A Stabilized 0.1% Retinol Facial Moisturizer Improves the Appearance of Photodamaged Skin in an Eight-Week, Double-Blind, Vehicle-Controlled Study

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ABSTRACT

Retinol is a cosmetic ingredient that is structurally similar to all-*trans*-retinoic acid, which has been shown to be effective in the treatment of photodamage. Since skin keratinocytes are reported to metabolize retinol to retinoic acid, investigators have hypothesized that retinol may also be helpful in improving skin photodamage. In this eight-week, double-blind, split-face, randomized clinical study, a stabilized 0.1% retinol-containing moisturizer was tested (36 subjects) against the vehicle (28 subjects) in women with moderate facial photodamage. Each product was applied once daily to the designated half side of the face. Subjects were evaluated at baseline and after four and eight weeks of treatment using a 0–9 scale for photoaging parameters. The results showed that, after eight weeks, the retinol moisturizer was significantly more efficacious than the vehicle in improving lines and wrinkles, pigmentation, elasticity, firmness and overall photodamage. Many of these differences were significant at week 4, with a progressive improvement to week 8. This study demonstrates that a formulation containing stabilized retinol is safe and effective to ameliorate the appearance of photoaged skin.

INTRODUCTION

Retinol has a history of usage as an antioxidant in cosmetic products[1] and has long been recognized as a safe cosmetic ingredient. Chemically, it is a precursor of retinaldehyde and retinoic acid (RA), the latter a topical drug approved by the U.S. Food and Drug Administration (FDA) for use in photodamaged skin. A multitude of studies have supported the efficacy of RA in improving facial wrinkles and hyperpigmentation.[2–6] There is evidence that topical retinol penetrates the skin when applied to test sites and that it is metabolized by skin keratinocytes to RA.[7,8] Studies have also shown that while retinol may exert similar effects to RA, it has less irritancy potential and it is safer to the skin.[9] Intrinsically aged as well as UV-damaged skin is characterized by increased synthesis of matrix metalloproteinases (MMPs), which mediate collagen destruction, and by decreased production of collagen.[10,11] Human in vivo studies have described epidermal as well as dermal changes after retinol application: epidermal thickening, decreased levels of MMPs, increased fibroblast growth and increased collagen synthesis have all been reported.[9,10]

Because of these retinoic acid-like effects but a higher skin tolerance, and because of its availability as a cosmetic ingredient, topical retinol has been proposed as a potential agent to ameliorate the cutaneous changes associated with photoaging. Despite these arguments, clinical studies on the efficacy of retinol in photoaging are scant.[12] A major problem with retinol formulations has been chemical instability. Significant advances in the stabilization and delivery of retinol have occurred and provide the opportunity for study of its clinical effects.[13] Here, the authors present a study evaluating the efficacy of a stabilized 0.1% retinol-containing moisturizer, which has been optimized for topical delivery to improve the appearance of photodamaged skin on the face.

MATERIALS AND METHODS

Study Design and Formulations

This was an eight-week, double-blind, split-face, vehicle-controlled, randomized study conducted during the winter in the Northeast region of the U.S. The study was approved by an institutional review board and patients' written informed consent was obtained prior to initiation of the investigation. A total of 80 female subjects, aged 40–65, Fitzpatrick phototype I–III, were enrolled in the study. To be included, subjects had to present with a moderate severity of: coarse wrinkles in crow's feet and upper cheek areas; facial pigmentation; facial sagging; and overall photodamage on both sides of the face. Subjects were excluded if they had used topical anti-aging treatments and/or topical retinoids within 30 days prior to study start.

Four facial moisturizers and a vehicle were tested in a round-robin randomization in a population of 80 subjects. Three moisturizers included in this clinical study were of a proprietary nature and cannot be disclosed in this publication. This manu-

script will discuss only the comparison between a 0.1% retinol-containing moisturizer and its vehicle. It should be noted that while the efficacy of these other moisturizers will not be disclosed, the tolerance profile was comparable among all five products. Of the total study population, 37 subjects tested the active retinol product and 29 subjects tested the vehicle. Each subject was assigned two formulations as per randomization. Each product was applied to the designated half side of the face for eight weeks. Applications were conducted once daily in the morning, and no other moisturizer was allowed for the duration of the study.

The novel active formulation discussed in this study has been developed to deliver a stabilized form of retinol, significantly reducing the issue of its chemical instability. Stabilization was achieved by using a combination of a chelating agent, a hydrophilic antioxidant and a lipophilic antioxidant,[13] and was assessed via HPLC analysis on unopened product samples stored at room temperature and further characterized with analytical studies under accelerated conditions. The list of ingredients for the active formulation is reported in Table 1.

Evaluation

Efficacy was measured by clinical evaluations. Digital photography was conducted to document the results. Safety was measured by the incidence and severity of both cutaneous irritation and adverse events.

Clinical evaluations were performed by the dermatologist at baseline and at weeks 4 and 8 on each side of the face. Variables were scored on a 0 (none) to 9 (severe) scale and included: forehead wrinkles; crow's feet wrinkles; crow's feet fine lines; cheek wrinkles; under eye wrinkles; mottled pigmentation; skin brightness; skin firmness; skin lifting; sub-orbital elasticity (by skin pulling); elasticity at jaw line (jowl-visual sagging); overall sagging; overall forced choice (left versus right); and overall photodamage severity. Overall cutaneous irritation was evaluated for safety, using a 0 (none) to 3 (severe) scale.

TABLE 1.

Ingredient List of the 0.1% Retinol Moisturizer

Water, Dimethicone, Glycerin, Isodecyl Neopentanoate, Ethylhexyl Hydroxystearate, Dimethyl MEA, Cetearyl Alcohol, Stearyl Alcohol, PEG 100 Stearate, Glyceryl Stearate, Ceteareth 20, Steareth 10, Citric Acid, Glycolic Acid, Phenoxyethanol, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer, Methylmethacrylate Crosspolymer, Aluminum Starch Octenylsuccinate, Squalane, Butyrospermum Parkii (Shea Butter), Fragrance, Methylparaben, Xanthan Gum, Propylparaben, Polysorbate 20, Polysorbate 60, Retinol, BHT, Disodium EDTA, Ascorbic Acid, Magnesium Aspartate, Zinc Gluconate, Copper Gluconate.

Subjects' self-evaluation for irritation and digital images were also conducted at weeks 0, 4 and 8. Camera set-up, lighting conditions and subject's position were standardized during the study.

Statistical Analyses

Primary data for efficacy analysis was the data at week 8. Analysis data at week 4 was considered secondary. Dermatologist's evaluations were analyzed with multiple methods. A paired T test was used to compare the individual scores at each time point, relative to their respective baseline, within each treatment group. A student's T test was used for each attribute for each cell, for both the actual and net change scores at each time point. Also, the net change scores for each attribute were converted to the number of panelists who showed "improvement", "stayed the same" or "worsened". For all analyses, a two-tailed $P \leq 0.05$ was used as the level of significance.

RESULTS

Thirty-six and 28 female subjects completed the applications of the active and vehicle, respectively. Two subjects were discontinued for reasons unrelated to the study.

Efficacy

The retinol group showed a significant and progressive improvement from baseline at weeks 4 and 8, in nearly all efficacy parameters. At week 8, the 0.1% retinol moisturizer was statistically

TABLE 2.

Net Improvement in Clinical Parameters From Baseline, Based on a 0–9 Dermatologist Score

	Week 4		Week 8	
	Retinol	Vehicle	Retinol	Vehicle
Cheek Wrinkles	-0.7 √ *	0	-0.9 √ *	-0.1
Under Eye Wrinkles	-0.3 √	-0.2 √	-0.6 √ *	-0.3 √
Crow's Feet Lines	-1.1 √ *	-0.8 √	-1.4 √ *	-1.0 √
Crow's Feet Wrinkles	-0.4 √ *	-0.1 √	-0.7 √ *	-0.1
Forehead Wrinkles	-0.4 √ *	0	-0.5 √ *	0
Mottled Pigmentation	-1.2 √ *	-0.3 √	-1.7 √ *	-0.9 √
Lack of Skin Brightness	-1.5 √	-1.3 √	-1.8 √	-1.7 √
Overall Photodamage	-0.8 √ *	-0.3 √	-1.0 √ *	-0.5 √
Lack of Elasticity-Sub-Orbital	-0.2 √ *	0	-0.4 √ *	0
Lack of Elasticity-Jaw Line	0	0	-0.2 √ *	0
Lack of Skin Firmness	-0.7 √ *	0	-0.6 √ *	0
Sagging	-0.1	0	-0.1	0

For all parameters, improvement is shown by a decrease in severity (negative direction). (√) indicates significant improvement ($P<0.05$) from baseline. (*) indicates significant improvement ($P<0.05$) of the retinol formulation versus vehicle, from baseline.

better than the vehicle ($P \leq 0.05$) in the improvement of all wrinkle parameters, pigmentation, elasticity, firmness and overall photodamage (Figure 1, Figure 2, Table 2). Particularly prominent were the improvements from baseline in mottled pigmentation by 53%, crow's feet lines by 39% (and crow's feet wrinkles by 16%), cheek wrinkles by 20% and overall photodamage by 18% after eight weeks of retinol applications (Figure 1). The vehicle group showed also a few significant improvements from baseline, but only for some of the surface parameters (Table 2).

Many parameters showed the superiority of retinol as early as week 4 of treatment (Table 2). Additionally, in the dermatologist's overall forced choice, where seven subjects received the split combination of retinol and vehicle, the side treated with retinol was more improved than the opposite side in 100% of the subjects, both at four and at eight weeks.

At the end of the study, a high percentage of the subjects using the retinol moisturizer showed improvement, with 86% showing an improvement in overall photodamage, 100% showing improvement in mottled pigmentation, 64% improving in crow's feet wrinkles and 97% in lines, 75% showing improvement in cheek wrinkles and 100% in skin brightness (Table 3). On the contrary, the vehicle group's population only demonstrated 54% of subjects showing improvement in overall photodamage, 71% showing improvement in mottled pigmentation, 86% improving for crow's feet lines and 100% for skin brightness.

Safety

Both agents were well tolerated, with only a few panelists showing small areas of minor irritation in both cells. Throughout the study, there was no significant increase in erythema, scaliness, and edema as evaluated by the dermatologist, and in self-assessed itching and burning/stinging. No adverse events related to the products occurred in the study.

TABLE 3.
Dermatologist Evaluations (0–9 scale).

	Week 4		Week 8	
	Retinol	Vehicle	Retinol	Vehicle
Cheek Wrinkles	69	0	75	11
Under Eye Wrinkles	33	18	56	25
Crow's Feet Lines	97	82	97	86
Crow's Feet Wrinkles	42	14	64	18
Forehead Wrinkles	42	0	47	3
Mottled Pigmentation	92	32	100	71
Lack of Skin Brightness	100	96	100	100
Overall Photodamage	81	32	86	54
Lack of Elasticity-Sub-Orbital	19	0	36	3
Lack of Elasticity - Jaw Line	0	0	22	0
Lack of Skin Firmness	67	0	58	3
Sagging	6	0	8	0

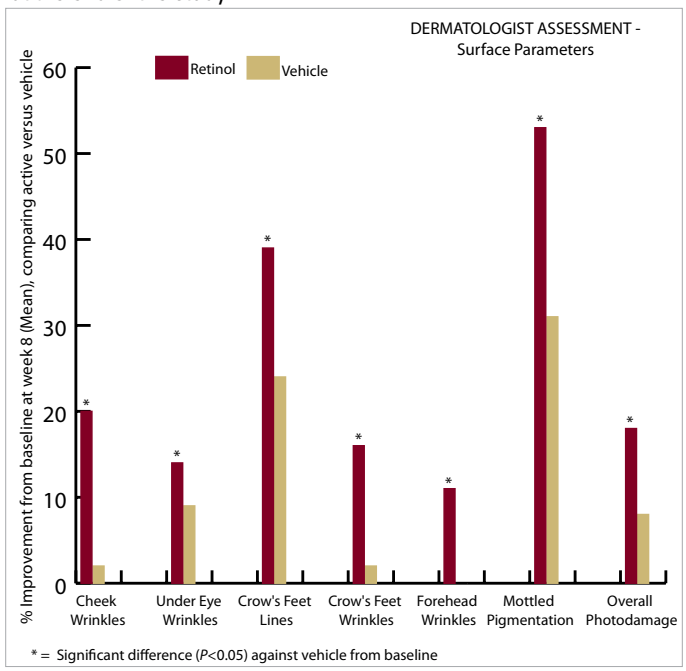
Comparison between active (0.1% retinol moisturizer) and vehicle in percentage of subjects showing at least 1 point improvement from baseline. Data shown in percentages.

DISCUSSION

Retinol is structurally similar to all-*trans*-retinoic acid (RA). It is reported that in keratinocytes, retinol is first converted to retinaldehyde, which is then irreversibly converted to RA.[14] The skin has all the enzymes required to convert retinol to RA and, therefore, it has been suggested that once retinol is applied in stable form to the skin, it can exert all the benefits of RA. Kurlandsky et al. have shown that retinol is metabolized to RA by human keratinocytes.[7]

The effects of RA on photodamaged skin are well documented, both clinically and histologically. Clinical studies have shown that RA improves various parameters of photoaging skin, such as wrinkles, mottled hyperpigmentation, roughness and laxity.[2–6] In vivo human studies have also shown that RA significantly increases epidermal thickness, decreases melanin content,[4,15]

FIGURE 1. Clinical efficacy parameters: Comparison in surface parameters between 0.1% retinol-containing moisturizer and vehicle at the end of the study.



At week 8, the retinol treated skin showed significant improvement ($P<0.05$) against vehicle (*) in all wrinkle parameters, pigmentation and overall photodamage.

FIGURE 2. Improvement in wrinkle appearance.

Patient using the 0.1% retinol moisturizer at baseline (left) and at the end of the study (right). After eight weeks, there is a visible improvement in the appearance of skin wrinkling.

increases deposition of collagen in the upper part of the dermis (papillary dermis)[16,17] and improves the morphology of elastic fibers.[18] These histological effects may contribute to the clinical effacing of wrinkles and improved skin toning.

Notwithstanding these important benefits, the use of RA is reduced by its availability by prescription and by reactions of mild and moderate skin irritation[4,5] in some patients. The proposed use of retinol in ameliorating visible photodamage has two major advantages over RA: it is a cosmetic ingredient, therefore easily available to consumers, and it is far more tolerated by the skin.[9] However, there are currently very few published studies documenting the use of retinol in improving photoaging.[19] Histological in vivo human studies have shown epidermal thickening, decreased levels of MMPs, increased fibroblast growth and increased collagen synthesis after retinol application.[9,10] Clinically, Kafi et al. improved fine wrinkling, roughness and overall severity of intrinsically aged skin in subjects over 80 years old, after 24 weeks of 0.4% retinol, with an average of 1.6 applications weekly.[20]

Here, the authors compared a stabilized 0.1% retinol moisturizer to the vehicle in a double-blind, split-face study on photodamaged women. The results support the efficacy of retinol in photodamage with effects on parameters similar to those seen in RA studies. In fact, after eight weeks of once a day application, the retinol treated side was significantly better than the vehicle side in lines and wrinkles, mottled pigmentation, elasticity, firmness and overall photodamage, with superiority as early as four weeks in some parameters.

In the vehicle group there was also some improvement from baseline, though far less than in the retinol group. It is likely that these effects were promoted by both the moisturizing properties of the vehicle, also containing glycerin, and by the passive lightening of skin during winter months.

This study demonstrates that the stabilized 0.1% retinol moisturizer was efficacious in the improvement of the appearance of photodamage, with very low irritation potentials.

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DISCLOSURES

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