a dermatologist for reasons other than superficial fungal infection reported 18.6% of the study population diagnosed with onychomycosis or tinea pedis in 2000, increasing to 24.1% by 2006; almost two thirds (63.2%) used topical medication only.⁵ An earlier epidemiological survey of dermatomycoses reported an increase of onychomycosis in the Summer, with a greater prevalence among the aged population and in males.⁶ An epidemiological investigation of workers in a dairy product company in Kanagawa, central Japan, estimated an overall prevalence of tinea pedis and onychomycosis of 18%.⁷

It is estimated that about 1.5million Japanese live in the US, especially in Hawaii and California. Clinical data on the treatment of onychomycosis in this population is lacking. 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.^{8,9} We provide a post hoc analysis of the Japanese patients in the first of these studies, and compare safety and efficacy data to the non-Japanese population studied in precisely the same manner.

Materials and Methods

Multicenter, randomized, double-blind, vehicle-controlled studies were designed to evaluate the efficacy, safety, and tolerability of efinaconazole topical solution, 10% relative to its vehicle in 870 male and female patients (aged 18 to 70 years) with mild-to-moderate toenail onychomycosis.⁸

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.

Efficacy evaluation

The primary efficacy 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 included mycologic cure and treatment success (<10% clinical involvement of the target toenail). All secondary end points

71 were assessed at week 52.

72 *Safety evaluation*

73 Safety assessments included monitoring and recording of adverse events (AEs)
74 throughout the study, until week 52.

75 **Results**

76 The study included 157 (64.6%) male and 86 (35.4%) female patients with mild-to-
77 moderate onychomycosis from Japan (**Table 1**, intent-to-treat [ITT] subjects). By
78 comparison, 490 (78.1%) male and 137 (21.9%) female patients were enrolled from
79 the US and Canadian study centers (ITT subjects).

80 At baseline, the mean area of target toenail involvement of those Japanese patients
81 subsequently treated with efinaconazole topical solution, 10% was 35.6% compared
82 to 38.1% respectively with vehicle, and 36.7% in the total study population. The
83 mean number of affected non-target toenails was 2.4 for both treatment groups
84 (**Table 2**), compared with 2.8 in the total study population.

85 The majority (81.1%) of patients had at least one non-target toenail affected in
86 addition. Diabetes was reported in 7.0% of patients, and co-existing tinea pedis in
87 72.8% of patients (**Table 2**).

88 *Primary efficacy endpoint (Observed Case [OC])*

89 At week 52, 52 (30.6%) of onychomycosis patients were complete cures with
90 efinaconazole compared with 7 (12.3%) on vehicle ($P=.006$). Efficacy rates with
91 efinaconazole were almost two-fold greater than those seen in the non-ethnic

Japanese patients from US and Canada (15.7%, $P<.001$), where no patients achieved a complete cure with vehicle, see **Figure 1**.

Supportive and secondary efficacy endpoints (OC)

At week 52, 55.6% ($N=95$) Japanese onychomycosis patients achieved mycologic cure on efinaconazole compared with 31.6% ($N=18$) on vehicle ($P=.002$). Mycologic cure became significant versus vehicle as early as week 24, see **Figure 2**.

Also, more patients achieved a complete or almost complete cure on efinaconazole (38.2%, $N=65$) compared to vehicle (19.3%, $N=11$) at week 52 ($P=.007$); and 60.6% ($N=103$) were considered treatment successes at week 52 ($\leq 10\%$ affected target toenail) compared to 33.3% ($N=19$) on vehicle ($P<.001$), see **Figure 2**. By comparison, 49.3% and 18.7% of patients from the total study population achieved treatment success with efinaconazole and vehicle respectively.

Safety

Overall, efinaconazole AE rates in the Japanese population were similar to those reported with vehicle (67.4% vs 71.2%). Adverse events were generally mild (16.6% with efinaconazole and 12.5% with vehicle) or moderate (81.1% and 87.5% respectively) in severity, not related to study medication (92.2% and 100% respectively) and resolved without sequelae. Eleven (6.0%) of subjects discontinued as a result of AEs following efinaconazole treatment (compared with zero treated with vehicle), see **Table 3**. By comparison 10 (1.1%) and 1 (0.3%) patient from the US and Canadian cohorts discontinued due to AEs.

113 Discussion

114 The incidence of onychomycosis appears to be relatively high in Japanese patients,
115 and they form an important cohort in certain geographic regions of the US. In Japan,
116 the traditional practice of walking barefoot in the house, which facilitates the spread
117 of the infection to family members, is likely the primary reason for the especially
118 high prevalence and intensity of toenail fungal disease.

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120 In our post hoc analysis of a phase 3 study on efinaconazole topical solution, 10%,
121 efficacy appears to be much greater than in those onychomycosis patients from US
122 or Canada study centers. There was a higher proportion of female patients in the
123 Japanese cohort which may have impacted these data, although disease severity
124 (based on affected target toenail) was similar to that reported in the overall study.⁸
125 Efficacy results in female patients treated with efinaconazole have previously been
126 reported to be higher than in male patients.¹⁰

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128 The number of Japanese patients with co-existing tinea pedis was unusually high
129 compared to the overall pooled data from the two pivotal studies (72.8% versus
130 19.0%). Many of these patients had their co-existing tinea pedis treated
131 concomitantly, and this may also have impacted on the better efficacy results seen.

132

133 The number of AEs reported, and their severity appeared higher than in the overall
134 patient population, however very few AEs were related to study medication, and the
135 level of discontinuation (6.0%) was still relatively low. The most common AE was
136 dermatitis at the site of drug application. Although there are differences in reporting

of AEs in several countries,¹¹ it is not known whether this factor may have influenced the findings.

There are a number of limitations with our study. Firstly, a study period of 52 weeks may be too brief to evaluate a clinical cure in onychomycosis. It is not known whether continued improvement would occur with either longer treatment courses or longer follow-up. Also, this was a post hoc analysis and the pivotal studies were not set up specifically to study Japanese patients with onychomycosis, where demographics and study disposition may not be representative of the general Japanese population, or any cultural or social differences seen in those Japanese living in the US or Canada.

Our analysis shows that once daily efinaconazole topical solution, 10% may provide an especially useful topical option in the treatment of mild-to-moderate onychomycosis in Japanese patients.

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184 **Table 1: Subject Demographics (Japanese sites Intent-To-Treat [ITT] population)**

	Efinaconazole (N=184)	Vehicle (N=59)
Age, y (SD)		
Mean	56.0 (9.9)	56.6 (9.0)
Median	58.0	58.0
Range	22.0-70.0	27.0-70.0
Sex		
Male	121 (65.8%)	36 (61.0%)
Female	63 (34.2%)	23 (39.0%)

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187 **Table 2: Subject Baseline Characteristics (Japanese sites ITT population)**

	Efinaconazole (N=184)	Vehicle (N=59)
Percent involvement of affected toenail (%)		
Mean (SD)	35.6 (10.1)	38.1 (10.5)
Median	40.0	40.0
Range	20-50.0	20.0-50.0
Number of affected non- target toenails		
Mean (SD)	2.4 (1.8)	2.4 (1.7)
Median	2.0	2.0
Range	0.0-5.0	0.0-5.0
Diabetes Reported	12 (6.5%)	5 (8.5%)
Tinea Pedis Reported	130 (70.7%)	47 (79.7%)
Disease Duration (1 year or more)	80 (43.5%)	24 (40.7%)

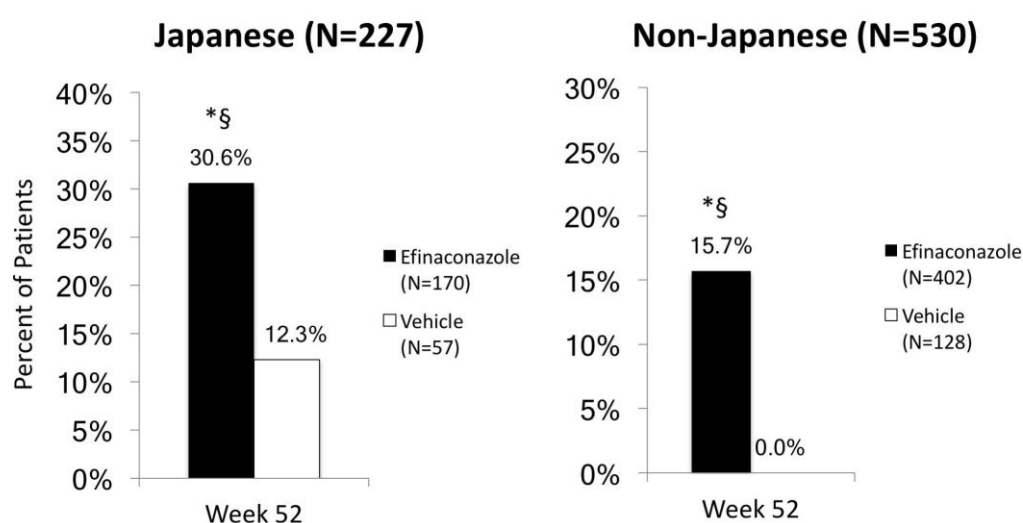
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190 **Table 3: Table 3: Summary of Treatment-Emergent Adverse Events (AEs)**
 191 **(Safety Subjects Japanese Sites)**

	Efinaconazole	Vehicle
Number of Subjects	184	59
Subjects with ≥ 1 AE	124 (67.4%)	42 (71.2%)
Subjects who discontinued study due to AE	11 (6.0%)	0 (0.0%)
AE Severity		
Mild	16.6%	12.5%
Moderate	81.1%	87.5%
Severe	2.4%	0.0%
Relationship of AE to Study Drug		
Not related	92.2%	100.0%
Related	7.8%	0.0%

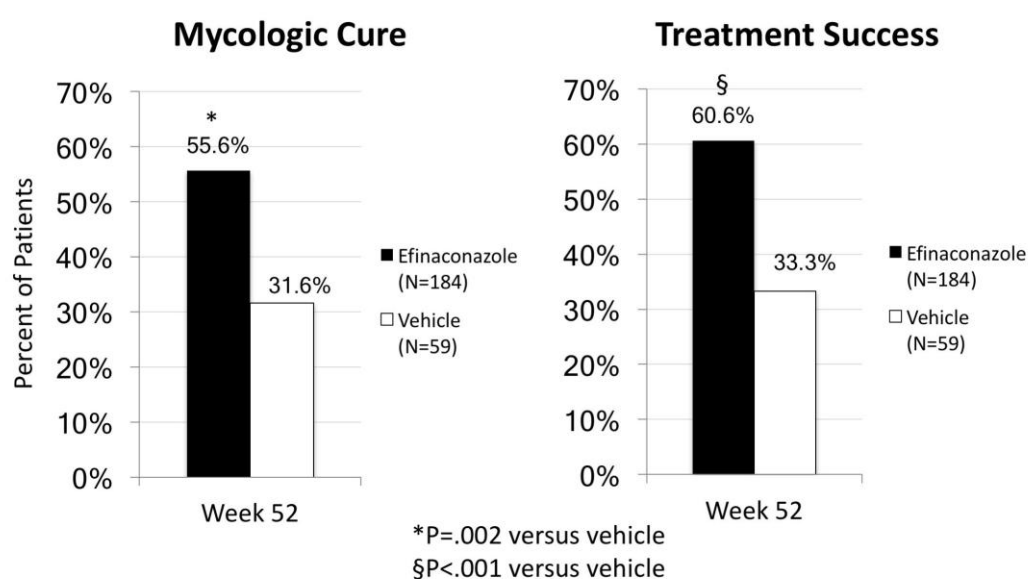
Figure 1



*P=.006 versus vehicle
 §P<.001 between the two efinaconazole groups

194 **Figure 1: Primary Efficacy Endpoint Complete Cure Week 52 (Observed Data):**
 195 **JAPANESE (N=227) and NON-JAPANESE SUBPOPULATIONS (N=530). N-values at**
 196 **Week 52**

Figure 2



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198 **Figure 2: Secondary Efficacy Endpoint Mycologic Cure and Treatment Success Week**
 199 **52 (Observed Case): JAPANESE SUBPOPULATIONS (N=243 at baseline)**

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