Long-term Efficacy and Safety of Topical PRK 124 (0.125%) Lotion (Pyratine-XR) in the Treatment of Mild-to-Moderate Rosacea

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ABSTRACT

Background: Many patients with rosacea cannot tolerate extended treatment periods with topical agents because their skin sensitivity is often increased.
Objective: To determine the long-term efficacy and tolerability of a new moisturizing lotion for improving the signs and symptoms of mild-to-moderate rosacea.
Methods: In a 48-week, open-label study, a moisturizing lotion containing furfuryl tetrahydropyranyladenine as PRK-124 (0.125%, Pyratine-XR™, Senetek PLC, Napa, CA) was applied twice daily by 18 subjects with mild-to-moderate rosacea. Clinical improvements were assessed by the treating physician. Skin barrier function was measured by transepidermal water loss after treatment. Tolerability and cosmetic outcome were evaluated by subjects.
Results: Subjects experienced a mean 44 percent reduction in erythema severity and a mean 89 percent reduction in inflammatory lesion count at week 48. Reductions were significant ($P \leq 0.05$) in both erythema and lesions at weeks 24, 36 and 48. Statistically significant ($P \leq 0.05$) improvements in telangiectasias, transepidermal water loss and dryness were noted. Overall clinical improvement was observed in 81 percent of subjects and the investigator's global assessment steadily improved throughout the study. Treatments were well-tolerated and cosmetically acceptable. Treatment-induced skin irritation was not observed.
Conclusion: The new moisturizing lotion containing furfuryl tetrahydropyranyladenine as PRK 124 is efficacious, does not irritate skin, and is well tolerated for at least 48 weeks.

INTRODUCTION

Rosacea is a common chronic skin disorder with varied clinical manifestations and a pathophysiology that is not completely understood.[1] The condition appears to be related to an inflammatory process, as well as vascular hyperactivity. It has been postulated that there is a breakdown in the skin-barrier function in which irritants invade the epidermis, causing vasodilatation, flushing and inflammation.[2]

Current therapies include topical agents (metronidazole, azelaic acid, tretinoin, clindamycin, erythromycin, sulfacetamide/sulfur) alone or in combination with systemic antibiotics (tetracycline family, erythromycin), light-based therapy (pulsed dye laser, intense pulsed light), or both.[3,4] The persistent nature of rosacea often leads to extended treatment periods with topical agents which many patients cannot tolerate due to the high skin sensitivity associated with this disorder. The result is an unsatisfactory treatment outcome. Treatments that provide sustained relief without side effects are needed.

Furfuryl tetrahydropyranyladenine (PRK 124) is a plant cytokinin shown to have growth modulatory, antioxidative and antisenescent effects on human skin cells.[5] A previous clinical study shows that fine wrinkles, skin roughness and mottled hyperpigmentation were improved in photodamaged facial skin after 12 weeks of treatment with PRK 124.[6]

Initially, the current study was designed to be carried out for 12 weeks. PRK 124 used twice daily was shown to reduce the signs and symptoms of mild-to-moderate rosacea.[7] The treatment regimen also decreased skin transepidermal water loss (TEWL) and increased skin moisture content[6,7] with no evidence of skin irritation.

The purpose of this study was to extend the treatment period to 48 weeks to assess the long-term efficacy and tolerability of PRK 124 (0.125%) for improving the clinical signs and symptoms of mild to moderate rosacea.

MATERIALS AND METHODS

Subjects

Healthy subjects (n=18, 13 females) aged 28–70 years (mean 53) with mild-to-moderate erythematotelangiectatic rosacea, papulopustular rosacea, or both participated in this single-center, open-label, 48-week study. Subjects who were previously enrolled in the 12 week (n=24) study were given the opportunity to continue treatment for another 36 weeks. Inclusion criteria included normal laboratory values and a negative pregnancy test for female subjects. Exclusion criteria did not change from

the 12-week study.[7] After 12 weeks, subjects were re-consented to continue in the study for 48 weeks. Assessments from the first 12 weeks were continued. The protocol was approved by the authors' institutional review board and was conducted in accordance with good clinical practices.

Treatment

Each subject was instructed to (1) wash his or her face with a mild cleanser, (2) apply PRK-124 lotion to the entire face twice daily (morning and evening) and (3) apply sunscreen (SPF 30) to the face every morning during the study period. They were also instructed to avoid non-approved lotions, moisturizers, cleansers or any medications on the facial area during the treatment period. Efficacy and adverse effects were evaluated at weeks 12, 24, 36 and 48. Subjects were told not to apply the study lotion or makeup on the days of evaluation. At each assessment visit the investigator manually counted papules and pustules and the entire face was photographed with a stereotactic facial device (Canfield Scientific, Fairfield, NJ).

Evaluation of Results

Results were evaluated on the basis of the changes in signs and symptoms of rosacea, overall clinical improvement, improvement of investigator's global assessment, skin tolerance to study lotion and objective measurements of TEWL relative to baseline. Signs and symptoms (burning/stinging, erythema/telangiectasia, papules/pustules) were graded by the investigator on a scale of 0–3 (0=none, 3=severe). The investigator graded overall clinical improvement with a scale of 1–6 (1=excellent improvement; 2=marked improvement (~75%), 3=moderate improvement (~50%), 4=slight improvement (~25%), 5=no improvement (0%), 6=worse); grades were assigned by comparing pre- and post-treatment photographs of the treated areas. A scale of 0–6 (0=clear, 1=minimal, 2=mild, 3=mild/moderate, 4=moderate, 5=moderate/severe, 6=severe) was used for the investigator global assessment. Skin tolerance (burning, stinging, dryness) was graded by subjects on a scale of 1–4. In the absence of sweat, TEWL is a measurement of water vapor loss through the stratum corneum and serves as an indicator of skin barrier function.[6] In the present study, TEWL was measured with an evaporimeter (Dermalab, Inc., Highland Park, IL) on the right and left cheeks. All assessments and measurements were done at baseline and at 12, 24, 36 and 48 weeks.

Results from the study were evaluated using descriptive and inferential statistics. The significance of changes in multinomial variables (e.g., stinging, burning, dryness) was determined with the non-parametric Wilcoxon signed rank test because grades were assigned according to scales, throughout which linearity was not assumed (e.g., the change from 1 to 2 is not necessarily the same as the change from 2 to 3). Probability values less than 0.05 ($P<0.05$) were considered significant. Since TEWL is a continuous variable, differences relative to baseline were

FIGURE 1. Physician's assessment of the mean percent improvement in lesions (papules and pustules), erythema and telangiectasia over the 48-week study. (The x-axis scale changes after week 12.)

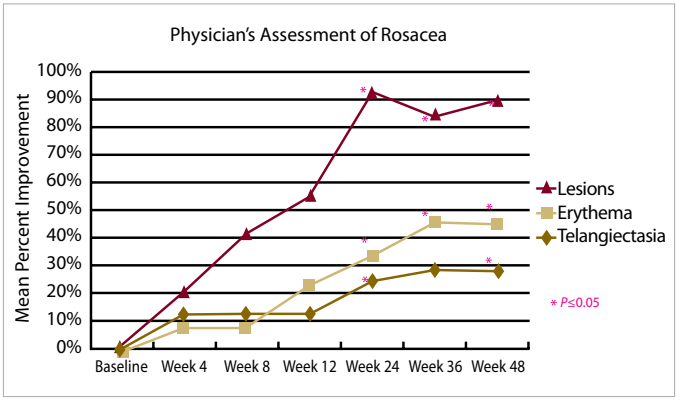


FIGURE 2. Physician's assessment of overall clinical improvement graded on a scale of 1–6 (1=excellent improvement; 2=marked improvement (~75%), 3=moderate improvement (~50%), 4=slight improvement (~25%), 5=no improvement (0%), 6=worse). The graph represents the percent of subjects in each category. The category "none", includes subjects graded a 5 or 6. The category "mild to moderate" includes subjects graded a 3 or a 4. The category "excellent" includes subjects graded a 1 or 2.

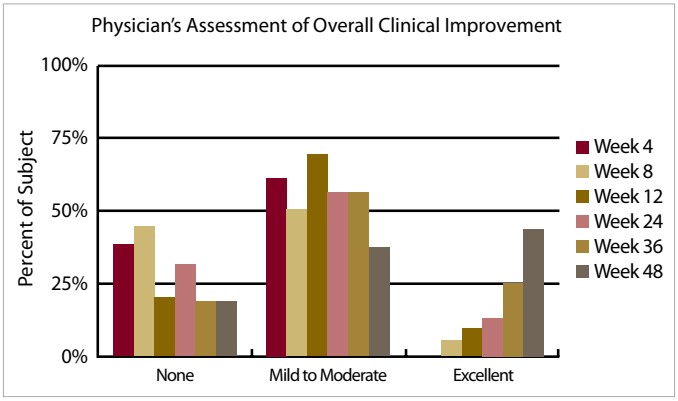
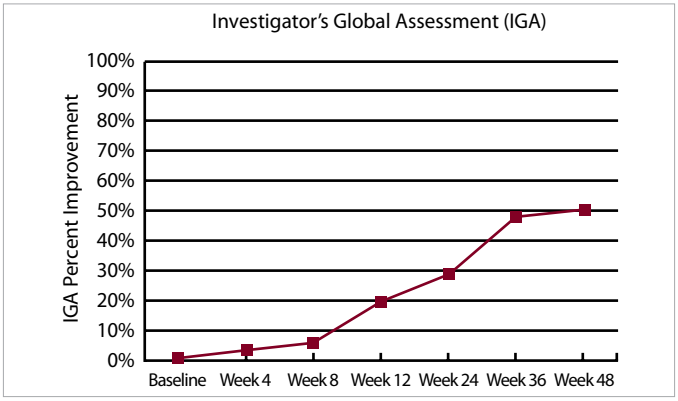


FIGURE 3. The mean percent improvement in the investigator's global assessment (IGA) score over 48 weeks as compared to baseline. (The X-axis scale changes after week 12.)



tested for significance with the paired difference *t* test. Probability values less than 0.05 ($P<0.05$) were considered significant. Routine blood hematology and chemistry, urine chemistry and pregnancy tests were performed at baseline and at 48 weeks.

FIGURE 4. The mean score (none, mild, moderate, severe) of clinically assessed rosacea-associated symptoms (stinging, burning, dryness) at each assessment.

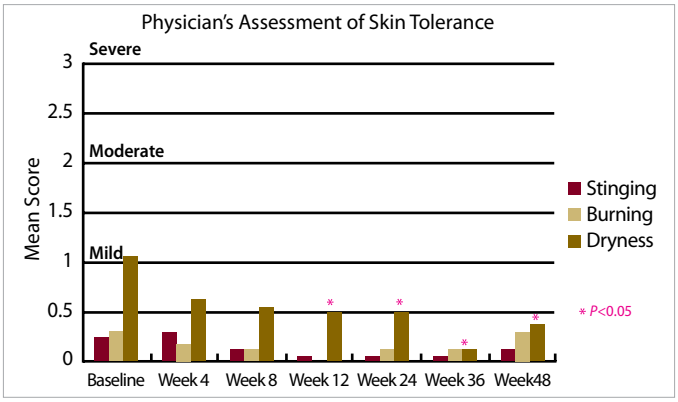
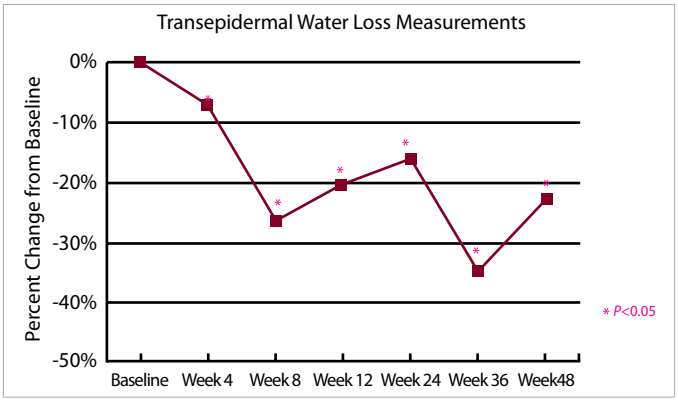


FIGURE 5. The change in transepidermal water loss (TEWL) at each assessment compared to baseline. (The x-axis scale changes after week 12.)



RESULTS

Clinical Assessment

Sixteen subjects completed the study. One withdrew after he moved to another state. The second was lost to follow-up. After 48 weeks of treatment with PRK 124, subjects had a mean 44 percent reduction in the severity of erythema at week 48 (22% at week 12) and a mean 89 percent decrease in inflammatory lesion count (papules and pustules) at week 48 (55% at week 12). There was a significant reduction ($P<0.05$) in lesions and erythema at weeks 24, 36 and 48 (Figure 1). At weeks 24 and 48 a statistically significant ($P<0.05$) improvement in telangiectasia was appreciated (Figure 1). Overall clinical improvement was observed in 81 percent of subjects (Figure 2) with week 48 showing the greatest proportion in the excellent category. The mean percent improvement of the investigator's global assessment steadily increased throughout the study with a 50 percent improvement at the end of 36 and 48 weeks (Figure 3). Clinically there was a statistically significant decrease ($P<0.05$) in dryness at weeks 12, 24, 36 and 48 (Figure 4). TEWL was significantly reduced ($P<0.05$) compared to baseline at weeks 8, 12, 24, 36 and 48 (Figure 5). The increase in TEWL at weeks 12, 24 and 48 may be secondary to environmental conditions, despite allowing the subject to acclimate to the room humidity prior to measurement. Also, TEWL is an average value of two sites and there may be variation between each site.

Safety Assessment

The treatments were well tolerated (Figure 6) and subjects rated cosmetic outcomes as acceptable (Figure 7). PRK 124 lotion-induced irritation was not observed in any subject during the 48-week study period. Results of routine blood and chemistry tests and urine chemistry tests showed no clinically significant changes from baseline.

DISCUSSION

The authors' results suggest that topical PRK 124 lotion applied twice daily for 48 weeks is well-tolerated and increasingly reduces the signs and symptoms of mild-to-moderate rosacea.

FIGURE 6. Subject self assessment of tolerance to treatment.

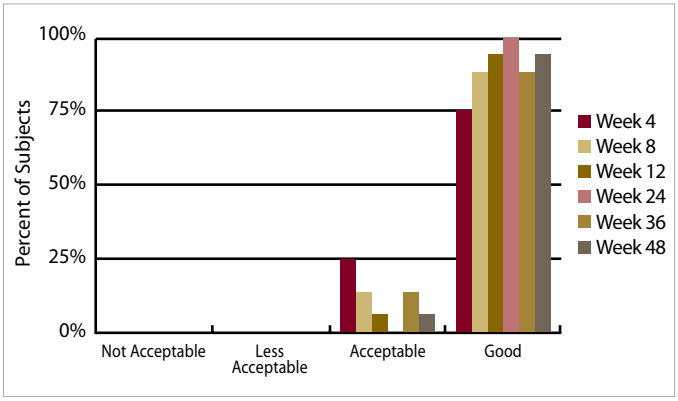
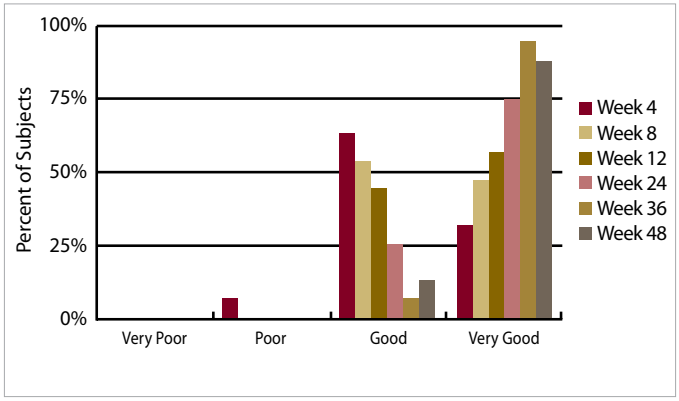


FIGURE 7. Subject self assessment of cosmetic acceptability.



The treatment significantly reduces the number of papules, pustules and telangiectasias, and reduces erythema and overall symptoms of burning, stinging and dryness. The decrease in TEWL provides objective evidence of improved skin barrier function, which is compromised in rosacea. Additional mechanisms require further study. The reduction in water loss correlates with the subjective improvement in dryness over the study period.

The 12-week study showed that treatment with the PRK 124 lotion is effective and well tolerated and that overall clinical improvement occurred in 80 percent of subjects. After 36 and 48 weeks, overall clinical improvement was observed in 81 percent of subjects, indicating that the improvement rate remains constant for at least 48 weeks. In contrast, the individual treatment effects and investigator's global assessments increased steadily from week 12 to week 48. High subject satisfaction is indicated by the subject-assessed cosmetic acceptability.

In summary, the results show that use of PRK 124 for 48 weeks provides continued improvement in the signs and symptoms of rosacea without irritating the skin. The absence of skin irritation is important because skin sensitivity commonly occurs in patients with rosacea after extended treatment with topical products.

CONCLUSION

The new moisturizing lotion containing furfuryl tetrahydropyranyladenine as PRK 124 provides long-term improvement in subjects with mild-to-moderate inflammatory rosacea. The extended period of treatment is well tolerated, adverse effects such as skin irritation are not observed, and results are cosmetically acceptable.

DISCLOSURES

The authors have no financial relationship with Senetek PLC, and have no conflicts of interest.

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