Facilitating Facial Retinization Through Barrier Improvement

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The utility of topical tretinoin as a treatment for improving the appearance of photodamaged skin is limited by irritation that occurs during the early phases of facial retinization. The observed side effects are consistent with stratum corneum barrier compromise. This paired double-blinded study was conducted to determine if preconditioning the skin with a barrier-enhancing cosmetic facial moisturizer before beginning tretinoin therapy and continuing moisturizer application during therapy would mitigate these side effects. Women with facial photodamage were recruited and randomly assigned to apply one cosmetic moisturizer to one side of the face and the other cosmetic moisturizer to the other side of the face twice daily for 10 weeks. One moisturizer contained a mixture of vitamins (niacinamide, panthenol, and tocopheryl acetate) to enhance stratum corneum barrier function, and the other moisturizer contained similar moisturizing ingredients but no vitamins. Daily full-face treatment with tretinoin cream 0.025% commenced 2 weeks into the study. Subjects' facial skin condition was monitored via investigator assessments, instrumental measurements, and subject self-assessments. The results show that improving stratum corneum barrier function before beginning topical tretinoin therapy and continuing use of a barrier-enhancing cosmetic moisturizer during therapy facilitates the early phase of facial retinization and augments the treatment response.

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Topical tretinoin is one of the most effective drugs for treating photodamage.[1] Tretinoin is reported to induce a number of important histologic and clinical changes resulting in the improved appearance of photodamaged skin, which is characterized histologically by epidermal dysplasia with varying degrees of cytologic atypia, loss of keratinocyte polarity, inflammatory infiltrate, decreased collagen, increased ground substance, and elastosis.[2,3] The initial clinical effect observed following the first few weeks of topical tretinoin treatment is improvement in tactile smoothness, attributed to a stratum corneum with a more compact pattern and increased epidermal thickness because of spongiosis.[4] Tretinoin also stimulates hyaluronic acid synthesis, which increases the water-holding capacity of the skin and contributes to improvement in skin smoothness.[5] Fine wrinkles improve with longer-term topical tretinoin therapy, representing an increase in dermal collagen production.[6]

There also are a number of side effects observed during the first weeks of tretinoin application to the face, a process called *facial retinization*. These effects are consistent with hypervitaminosis A of the skin and include skin irritation manifested as dryness or peeling, stinging or burning, and erythema.[7] These side effects, which are expected and are signs of barrier damage, are of sufficient severity to cause many patients to discontinue topical tretinoin therapy during the first weeks of use. Improving stratum corneum barrier function before starting tretinoin therapy could reduce barrier damage and side effects during facial retinization. This study was conducted to compare the effects of preconditioning the face with 2 different cosmetic facial moisturizers, one a product previously shown to enhance the skin's barrier function,[8] on subsequent treatment with topical tretinoin.

Methods

Schulman Associates Institutional Review Board approved the study design and subjects provided

informed consent. Fifty women aged 35 to 55 years were enrolled in a 10-week randomized double-blinded study. The subjects were in good general health and had Fitzpatrick skin types I to III. The dermatologist investigator used pictorial criteria defined by Griffiths et al[9] to identify subjects with mild to moderately severe facial photodamage. Any subject who applied a retinoid-containing product to her face within the 4-week period prior to study start was excluded, as were subjects who were pregnant or planning a pregnancy during the study period.

The 10-week study was comprised of a 2-week preconditioning period and an 8-week tretinoin treatment period. At study start (week −2), subjects received a standardized face wash product (Olay® Sensitive Skin Gentle Foaming Face Wash) to use in place of their regular facial cleanser. They also were given the blinded moisturizer test products, both of which provided sun protection factor (SPF) 15 photoprotection to counter the photosensitization caused by tretinoin. Moisturizer A contained niacinamide, panthenol, and tocopheryl acetate (Olay® Total Effects with VitaNiacin Moisturizing Vitamin Complex with UV Protection, SPF 15); moisturizer B contained no vitamin additives (Purpose® Daily Use UV Moisturizer, SPF 15). Subjects were randomized to apply one of the test moisturizers to the right side of their face and the other test moisturizer to the left side of their face twice daily for the entire study. Application of any other moisturizer, cream, or lotion to the face was prohibited. Subjects were permitted to use their regular facial makeup or foundation during the study.

At the end of the 2-week preconditioning period (week 0), subjects began the 8-week tretinoin treatment period. Subjects were given tretinoin cream 0.025% and instructed to apply the product to their entire face at night, one hour before bedtime. Approximately 5 minutes after applying the tretinoin, subjects applied each of the test moisturizers to the designated part of the face over the tretinoin. In the morning, subjects applied the test moisturizers as instructed but did not use the tretinoin cream. Subjects were instructed to wash their face 1 to 2 hours before each scheduled evaluation and to apply no moisturizer or makeup.

During treatment, the investigator evaluated each side of the face for tretinoin tolerance and side effects commonly observed with tretinoin therapy, including dryness/peeling, burning/stinging, irritation, pruritus, and acnelike lesions. Each parameter was evaluated on a 0 (none) to 3 (severe) scale at week 0, to account for any effect due to application of the test moisturizers during preconditioning, and at weeks 1, 2, 4, 6, and 8. The investigator also assessed facial appearance at the start of tretinoin therapy (week 0) and at weeks 2, 4, 6, and 8. Parameters associated with photodamage, including superficial fine lines, wrinkles, mottled hyperpigmentation, sallowness, roughness, blotchiness, cheek texture/roughness, and pores, were scored on each side of the face. Subjects completed a self-assessment questionnaire covering parameters related to skin feel and facial skin appearance at weeks 0, 2, 4, 6, and 8. Subjects also chose which moisturizer product prevented irritation better (ie, which side of their face was less irritated) at weeks 2, 4, 6, and 8.

Stratum corneum barrier function was measured using a DermaLab® Evaporimeter and stratum corneum hydration was measured using a Corneometer® CM 825. Measurements were made following recommended guidelines at mid cheek on each side of the face at study start (week −2);

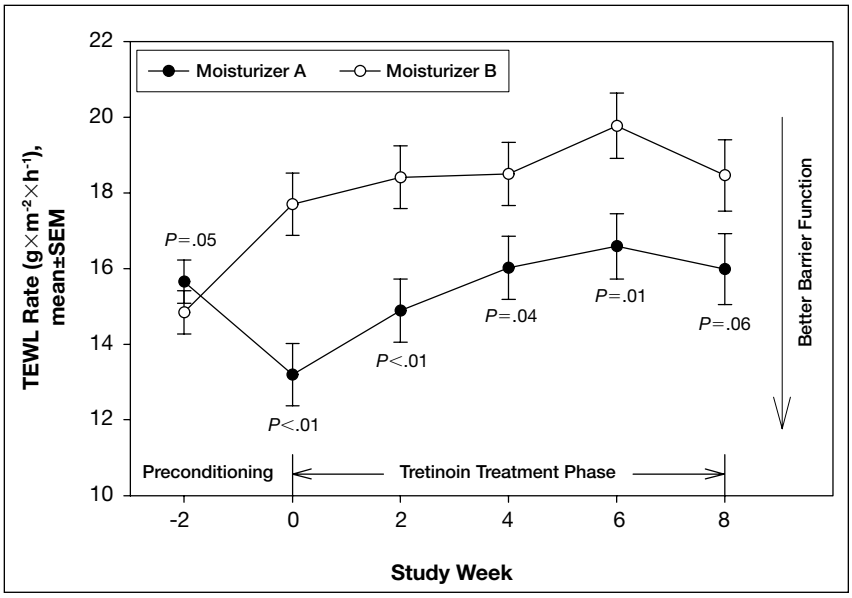

Figure 1. Stratum corneum barrier function (transepidermal water loss [TEWL]) measured on the cheeks over the course of the study. Moisturizer A improved TEWL during the 2-week preconditioning period and helped maintain TEWL at or below enrollment visit levels during the 8-week course of tretinoin therapy. In contrast, TEWL values measured on the cheek treated with moisturizer B were elevated from the value at enrollment during the course of the study. SEM indicates standard error of the mean.

at the start of tretinoin therapy (week 0); and at weeks 2, 4, 6, and 8.

Statistical Analysis—The dermatologist's evaluation scores, subjects' self-assessment responses, and instrumental data were analyzed by a mixed-model technique using appropriate baseline values (week −2 or week 0, depending on the end point) as covariates. A repeated-measures mixed model was used to obtain an overall assessment of the measured parameters during the tretinoin treatment phase (weeks 0–8), with baseline values included as covariates, if available. Pairwise comparisons of the responses obtained with the 2 facial moisturizers were considered statistically different if $P \leq .05$ (2 tailed).

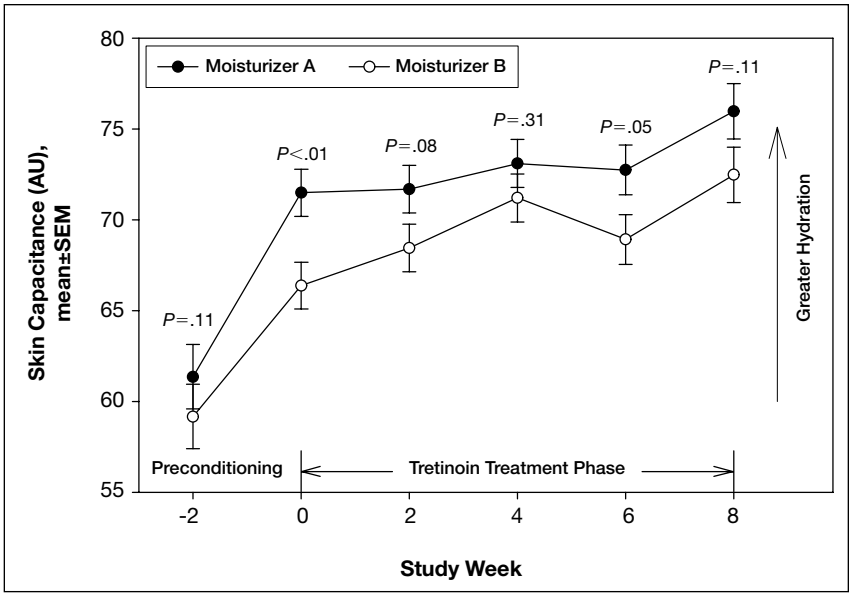

Figure 2. Stratum corneum hydration (skin capacitance) measured on the cheeks during the course of the study. Both moisturizer products improved stratum corneum hydration, but moisturizer A provided a greater benefit than moisturizer B (the overall *P* value for comparison of moisturizer A vs moisturizer B during the tretinoin treatment phase is $P<.01$). AU indicates arbitrary unit; SEM, standard error of the mean.

Results

Subject Accountability—Thirty-seven of the 50 subjects enrolled completed the study. The remainder were lost to follow-up or failed to return at some point during the study. No adverse events were reported.

Preconditioning Period (Weeks −2–0)—A significantly higher ($P=.05$) transepidermal water loss (TEWL) rate was found on cheeks assigned to moisturizer A at study start (week −2), indicating that stratum corneum barrier function on cheeks assigned to moisturizer A was initially poorer than on cheeks assigned to moisturizer B. However, by the end of preconditioning (week 0), the TEWL rate measured on cheeks treated with moisturizer A decreased from its initial value and was significantly lower ($P<.01$) than the value measured on cheeks treated with moisturizer B, which increased from the starting value (Figure 1). The improvement in stratum corneum barrier function found for moisturizer A is consistent with previous experience.[8]

Stratum corneum hydration was not significantly different ($P=.11$) at study start between cheeks assigned to moisturizers A and B. As expected, both moisturizer products increased stratum corneum hydration from baseline (week 0) values over the pretreatment period; however, overall stratum corneum hydration measured on cheeks treated with moisturizer A was significantly higher ($P<.01$) than cheeks treated with moisturizer B (Figure 2).

Treatment Period (Weeks 0–8)—Tretinoin treatment compromised stratum corneum barrier function on both sides of the face compared with treatment baseline (week 0). However, TEWL values measured on cheeks assigned to moisturizer A remained significantly lower overall ($P<.01$) than on cheeks assigned to moisturizer B for the entire course of treatment and, in general, remained at or below the value measured at study start (week −2)(Figure 1). Corneometer measurements showed both moisturizer products increased stratum corneum hydration, with moisturizer A providing a significantly greater increase overall ($P<.01$) than moisturizer B (Figure 2).

Of the side effects commonly associated with facial retinization, investigator-scored dryness/peeling showed the greatest response (Figure 3). The magnitude of the observed changes in burning/stinging, irritation, pruritus, and acnelike lesions was less but were, in nearly all cases, lower on the side of the face treated with moisturizer A than on the side treated with moisturizer B (data not shown). In general, the trends in these parameters over the course of treatment mirrored changes in stratum corneum barrier function (ie, the side effect magnitudes were greatest when TEWL measurements showed barrier function was poorest).

The investigator also judged that tretinoin was better tolerated on the side of the face treated with moisturizer A than on the side treated with moisturizer B (Figure 4). In fact, tolerance on the side of the face treated with moisturizer A returned to the mean baseline level (week 0) by study end.

The level of assessed tolerance paralleled changes in stratum corneum barrier function over the course of treatment.

The investigator's assessment of parameters associated with photodamage showed that tretinoin therapy decreased superficial fine lines/wrinkles, mottled pigmentation, blotchiness, and cheek texture/roughness, with significantly greater ($P<.01$) decreases for each parameter found on the side of the face treated with moisturizer A (Table 1). Investigator-assessed scores for sallowness and pores showed no change in this study (data not shown).

Subject ratings of overall skin feel and overall facial skin appearance improved on both sides of the face over the 8-week course of tretinoin therapy (Table 2). Ratings for each of these parameters at study end favored the side of the face treated with moisturizer A over the side treated with moisturizer B, though the differences were not significant. Interestingly, subjects judged the side of the face treated with moisturizer A significantly better than the side treated with moisturizer B for both overall facial skin appearance ($P=.04$) and overall skin feel ($P=.03$) at baseline (week 0), suggesting that moisturizer choice alone can affect subjects' perception of their photoaged skin. In general, subjects chose the side of the face treated with moisturizer A as being less irritated than the side of the face treated with moisturizer B during the course of tretinoin therapy (Figure 5).

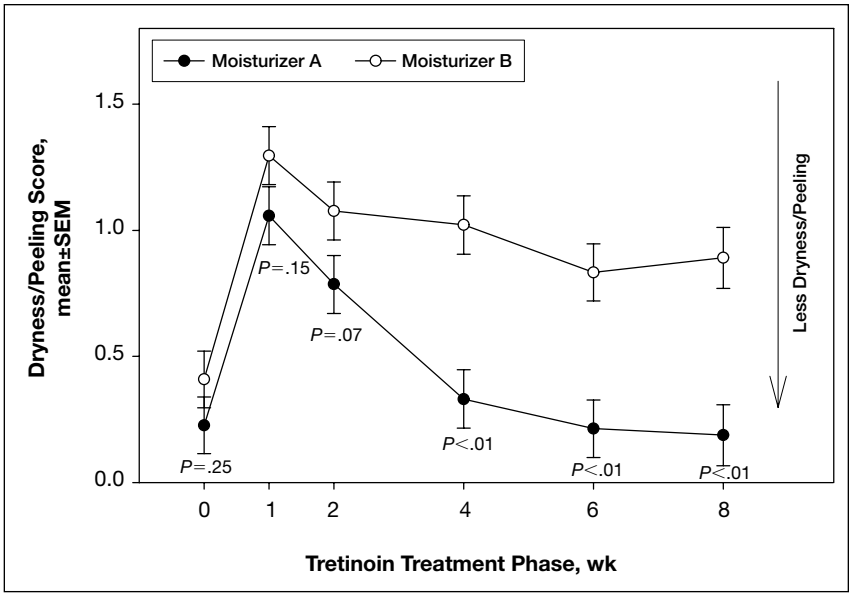

Figure 3. Investigator-assessed facial dryness/peeling during the 8-week course of tretinoin therapy. This parameter was scored on a 0 (none) to 3 (severe) scale. Although dryness/peeling increased on both cheeks during the initial stage of retinization, this side effect abated more rapidly on cheeks treated with moisturizer A. Dryness/peeling on cheeks treated with moisturizer A returned to baseline levels by the end of the therapeutic course, while dryness/peeling on cheeks treated with moisturizer B remained elevated from baseline levels for the entire study. SEM indicates standard error of the mean.

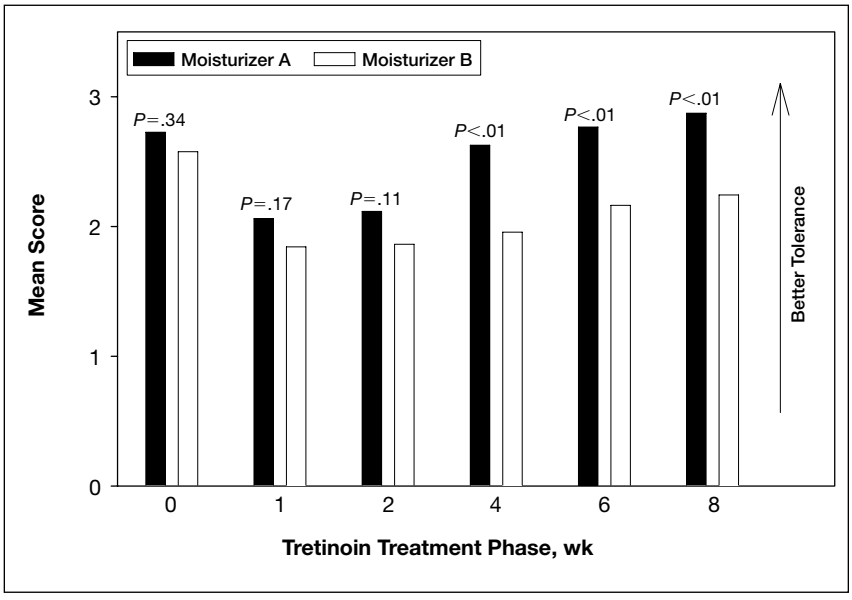

Figure 4. Investigator-assessed tolerance of tretinoin therapy during the 8-week course of treatment. Tretinoin therapy was better tolerated overall on cheeks treated with moisturizer A ($P<.01$).

Comment

Tretinoin is a valuable topical agent in the treatment and prevention of photodamage. Many patients are reluctant to undertake treatment with tretinoin because of the unavoidable irritation that often is encountered during the early weeks of its application. This irritation presents as excessive facial dryness or peeling accompanied by burning, stinging, and/or itching. These side effects are in part due to a stratum corneum barrier defect induced by tretinoin. We hypothesized that improving the barrier before commencing

tretinoin therapy would mitigate some of the associated side effects.

This study was designed to compare the effects of 2 sunscreen-containing cosmetic facial moisturizers during tretinoin therapy. One moisturizer, moisturizer A, contained niacinamide, panthenol, and tocopheryl acetate, ingredients that can enhance stratum corneum barrier function.[8,10] The comparative moisturizer, moisturizer B, contained similar moisturizing agents but no vitamins.

TEWL measurements confirmed that moisturizer A enhanced stratum corneum barrier function during the 2-week preconditioning period preceding tretinoin treatment. In contrast, barrier function was degraded on the side of the face treated with moisturizer B. This change was unexpected because the moisturizer and supplied face wash product should be minimally irritating. The observed change may reflect an inability of the moisturizer to mitigate barrier compromise because of a change in an external factor (eg, environmental conditions) rather than damage caused by the treatments themselves. Tretinoin therapy compromised barrier function on both sides of the face. However, barrier function on the side of the face treated with moisturizer A was consistently better than on the side of the face treated with moisturizer B and, as noted earlier, was maintained at or below the level measured at study start.

The potential benefit of enhancing stratum corneum barrier function prior to beginning tretinoin therapy and coapplying a cosmetic moisturizer that can enhance barrier function during tretinoin therapy is evident in the investigator's assessments of side effects such as dryness/peeling and overall tolerance. Although these steps did not eliminate the negative aspects of tretinoin therapy, this study showed that improved barrier function and cosmetic moisturizer coapplication can reduce side effect severity over the course of treatment. For example, by later weeks of this study, dryness/peeling scores and investigator-judged tolerance returned to baseline levels for the side of the face treated with moisturizer A; the same was not true for moisturizer B. Subjects perceived a similar difference in the moisturizers' abilities to mitigate facial irritation during tretinoin therapy.

In addition, the investigator's assessments of photodamage end points indicate that using moisturizer A in conjunction with tretinoin application improved the therapeutic outcome. If this improved outcome is due to an enhanced effect of tretinoin or a reduction in the negative background

Table 1.

Investigator-Assessed Signs of Photodamage*

	Baseline (Week 0)†		Week 8‡		
	Moisturizer A, mean±SEM	Moisturizer B, mean±SEM	Moisturizer A, mean±SEM	Moisturizer B, mean±SEM	*P* Value
Superficial fine lines/ wrinkles (eyes)§	2.9±0.04	2.9±0.04	2.5±0.05	2.8±0.05	<.01
Superficial fine lines/ wrinkles (cheeks)§	2.6±0.06	2.7±0.06	2.1±0.06	2.5±0.06	<.01
Mottled pigmentation§	2.9±0.06	2.9±0.06	2.3±0.07	2.6±0.07	<.01
Blotchiness§	3.0±0.07	3.0±0.07	2.3±0.07	2.5±0.07	<.01
Texture/ Roughness (cheeks)‖	2.1±0.09	2.3±0.09	1.5±0.09	2.1±0.09	<.01

*SEM indicates standard error of the mean.
†Differences at baseline were not significant ($P \geq .15$).
‡Greater improvement at week 8 was observed on the side of the face treated with tretinoin and moisturizer A.
§Scored on a 0 (none) to 5 (severe) scale. A lower score corresponds with better skin condition.
‖Scored on a 0 (none) to 6 (extremely severe) scale. A lower score corresponds with better skin condition.

Table 2.

Subject Self-assessment of Overall Skin Feel and Overall Facial Skin Appearance*

	Baseline (Week 0)†			Week 8		
	Moisturizer A, mean±SEM	Moisturizer B, mean±SEM	*P* Value	Moisturizer A, mean±SEM	Moisturizer B, mean±SEM	*P* Value
Overall Skin Feel‡	1.6±0.18	1.0±0.18	.03	2.3±0.20	1.9±0.20	.24
Overall Facial Skin Appearance‡	1.3±0.18	0.8±0.18	.04	2.0±0.19	1.6±0.19	.18

*SEM indicates standard error of the mean.
†The significant differences present at baseline suggest that moisturizer choice alone can impact the self-perception of photodamage.
‡Rated on a +4 (extremely better) to −4 (extremely worse) scale. A higher score corresponds with a better rating.

associated with tretinoin side effects is unclear. Reducing side effect severity or duration, and increasing the potential for greater perceived benefits, may improve compliance and encourage patients to continue tretinoin therapy.

Interestingly, subjects rated moisturizer A significantly better than moisturizer B for benefiting overall facial skin feel (*P*=.03) and overall facial skin appearance (*P*=.04) at baseline, before tretinoin therapy was started. Although self-evaluation scores for both of these parameters improved over the 8-week course of tretinoin therapy, this outcome suggests that patients may be able to achieve some level of improvement in their photodamage simply by choosing an appropriate facial moisturizing product.

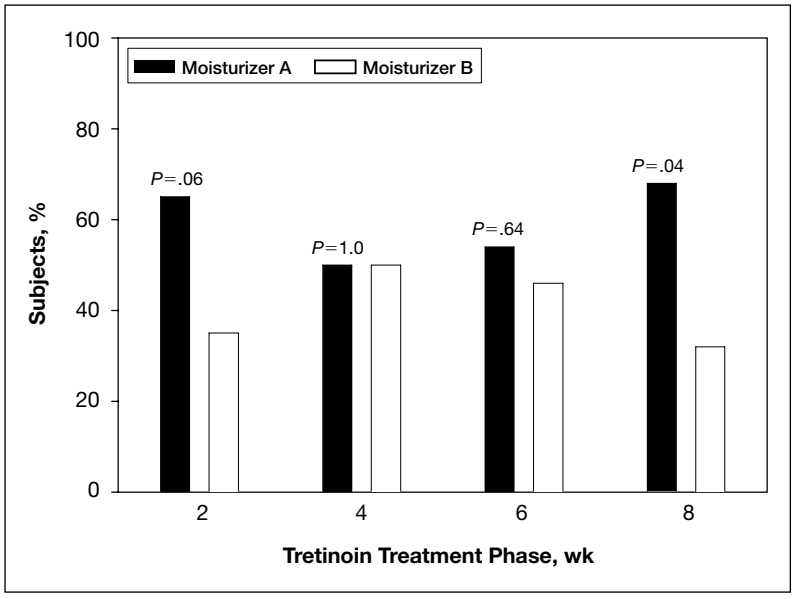

Figure 5. Subject self-assessment of the moisturizer preferred for helping to prevent irritation during tretinoin therapy. Subjects preferred moisturizer A to moisturizer B for preventing irritation, particularly during the early retinization period and in the final phase of the study.

Conclusion

This study shows that enhancing stratum corneum barrier function with a cosmetic moisturizer before therapy with topical tretinoin and continuing moisturizer application during therapy facilitates the early phase of facial retinization. This may increase patients' willingness to undergo tretinoin therapy and improve their compliance after therapy is initiated.

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