Topical PRK 124 (0.125%) Lotion for Improving the Signs and Symptoms of Rosacea

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Editor's note: The information in this paper was presented as a poster presentation at the 2008 International Investigative Dermatology conference in Kyoto, Japan.

ABSTRACT

Background: Current treatments for acne rosacea are often associated with unsatisfactory outcomes and adverse effects.
Objective: To determine the efficacy and tolerability of a new moisturizing lotion for improving the clinical signs and symptoms of mild-to-moderate acne rosacea.
Methods: In a 12-week, open-label study, a moisturizing lotion containing furfuryl tetrahydropyranyladenine as PRK124 (0.125%, Pyratine-XR™, Senetek PLC, Napa, CA) was applied twice daily to subjects with mild-to-moderate rosacea. Improvement in the appearances of erythema and papules were assessed by the treating physician. Skin barrier function was measured by transepidmal water loss after treatment. Tolerability and cosmetic outcome were evaluated by patients.
Results: Twenty-one participants completed the study. Overall clinical improvement was observed in 80% of subjects, with most showing mild-to-moderate improvement. Erythema, papule counts, and telangiectasia were reduced. The reduction in TEWL was significant at weeks 4 ($p = 0.01$), 8 ($p < 005$), and 12 ($p<0.001$). Rosacea symptoms (burning, stinging, dryness) were progressively reduced, with reduction in dryness achieving statistical significance at weeks 4 ($p = 0.035$), 8 ($p = 0.037$) and 12 ($p = 0.016$). Treatments were well tolerated and cosmetic outcomes were acceptable. Treatment-induced irritation was not observed.
Conclusion: The new moisturizing lotion containing furfuryl tetrahydropyranyladenine as PRK124 shows a continued trend toward improvement of skin barrier function and the appearances of erythema and papules associated with mild-to-moderate rosacea during 12 weeks of treatment.

INTRODUCTION

Rosacea is characterized by transient or persistent erythema, telangiectasia and the presence of papules and pustules. A facial dermatosis, rosacea may be erythematotelangiectatic, papulopustular, phymatous or ocular.[1,2] Current therapies include topical agents (metronidazole, clindamycin, sulfacetamide/sulfur) alone, or in combination with systemic antibiotics (tetracycline, erythromycin), and/or light-based therapy (pulsed dye laser, intense pulsed light).[3,4]

Outcomes with current therapies are often unsatisfactory because the pathophysiology of rosacea is not completely understood.[2] It has been postulated that rosacea is a disorder of skin-barrier function in which irritants invade the epidermis, causing vasodilation, flushing and inflammation.[5] Since rosacea is a chronic condition and extended treatment periods with topical agents may be accompanied by high skin sensitivity, treatments that provide sustained relief of signs and symptoms are needed.

Furfuryl tetrahydropyranyladenine (PRK-124) is a plant cytokinin shown to have growth modulatory, antioxidative and anti-senescent effects on human skin cells (SenetekPLC, unpublished data, 2004). A recent 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] The treatment also decreased skin transepidermal water loss (TEWL) and increased skin moisture content.[6]

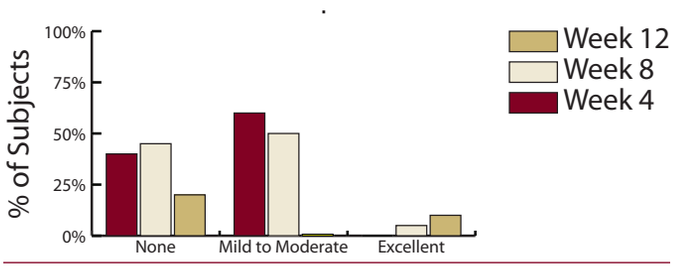

FIGURE 1. Physicians' assessment of overall clinical improvement in subjects after 4, 8 and 12 weeks of treatment. More than 50% showed improvement by week 4, nearly 75% were improved by week 8 and 80% showed improvement at week 12.

The purpose of this study was to determine the efficacy and tolerability of a lotion containing PRK 124 (0.125%) for improving the clinical signs and symptoms of mild-to-moderate acne rosacea.

MATERIALS AND METHODS

Subjects

Healthy subjects (n=24, 18 women) aged 29 to 69 years (mean 51) with mild-to-moderate erythematotelangiectatic rosacea, papulopustular rosacea, or both participated in this single-center, open-label, 12-week study. Subjects had: 0 to 10 inflamed facial papules, pustules, or both; persistent erythema; and telangiectasias. Global severity of rosacea was initially graded on an investigator-developed scale of 0 to 6, in which 6 represented maximum severity. Eleven (46%) subjects had mild (grade 2), 10 (42%) had mild-to-moderate (grade 3) and three (12%) had moderate (grade 4) rosacea. Erythema and telangiectasia were graded separately on a 0 to 3 scale in which 3 denoted maximum severity, while lesion counts were the basis for assessing papulopustular severity.

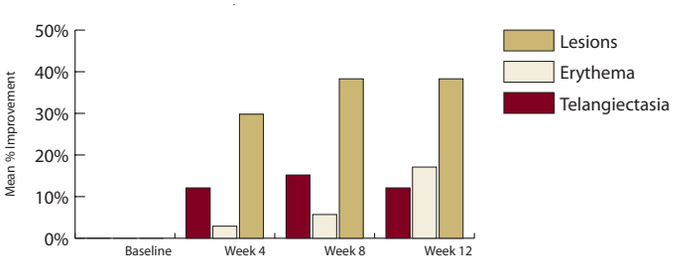

FIGURE 2. Physicians' assessment of changes in lesion counts and erythema grades during the 12-week study period. For lesion (papules and pustules) counts, the mean improvement was 30% at week 4 and approached 40% at weeks 8 and 12. For erythema, improvement grades were lower but improvement was noticeable.

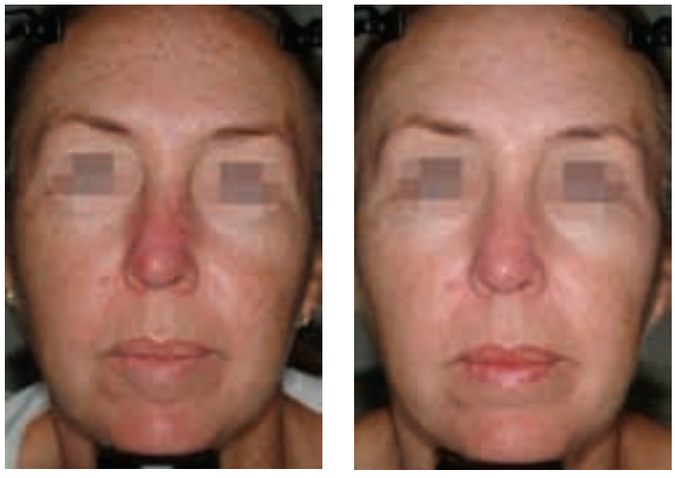

FIGURE 3. A woman with rosacea **a)** before treatment and **b)** after 12 weeks of treatment

Exclusion criteria included: severe disease (grades 5-6) with phymata, rosacea conglobata, rosacea fulminans, marked ocular manifestations or steroid rosacea; more than 10 papules and pustules; other chronic or recurring skin disease or disorder affecting the face; pregnancy; systemic retinoid use within 6 months; systemic corticosteroids or antibiotic use within 1 month; topical retinoid, antibiotic, or corticosteroid use two weeks before the study began; involvement in a clinical trial within the previous 30 days; hypersensitivity to the study treatment; and unwillingness to use a sunscreen with at least an SPF of 30 during the study. The protocol was approved by an institutional review board of the University of California, Irvine. Informed consent was obtained in writing from all subjects.

Treatment

Each subject was instructed to (1) wash his or her face with a mild cleanser, (2) apply PRK-124 (0.125%) 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. Efficacy and adverse effects were evaluated at 0, 4, 8 and 12 weeks. Subjects were told not to apply the study lotion on the days of evaluation. At each 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 overall clinical improvement and changes in signs and symptoms of rosacea, skin tolerance to treatment and transepidermal water loss (TEWL) relative to baseline. Overall clinical improvement was graded by the investigator on a scale of 1 to 3 (1 = none; 2 = mild to moderate, 3 = excellent); grades were assigned by comparing pre- and posttreatment photographs of the treated areas. Signs and symptoms of rosacea (burning/stinging, erythema/telangiectasia, papules/pustules) were graded by the investigator on a scale of 0 to 3 (0 = none; 3 = severe). Skin tolerance (burning,

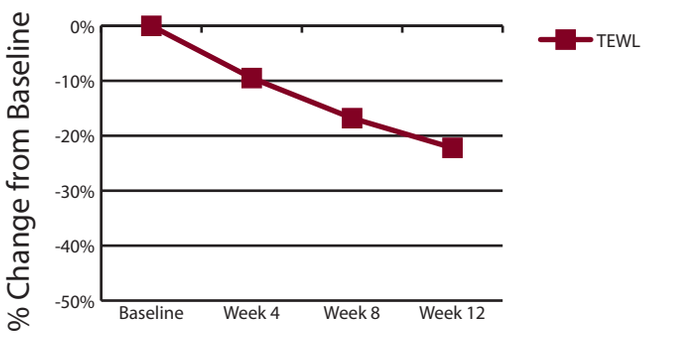

FIGURE 4. Reduction (%) in transepidermal water loss (TEWL) during the 12-week study period. Negative values indicate improvement in skin barrier function. The mean TEWL was calculated from measurements of the right and left cheeks of each subject. TEWL decreased with continued treatment, reaching 22% at 12 weeks. The reduction in TEWL was statistically significant at weeks 4, 8 and 12.

stinging, dryness) was graded by subjects on a scale of 0 to 3. 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 this study, TEWL was measured with an evaporimeter (Dermalab, Inc., Highland Park, IL) on the right and left cheeks at 0, 4, 8 and 12 weeks.

Results from the study were evaluated using descriptive and inferential statistics. The significance of changes in multinomial variables (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 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 0 (baseline) and at 12 weeks.

RESULTS

Clinical Assessment

Twenty-one subjects completed the study. One withdrew after 4 weeks because his rosacea worsened as a result of having to discontinue an excluded medication that he was taking for rosacea. Another subject withdrew after 8 weeks due to subjective lack of improvement. The third subject was lost to follow-up.

After 12 weeks of treatment, overall clinical improvement was observed in 80% of subjects (Figure 1), with most showing mild-to-moderate improvement. Erythema was reduced, and papule count was reduced as well (Figures 2 and 3). Although the average subject achieved a 12% reduction in telangiectasia at week 12, the decrease was not statistically significant. The reduction in TEWL was significant at weeks 4 ($p = 0.01$), 8 ($p < 0.05$) and 12 ($p<0.001$) (Figure 4). Rosacea symptoms (burning, stinging, dryness) were progressively reduced (Figure 5), with reduction in dryness achieving statistical significance at weeks 4 ($p = 0.035$), 8 ($p = 0.037$) and 12 ($P = 0.016$). These changes clearly indicate an increased beneficial effect over time.

Safety

Treatments were well tolerated (Figure 6) and cosmetic outcomes were acceptable (Figure 7). Treatment-induced irritation was not observed. Routine blood and urine chemistry and hematology tests showed no pathologic changes.

DISCUSSION

The results suggest that topical PRK 124 (0.125%) lotion applied twice daily for 12 weeks is a well-tolerated moisturizing lotion that progressively reduces the signs and symptoms of mild-to-moderate acne rosacea. Reduction in TEWL provides strong objective evidence that confirms the subjective assessments of improvement in dryness over the 12-week study period. The subject-assessed cosmetic acceptability is an indicator of high patient satisfaction. One of the mechanisms of action of PRK 124 in the improvement of rosacea is the improvement of skin barrier function, which is compromised in rosacea. Additional mechanisms require further study.

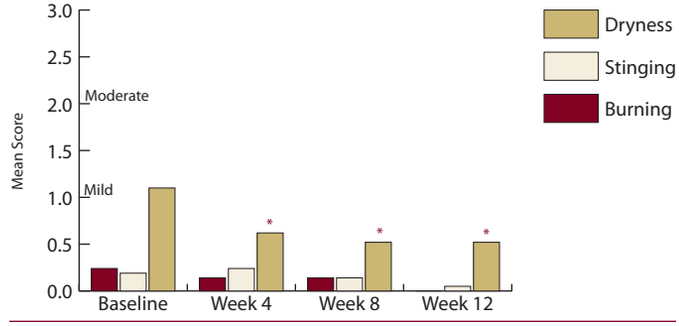

FIGURE 5. Physicians' assessment of changes in acne rosacea-associated symptoms (stinging, burning, dryness) at each assessment visit. The grade of each symptom decreased progressively at each visit with the exception of a slight increase in stinging at week 4. The reduction in dryness was significant at weeks 4, 8 and 12.

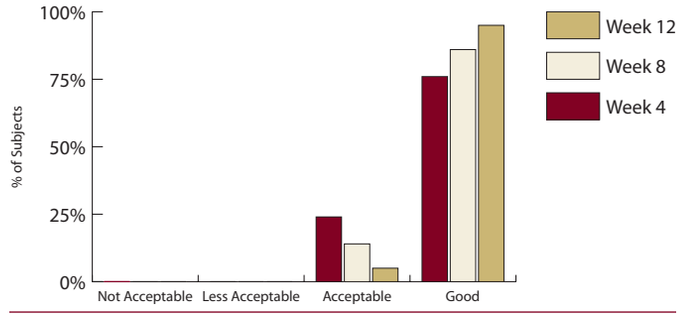

FIGURE 6. Participants' self-assessment of tolerance to treatment. All subjects reported "acceptable" or "good" at each treatment visit, with most subjects judging tolerance as "good."

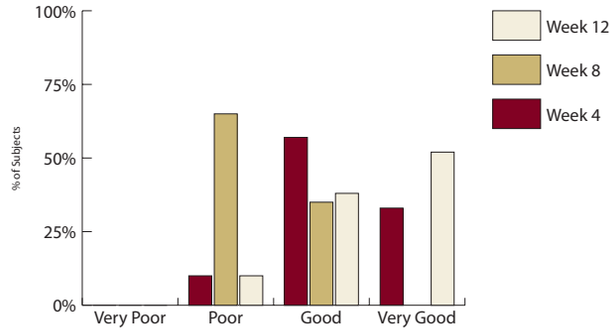

FIGURE 7. Participants' self-assessment of cosmetic acceptability. With a few exceptions, cosmetic acceptability was "good" or "very good."

An important finding in this study is that, unlike other topical therapies, PRK-124 did not irritate the sensitized skin of the rosacea subjects. In view of the promising results and excellent tolerability, the authors are conducting a 48-week trial to evaluate the long-term efficacy and tolerability of the PRK-124 lotion in the treatment of acne rosacea.

CONCLUSION

The new moisturizing lotion containing furfuryl tetrahydropyranyladenine as PRK-124 shows a continued trend toward improvement of skin barrier function and the appearance of erythema and papules associated with mild-to-moderate acne rosacea during 12 weeks of treatment. The treatments were well tolerated, adverse effects such as skin irritation were not observed and results were cosmetically acceptable.

DISCLOSURES

The clinical study was funded by an unrestricted grant from Senetek, PLC. The authors have no conflicts of interest to disclose.

ACKNOWLEDGEMENTS

Each author took part in the creation and revision of this case.

REFERENCES

1. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46(4):584-587.
2. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51(3):327-341.
3. Bikowski JB, Goldman MP. Rosacea: Where are we now? *J Drugs Dermatol.* 2004;3(3):251-261.
4. Van Zuuren EJ, Gupta AK, Gover MD, et al. Systematic review of rosacea treatments. *J Am Acad Dermatol.* 2007;56(1):107-115.
5. Draelos ZD. Clinical situations conducive to proactive barrier enhancement. *Cutis.* 2002;70:(6 Suppl)17-20.
6. McCullough JL, Garcia RL, Reece B. A clinical study of topical Pyratine 6 for improving the appearance of photodamaged skin. *J Drugs Dermatol.* 2008;7(2):131-135.

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