Efficacy and Safety Study of Tazarotene Cream 0.1% for the Treatment of Brittle Nail Syndrome

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Brittle nail syndrome refers to nails that exhibit surface roughness, raggedness, and peeling. It is a common problem, with a higher prevalence among elderly patients. The goal of this study was to determine if tazarotene cream 0.1% ameliorates the signs and symptoms of brittle nails. In this open-label, single-center trial, participants applied tazarotene cream to the nails twice daily for 24 weeks. Signs and symptoms were rated by the investigators and by the participants during treatment and 12 weeks after discontinuation. Twenty participants were enrolled in the study; 1 participant withdrew prior to the 4-week follow-up visit. Of the 18 participants available for analysis (1 participant was excluded because baseline photographs were not available) for the primary end point of improvement in the physician global improvement assessment (PGIA), all 18 participants achieved improvement of the target nails at week 12 as well as 16 participants (88.9%) at week 24. All 18 participants had improvement in the PGIA score 12 weeks posttreatment at week 36. The physician global assessment (PGA) improved for 14 of 19 participants (73.7%) at both weeks 12 and 24; at week 24, 4 of 19 participants had achieved a PGA score of none. At week 36, 17 of 19 participants (89.5%) agreed that their nails had improved overall. Only 1 participant (5.3%) reported mild local irritation. This study demonstrated that tazarotene improves some of the changes noted in conjunction with brittle nail syndrome with minimal to no irritation.

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Brittle nail syndrome refers to nails that exhibit surface roughness, raggedness (fraying of the distal edge), and peeling (lamellar onychoschizia).[1] It is a common problem, affecting approximately 20% of women and fewer men, with a higher prevalence among elderly patients.[2] A number of factors have been proposed as possible causes of nail brittleness, such as anemia, biotin deficiency, or cysteine deficiency.[3,4] However, most authors believe that brittle nails usually are caused by dehydration of the nail plate, either from repetitive cycles of hydration and dehydration related to hand washing or from exposure to dehydrating chemicals, such as those found in nail enamel and cuticle removers.[5,6] However, Stern et al[7,8] found that there was no statistically significant difference in percentage of water content in nails from 102 patients with brittle or normal nails. Characteristic features of brittle nails, as demonstrated by electron microscopy, have been reproduced in clippings taken from normal nails by repetitive exposure to alternate periods of wetting and drying.[9] Treatment of brittle nails involves restoration and

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maintenance of a normal degree of nail plate hydration by minimizing exposure to dehydrating chemicals and using moisturizers, such as α-hydroxy acids.[5,10]

Retinoids are vitamin A analogues that play a role in keratinocyte differentiation and proliferation. Tazarotene is a receptor-selective synthetic retinoid that normalizes epidermal differentiation and reduces the influx of inflammatory cells into the skin. Its topical delivery targets the skin where these processes occur.

We report a pilot study that evaluated the effect of tazarotene cream 0.1% (applied twice daily for 24 weeks) on the signs and symptoms of brittle nails.

Materials and Methods

Participants—This study was an open-label, single-center, investigator-initiated trial. Institutional review board approval was obtained prior to participant enrollment. All participants were aged 55 to 76 years and at screening had evidence of at least 2 of the following signs of brittle nails in each of the selected nail plates: surface roughness, raggedness (fraying of the distal edge), and peeling (lamellar onychoschizia). Onychomycosis was an exclusion criterion; therefore, prior to enrollment in the study, each participant was required to test negative for fungal infection by direct microscopy with potassium hydroxide. No other topical nail products were permitted in the 2 weeks prior to enrollment or during the study itself. Participants were specifically asked not to alter their baseline habits regarding use of emollients for the skin or frequency of hand washing.

Treatment Regimen—All participants applied tazarotene cream 0.1% twice daily to all affected fingernails for 24 weeks, followed by a 12-week observation period off therapy.

End Points—The primary end point was the physician global improvement assessment (PGIA) of the 2 target nails (selected as the 2 fingernails that had the most severe changes) at weeks 12 and 24. The PGIA also was documented for week 36. To generate the PGIA, 2 investigators (N.S.S. and J.M.M-W.) independently and separately compared photographs of each participant's target nails taken at baseline to those taken at weeks 12, 24, and 36. The results were then averaged. Secondary outcomes included the physician global assessment (PGA)—the physician's rating of each participant's brittle nail symptoms at baseline and weeks 12 and 24—as well as separate ratings at each visit of the surface roughness, raggedness, and peeling of the target nails. Transonychial water loss (TOWL) was measured twice at each visit using the *Vapo*Meter. Participants also were asked to provide their assessments of nail breakage at each visit and were asked about their overall satisfaction with treatment, whether they would recommend the treatment to a friend, and whether they experienced any irritation from use of the product.

Safety—Adverse events were evaluated at each visit.

Statistical Analysis—Only data from participants who completed the study were included in the data analysis. All statistical analyses were generated using SAS version 8 and presented as tables and graphs using Microsoft® Excel, with the exception of the TOWL analysis, which was done in R 2.2.1.

Results

Participants—Twenty participants were enrolled in the study, but 1 participant withdrew prior to the 4-week follow-up visit because of the time and travel commitment required to complete the study. Eighteen women and 1 man with brittle nails completed the study. Participants ranged in age from 55 to 76 years, with a mean age (standard deviation) of 65.7 (6.67) years.

Primary End Point—One participant was excluded from the analysis of the primary end point (PGIA) because baseline photographs were not available. A representative set of photographs documenting a participant's nail at baseline as well as weeks 12, 24, and 36 is shown in Figure 1. Improvement in PGIA was defined as a rating of excellent, good, or fair. Participants also could be given PGIA ratings of no improvement or worse.

All 18 participants analyzed (100%; 95% confidence interval [CI], 81.47%-100%) achieved the primary end point of improvement as measured by the PGIA of the target nails at week 12 (Table 1). At week 24, 16 participants (88.9%; 95% CI, 65.29%-98.62%) had improved as measured by the PGIA, while 2 participants (11.1%) demonstrated no improvement. At week 36, representing follow-up 12 weeks posttreatment, all 18 participants (100%; 95% CI, 81.47%-100%) again showed improvement in the PGIA score.

Secondary Outcomes—The PGA score improved for 14 of 19 participants (73.7%) at both weeks 12 and 24 (Table 2). By week 12 onward, none of the participants had a PGA score of moderate/severe, and at week 24, 4 participants had achieved a PGA score of none. Two participants at week 12 and 1 participant at week 24 had worsening of the PGA score, but in each case, it was a matter of only one decrement (mild to mild/moderate, 1 participant [week 12]; mild/moderate to moderate, 2 participants [1 each at week 12 and week 24]), which may not be clinically significant.

Surface roughness, raggedness, and peeling were assessed for the 2 target nails of all 19 participants. Roughness improved less than raggedness or peeling

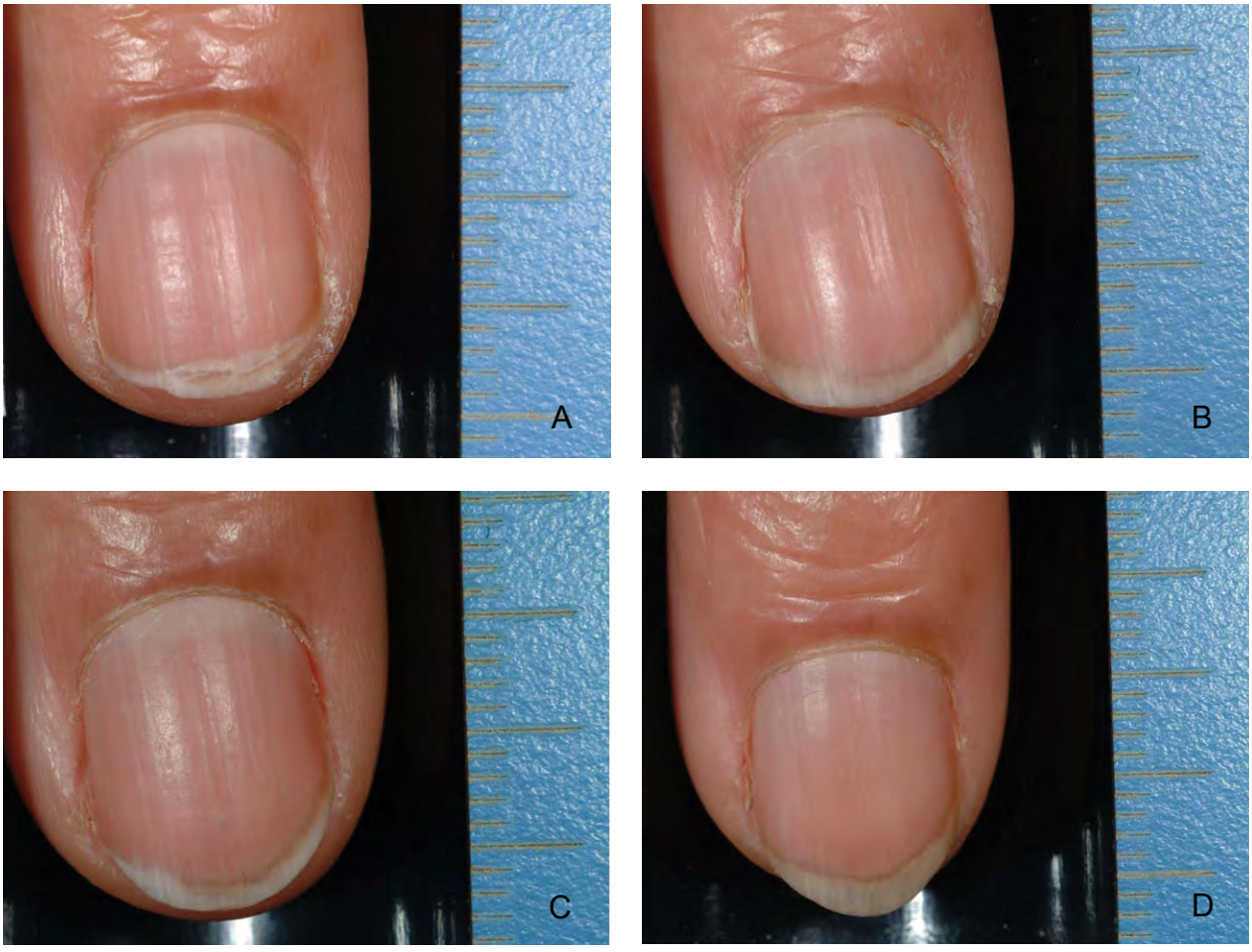

Figure 1. Target 2 of a participant with brittle nail syndrome at baseline (A), as well as 12 weeks (B), 24 weeks (C), and 36 weeks (D) following treatment with tazarotene cream 0.1%.

Table 1.

PGIA Score of Target Nails[a]

	Participants, n (%)		
PGIA Score	**Week 12**	**Week 24**	**Week 36**
Excellent	9 (50)	7 (38.9)	7 (38.9)
Good	5 (27.8)	6 (33.3)	7 (38.9)
Fair	4 (22.2)	3 (16.7)	4 (22.2)
No improvement	0 (0)	2 (11.1)	0 (0)
Worse	0 (0)	0 (0)	0 (0)

Abbreviation: PGIA, physician global improvement assessment.
[a]Eighteen participants were analyzed for PGIA.

Table 2.

PGA Score

	Week 12, n						
Baseline	**None**	**Mild**	**Mild/ Moderate**	**Moderate**	**Moderate/ Severe**	**Severe**	**Total**
None	0	0	0	0	0	0	0
Mild	0	2	1	0	0	0	3
Mild/Moderate	0	5	1	1	0	0	7
Moderate	0	3	1	0	0	0	4
Moderate/Severe	0	4	1	0	0	0	5
Severe	0	0	0	0	0	0	0
Total	0	14	4	1	0	0	19
	Week 24, n						
Baseline	**None**	**Mild**	**Mild/ Moderate**	**Moderate**	**Moderate/ Severe**	**Severe**	**Total**
None	0	0	0	0	0	0	0
Mild	1	2	0	0	0	0	3
Mild/Moderate	2	3	1	1	0	0	7
Moderate	1	2	0	1	0	0	4
Moderate/Severe	0	2	3	0	0	0	5
Severe	0	0	0	0	0	0	0
Total	4	9	4	2	0	0	19

Abbreviation: PGA, physician global assessment.

(Tables 3–5), possibly because it is also age related and possibly not specific to brittle nails.

The majority of participants reported that the use of tazarotene improved the condition of their nails. At the final study visit at week 36, 17 of 19 participants (89.5%) agreed that their nails had improved overall (Figure 2). Participants also assessed their nail breakage specifically. At the conclusion of the treatment period (24 weeks), all 7 participants who reported severe breakage at baseline

Table 3.

Surface Roughness

	None	Mild	Moderate	Severe
None at baseline (n=9)				
Week 12	8	1	0	0
Week 24	7	2	0	0
Week 36	8	1	0	0
Mild at baseline (n=16)				
Week 12	5	9	2	0
Week 24	8	8	0	0
Week 36	7	7	2	0
Moderate at baseline (n=10)				
Week 12	1	7	1	1
Week 24	1	2	7	0
Week 36	2	4	3	1
Severe at baseline (n=3)				
Week 12	0	0	1	2
Week 24	0	0	1	2
Week 36	0	0	0	3

had improved, and this improvement continued through follow-up at week 36 (data not shown).

Overall, when the study concluded at week 36, 15 of 19 participants (78.9%) agreed that they were satisfied with the performance of the product (Figure 3), and 15 participants (78.9%) agreed that they would recommend the product to others (data not shown).

Twice-daily application of tazarotene to the nails might raise concern about irritation of the surrounding skin. However, after twice-daily application of tazarotene for 24 weeks, only 1 participant (5.3%) somewhat agreed that the tazarotene caused irritation, whereas the other 18 participants (94.7%) disagreed. Only 1 participant (5.3%) reported mild local irritation.

The TOWL measurements of the target nails were taken twice at each visit (1 minute apart). Summary statistics of these measurements demonstrated that this evaluation did not produce consistent results.

Table 4.

Raggedness

	None	Mild	Moderate	Severe
None at baseline (n=4)				
Week 12	1	3	0	0
Week 24	3	1	0	0
Week 36	3	1	0	0
Mild at baseline (n=14)				
Week 12	7	7	0	0
Week 24	12	1	1	0
Week 36	11	3	0	0
Moderate at baseline (n=12)				
Week 12	6	5	1	0
Week 24	6	6	0	0
Week 36	9	2	1	0
Severe at baseline (n=8)				
Week 12	4	4	0	0
Week 24	4	3	0	1
Week 36	7	1	0	0

With consistent results, the absolute difference between sequential measurements should be close to 0. However, the median absolute difference was 11.1 (interquartile range, 16.7), and 25% of absolute differences were between 21.8 and 119.5. The difficulty of uniformly apposing the *Vapo*Meter to the convex surface of the nail plate may be to blame rather than the inherent accuracy of the device. Without consistency, further analysis of the TOWL data was not performed.

Safety—There were no adverse events related to the tazarotene application.

Comment

Topical tazarotene resulted in improvement in the primary end point—PGIA of the target nails—in all 18 participants who were able to complete the trial at 12 weeks and in 16 of 18 (88.9%) participants at 24 weeks. Although roughness improved less than raggedness and peeling when assessed independently,

Table 5.

Peeling

	None	Mild	Moderate	Severe
None at baseline (n=5)				
Week 12	5	0	0	0
Week 24	4	1	0	0
Week 36	5	0	0	0
Mild at baseline (n=18)				
Week 12	15	3	0	0
Week 24	12	6	0	0
Week 36	12	6	0	0
Moderate at baseline (n=11)				
Week 12	8	3	0	0
Week 24	7	4	0	0
Week 36	8	1	2	0
Severe at baseline (n=4)				
Week 12	1	3	0	0
Week 24	1	2	1	0
Week 36	2	2	0	0

4 participants achieved a PGA score of none at week 24 and all 5 of the participants with the worst PGA score at baseline (moderate/severe) improved by week 12.

The small sample size and open-label design of the study need to be emphasized, as these results should be viewed as descriptive. In addition, there was no highly quantitative assessment of outcomes, as the participants' self-assessments, PGIA, and PGA were subjective measurements. The noticeable improvement in PGIA seen in all 18 participants at week 12 could be attributed in part to the emollient effect of the vehicle used in tazarotene cream. However, a physiologic effect from tazarotene could reasonably be seen at 12 weeks.[11]

With many different measurements taken at each visit, perhaps the most telling result is the participant satisfaction reported at week 36 in which 15 of 19 participants (78.9%) agreed that they were satisfied with the product. Of note, many participants reported having lost their allocations of medication, failing to return the study medication

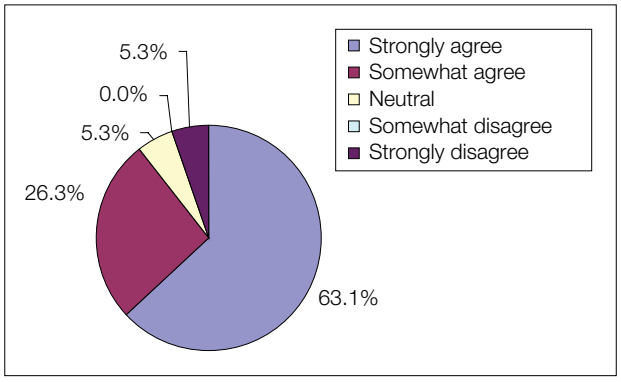

Figure 2. Participants' assessment of improvement at 36 weeks (N=19).

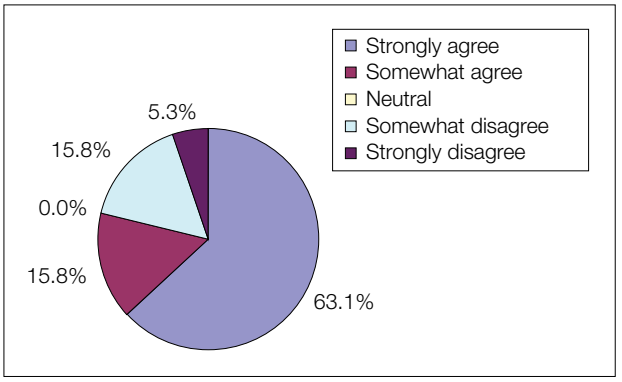

Figure 3. Participant satisfaction at 36 weeks (N=19).

at the end of the treatment period. Participants also frequently requested prescribing information so that they could obtain more tazarotene from their own physicians. Although the investigators emphasized that the protocol prohibited the use of tazarotene between weeks 24 and 36, it was our suspicion that some participants may have continued to use the medication during this period because of their satisfaction with its performance.

Conclusion

Although the limitations of this study include small sample size and lack of vehicle control because of restrictive financing, participants considered tazarotene to have improved their nails' brittleness without irritation. The PGIA and PGA scores indicate that most participants' nails did improve by physician assessment.

In this study, tazarotene appears to have a beneficial effect on brittle nails. However, larger, placebo-controlled studies will be needed to confirm these observations.

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