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Efficacy of a Tretinoin/Hydroquinone–Based Skin Health System in the Treatment of Facial Photodamage

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Published studies have confirmed the safety and efficacy of either tretinoin or hydroquinone. This report is the first comparing a tretinoin/hydroquinone–based skin health system (Obagi Nu-Derm® System) with a regimen of tretinoin plus over-the-counter (OTC) products, hydroquinone plus OTC products, and OTC products alone in women with photodamaged skin. Each regimen improved appearance and texture, but the tretinoin/hydroquinone–based system produced the greatest improvement in perioral and periocular fine wrinkles, mottled hyperpigmentation, clarity, sallowness, laxity, and tactile roughness.

Tretinoin and hydroquinone are among the most commonly used topical treatments for photodamaged facial skin. Multiple studies have demonstrated the ability of each of these agents to lighten patches of hyperpigmentation, produce epidermal thickening, induce collagen formation, and generally improve skin appearance and texture.¹⁻⁸ However, given the complex pathophysiology of skin aging and its multiple manifestations (eg, fine lines and wrinkles, hyperpigmentation, loss of elasticity), treatment with therapeutic combinations of tretinoin and hydroquinone that address different components of photodamage may be more effective than either treatment alone.⁹ We report the results of a randomized study comparing a tretinoin/hydroquinone–based skin health system with a regimen of tretinoin plus over-the-

counter (OTC) products, hydroquinone plus OTC products, and OTC products alone in 387 women with photodamaged skin.

METHODS

This randomized study compared 4 treatment strategies (Table 1) over a 24-week period in 387 women aged 38 to 65 years with Fitzpatrick skin type I to IV and investigator-determined moderate photodamage. Perioral, periocular, and facial fine wrinkles; mottled hyperpigmentation; sallowness; laxity; and tactile roughness were evaluated using an 11-point assessment scale (0=no damage; 10=extensive damage). Clarity was evaluated using an 11-point scale (0=dull matte appearance; 10=bright luminous appearance). Per protocol, 50% of the subjects were required to have fine perioral wrinkles. All subjects agreed to avoid tanning beds and direct sun exposure and replace their regular facial skin care regimen with the assigned products during the study period. Subjects were permitted to use color cosmetics.

Exclusion criteria were: a chemical peel within 6 months; use of topical or systemic skin treatments within 8 weeks or isotretinoin within 1 year; current use of a

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TABLE 1

Treatment Groups (N=301)*

Group 1: Tretinoin/Hydroquinone–Based System (Obagi Nu-Derm®)(n=71)**Morning**

- Cleanser I (proprietary)
- Toner (proprietary)
- Cream H (proprietary 4% hydroquinone)
- Day cream G (proprietary α -hydroxy acids)
- Day cream S (proprietary 4% hydroquinone with SPF 15)

Evening

- Cleanser I (proprietary)
- Toner (proprietary)
- Cream H (proprietary 4% hydroquinone)
- Night cream A (0.1% tretinoin)
- Night cream B (proprietary 4% hydroquinone)

Group 2: 0.1% Tretinoin Regimen (n=74)**Morning**

- Cetaphil® Daily Facial Cleanser
- Neutrogena® Healthy Defense® SPF 30 Daily Moisturizer

Evening

- Cetaphil Daily Facial Cleanser
- 0.1% tretinoin cream
- Neutrogena Healthy Defense SPF 30 Daily Moisturizer (as needed)

Group 3: 4% Hydroquinone Regimen (n=79)**Morning**

- Cetaphil Daily Facial Cleanser
- Neutrogena Healthy Defense SPF 30 Daily Moisturizer

Evening

- Cetaphil Daily Facial Cleanser
- 4% hydroquinone cream
- Neutrogena Healthy Defense SPF 30 Daily Moisturizer (as needed)

Group 4: Nonprescription Control Regimen (n=77)**Morning**

- Cetaphil Daily Facial Cleanser
- Neutrogena Healthy Defense SPF 30 Daily Moisturizer

Evening

- Cetaphil Daily Facial Cleanser
- Neutrogena Healthy Defense SPF 30 Daily Moisturizer (as needed)

*Each regimen was applied as described every day for 24 weeks.

†SPF indicates sun protection factor.

photosensitizing drug; history of skin disease; and known allergy to any personal skin care product. Subjects also were excluded if they were pregnant, nursing, or of child-bearing age and not using an accepted method of birth control. Consistent hormone therapy for 3 months before enrollment and for the duration of the study was required.

Subjects were screened and enrolled during an initial physician visit and randomized. Baseline evaluation

occurred 1 week later. Randomization was adjusted by the study's statistician to ensure that the groups were balanced for age (38–48, 49–56, and 57–65 years), Fitzpatrick skin type, presence of perioral fine wrinkles, and skin type (normal, normal to dry, normal to oily, dry, or oily). Adjustments in randomization were not revealed to investigators.

The study was conducted in Carrollton, Texas, and Arlington, Texas. It was approved by the IntegReview

Institutional Review Board and was conducted under the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice and regulatory guidelines. Written informed consent was obtained at the screening visit, after which candidates were evaluated for inclusion.

Procedures

Clinical evaluations were conducted at baseline and after 1, 6, 12, 18, and 24 weeks of treatment. Investigators decided whether clinical assessments, instrumentation, and photography would be done on the right or left side of the face.

Digital photographs were taken at baseline and after 3 and 12 weeks of treatment. A visible, cross-polarized light image was obtained using a Fuji FinePix S2 Pro digital camera with AF Micro Nikon lens (zoom: 70–180 mm). A Canfield head positioner stabilized the head at a 45° angle, turned to the right or left, and a Gertagmacbeth ColorChecker® was photographed at the beginning and the end of each visit. Baseline images were used to ensure exact head positioning and for reference when making efficacy evaluations.

Ultrasound skin density measurements were performed using a DUB20 ultrasound unit. A standard 20-MHz transducer with 15-mm focal distance and 40-dB amplification was used. The axial system resolution was approximately 31 μm ; the usable tissue penetration was estimated to be 6 to 8 mm. A gain setting of approximately 28 dB was used, which enabled optimal overall visualization of the full skin thickness and density at the test sites. Measurements were taken on the lateral orbital (crow's-foot) area. Silicone replicas were taken at baseline and after 12 and 24 weeks of treatment. One replica was taken in the right or left crow's-foot area and another was taken above the right or left upper lip (graded side) to document the degree of periocular and perioral wrinkling. A foam ring was used for aligning the crow's-foot area but not for performing the lip replica. Baseline replicas were used to guide placement.

A 10-patient subgroup from each treatment group had a skin biopsy (2-mm diameter) taken from the right or left cheek according to a predetermined randomization at baseline and on the opposite cheek at week 24. The samples were taken from the cheek approximately 1.5 cm anterior to the center of the ear. An injection of 1% lidocaine was used; and sutures were removed 7 to 10 days later. Skin specimens were analyzed for stratum corneum compaction, granular cell layer thickness, epidermal thickness, spongiosis, dermal and epidermal pigmentation, collagen, elastin, and glycosaminoglycan/extracellular matrix.

Test Material Disposition

Subjects were randomly assigned to treatment at baseline. Usage instructions and the potential for irritation were reviewed. Diaries to document times of product use, journals to record comments, and a calendar of future visits were provided. The study design was not double-blind because the number of test materials varied. However, the investigator/evaluator was blinded to treatment assignments (Table 1). Test material packaging was wrapped with gray tape and covered with a generic label.

Tolerability and Side Effects

Tolerability was assessed during each visit using ratings of objective irritation (ie, scaling, erythema, papular rash, and edema) and by assessment of subjective sensations (ie, burning, stinging, itching, tightness, and tingling). Tolerability was graded according to a 4-point scale (0=none; 3=severe).

Statistical Analysis

Mean values for clinical grading parameters at weeks 1, 6, 12, 18, and 24 and ultrasound measurements at weeks 12 and 24 were compared with mean baseline values using a paired *t* test. Changes from baseline were compared among the 4 test groups using analysis of variance with paired comparisons (Fisher's least significant difference). *P* values of ≤ 0.05 were considered to be statistically significant. Mean percentage of change from baseline and the incidence of improvement were calculated for all attributes at each time point. Silicone replicas taken at baseline and weeks 12 and 24 as well as 24-week biopsy samples were sent to reference laboratories.

RESULTS

Demographics

A total of 387 women were enrolled and randomized, of which 301 completed the study and were included in this analysis. Of the 86 patients who withdrew, 57 left voluntarily, 17 missed their scheduled follow-up, 8 were lost to follow-up, and 4 had medical or compliance issues that precluded completion. Mean age was 52 years. White subjects comprised 91% of the population; Hispanics, 4.7%; Asians, 3.3%; Native Americans, 0.66%; and African Americans, 0.33%.

Investigator Assessments of Efficacy

After 12 and 24 weeks of treatment, improvements in all parameters relative to baseline were evident in all groups (Table 2). However, the mean changes observed in group 1 (tretinoin/hydroquinone-based system plus OTC products) were consistently greater than and statistically superior ($P \leq 0.05$) to those observed with the other

TABLE 2

Mean Changes in Performance Parameters (N=301)*

	Group 1 (n=71) [†]			Group 2 (n=74) [†]			Group 3 (n=79) [†]			Group 4 (n=77) [†]		
	Baseline	Wk 12 [‡]	Wk 24 [‡]	Baseline	Wk 12 [‡]	Wk 24 [‡]	Baseline	Wk 12 [‡]	Wk 24 [‡]	Baseline	Wk 12 [‡]	Wk 24 [‡]
Perioral wrinkles	3.80	2.48	1.56	4.45	3.99	3.85	4.03	3.38	2.97	3.83	3.66	3.69
Periocular wrinkles	5.97	4.24	2.69	6.13	5.47	5.28	5.86	4.91	4.19	5.53	5.22	5.13
Facial fine wrinkles	4.64	3.33	2.17	4.88	4.49	4.40	4.79	4.03	3.58	4.26	4.08	3.99
Mottled hyperpigmentation	5.84	2.98	1.63	5.52	4.53	3.64	5.47	4.25	3.58	5.29	5.03	4.94
Clarity	3.98	6.43	7.70	3.93	5.59	6.21	4.01	6.04	6.76	4.10	5.38	6.02
Sallowness	5.70	3.08	1.77	5.65	4.63	3.80	5.51	4.25	3.55	5.30	5.03	5.05
Laxity	6.03	4.83	3.69	5.96	5.72	5.61	6.04	5.44	5.04	5.80	5.63	5.59
Tactile roughness	4.48	2.20	0.91	4.72	3.08	2.30	4.39	2.53	1.81	4.42	2.67	1.91

*Perioral, periocular, and facial fine wrinkles; mottled hyperpigmentation; sallowness; laxity; and tactile roughness were evaluated according to an 11-point scale (0=no damage; 10=extensive damage). Clarity was evaluated using an 11-point scale (0=dull matte appearance; 10=bright luminous appearance). Study duration was 24 weeks.

[†]Group 1 used tretinoin/hydroquinone-based system (Obagi Nu-Derm®); group 2, 0.1% tretinoin plus nonprescription cleanser and moisturizer; group 3, 4% hydroquinone plus nonprescription cleanser and moisturizer; group 4, nonprescription cleanser and moisturizer.

[‡]Statistically significant change from baseline ($P \leq .05$).

treatment regimens (Table 3). Of particular note were the changes in perioral fine wrinkles, mottled hyperpigmentation, and laxity. After 12 weeks of treatment, improvements in fine lines and wrinkles in group 1 were twice those observed in the other groups. At 24 weeks, group 1 was associated with a 4-fold improvement in perioral and periocular wrinkles, as well as markedly greater improvements in fine lines and laxity compared with the other groups (Figure). Results observed in group 3 (4% hydroquinone plus OTC products) were slightly better than group 2 (0.1% tretinoin plus OTC products); results in groups 1, 2, and 3 were better than those observed in group 4 (control/OTC products alone). The most notable changes in group 4 were improvements in clarity and tactile roughness.

Ultrasound

Skin density measurements were taken at baseline and after 12 and 24 weeks of treatment. Baseline values in groups 1, 2, 3, and 4 were 42.80, 44.86, 43.08, and 42.61, respectively. At the study's conclusion, these

values increased to 53.10, 50.05, 48.53, and 44.42, respectively ($P \leq .05$). Mean increases in density scores were greater in group 1 than in the other groups. Mean density scores were 10.3, 5.19, 5.46, and 1.81 in groups 1, 2, 3, and 4, respectively. There was no difference between groups 2 and 3 (tretinoin and hydroquinone, respectively); however, the increases in these groups were significantly greater than those observed in group 4 (control) ($P = .0001$).

Skin Biopsy Results

At week 24, a statistically significant increase from baseline in cornified layer compaction (0.10 vs 0.50; $P \leq .05$) was observed in group 1, as was a strong trend toward increased granular layer thickness (1.70 vs 2.50). In group 2, a significant decrease in dermal melanophages was observed (0.90 vs 0.27; $P \leq .05$). The same change was observed in group 3, along with a significant increase in granular layer thickness (1.40 vs 2.30; $P \leq .05$). No significant changes were observed in group 4. Group 3 had the greatest granular layer thickness at 24 weeks

TABLE 3

Comparison of Performance Parameter Changes From Baseline (N=301)*

	Group 1, (n=71) [†]		Group 2 (n=74) [†]		Group 3 (n=79) [†]		Group 4 (n=77) [†]		P
Wk 12	Δ	%	Δ	%	Δ	%	Δ	%	
Perioral fine wrinkles	-1.32	-35	-0.46	-10	-0.65	-16	-0.17	-4	.0001
Periocular fine wrinkles	-1.73	-29	-0.66	-11	-0.95	-16	-0.31	-6	.0001
Facial fine wrinkles	-1.31	-28	-0.39	-8	-0.76	-16	-0.18	-4	.0001
Mottled hyperpigmentation	-2.86	-49	-0.99	-18	-1.22	-22	-0.26	-5	.0001
Clarity	2.45	62	1.66	42	2.04	51	1.28	31	.0001
Sallowness	-2.63	-46	-1.02	-18	-1.27	-23	-0.27	-5	.0001
Laxity	-1.20	-20	-0.25	-4	-0.60	-10	-0.17	-3	.0001
Tactile roughness (week 18)	-3.14	-51	-2.10	-35	-2.36	-42	1.75	-40	.0005
Wk 24									
Perioral fine wrinkles	-2.24	-59	-0.61	-13	-1.06	-26	-0.15	-4	.0001
Periocular fine wrinkles	-3.27	-55	-0.83	-14	-1.66	-28	-0.40	-7	.0001
Facial fine wrinkles (week 18)	-2.04	-53	-0.50	-10	-1.06	-25	-0.21	-6	.0001
Mottled hyperpigmentation	-4.21	-72	-1.88	-34	-1.88	-35	-0.35	-7	.0001
Clarity	3.69	93	2.28	58	2.76	69	1.92	47	.0001
Sallowness	-3.93	-69	-1.85	-33	-1.97	-36	-0.25	-5	.0001
Laxity	-2.34	-39	-0.36	-6	-1.00	-17	-0.21	-4	.0001
Tactile roughness	-3.57	-80	-2.42	-51	-2.58	-59	-2.51	-57	.0001

*Values were determined using a paired *t* test. Study duration was 24 weeks.

[†]Group 1 used tretinoin/hydroquinone-based system (Obagi Nu-Derm®); group 2, 0.1% tretinoin plus nonprescription cleanser and moisturizer; group 3, 4% hydroquinone plus nonprescription cleanser and moisturizer; group 4, nonprescription cleanser and moisturizer.

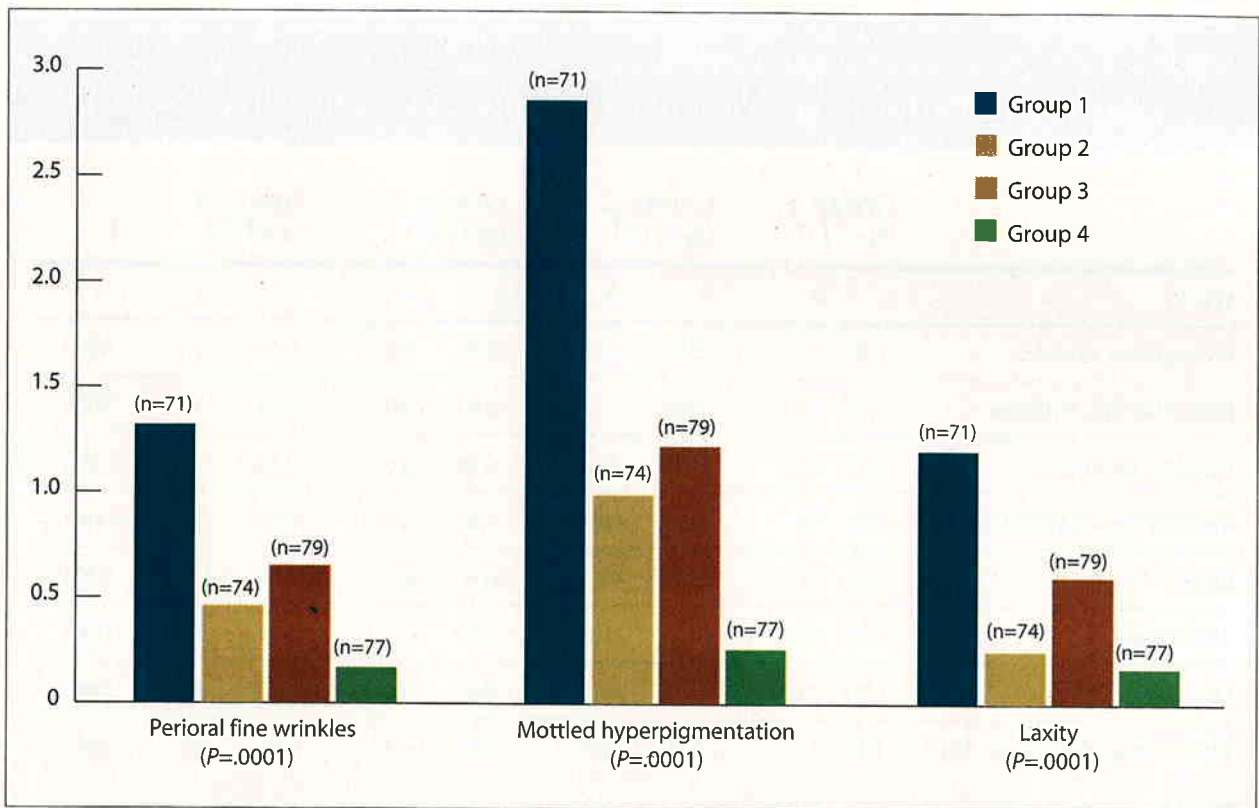
(0.90 versus 0.70 in group 1, 0.09 in group 2; and 0.14 in group 4; $P \leq .05$).

Irritation

Subjects in groups 1 and 3 tended to experience increased rates of erythema, scaling, burning, stinging, and itching ($P \leq .05$) relative to baseline at 12 and 24 weeks. Subjects in group 2 had increased skin tightness at weeks 12 and

24. No irritation was reported in group 4. Changes in irritation from baseline tended to be highest in group 1 (Table 4). Most irritation peaked after the first week of treatment and then began to resolve.

Two adverse events were reported. One subject in group 2 reported erythema and swelling around the eyes. She discontinued treatment for 1 week, received an injection (unknown) from her primary care physician, and



Mean changes from baseline at week 24 (N=301). Group 1 used tretinoin/hydroquinone-based system (Obagi Nu-Derm®); group 2, 0.1% tretinoin plus nonprescription cleanser and moisturizer; group 3, 4% hydroquinone plus nonprescription cleanser and moisturizer; group 4, nonprescription cleanser and moisturizer. Study duration was 24 weeks.

reported no additional events. A subject in group 4 developed a scaly erythematous plaque near the left corner of the mouth that lasted 1 month. She was prescribed minocycline 100 mg once daily; the lesion resolved by follow-up visit at week 12.

COMMENT

Combination therapy with tretinoin and hydroquinone, supplemented with OTC cleansers, moisturizers, and sunscreens, is a standard approach to rejuvenating photodamaged skin. However, given the complex pathophysiology of skin aging and the various manifestations of photodamage, ranging from fine lines and wrinkles to hyperpigmentation and solar lentigines, investigators have begun combining multiple therapeutic regimens. Several trials have indicated that combinations of retinol/hydroquinone,¹⁰ tretinoin/hydroquinone/fluocinolone,¹¹ hydroquinone/salicylic acid,¹² and mequinol/tretinoin¹³ are safe, effective, and in some cases superior to monotherapy.

Our results support the use of combination therapy for the treatment of photodamaged skin. The combination system of 4% hydroquinone and 0.1% tretinoin plus

OTC cleanser, toner, exfoliant, and sunblock evaluated in this study produced superior results to those of the more standard regimens of tretinoin or hydroquinone plus OTC products. The combination system increased epidermal thickness and lightened patches of hyperpigmentation. Compared with other treatments, it produced significantly greater improvements in perioral fine wrinkles, laxity, and mottled hyperpigmentation ($P \leq .05$) after 12 and 24 weeks of treatment.

The skin health system evaluated in this study is a collection of proprietary agents organized by composition, time, and sequence of application to maximize their individual properties. This system combines 2 prescription, or active, components with 3 OTC products. Tretinoin, associated with reversing photodamage, increasing collagen synthesis, improving overall appearance, and slowing the photoaging process,^{1,4,7,8} is a key active drug in the combination system. Hydroquinone, considered the gold standard of bleaching agents, is capable of targeting hyperpigmented regions of skin without significantly affecting the pigmentation of surrounding areas thereby correcting melasma, another component of photodamage.¹⁴

TABLE 4

Comparison of Mean Changes in Irritation Scores From Baseline (N=301)*

	Group 1 [†] (n=71)	Group 2 [†] (n=74)	Group 3 [†] (n=79)	Group 4 [†] (n=77)	P
Wk 12					
Erythema	0.72	0.10	0.15	-0.12	.0001
Scaling	0.48	0.01	0.25	0.01	.0001
Burning	0.37	0.04	0.33	0.01	.0001
Stinging	0.18	0.04	0.22	-0.01	.0001
Itching	0.15	-0.03	0.16	-0.01	.0013
Tightness	-0.08	-0.32	0.02	-0.12	.0368
Wk 24					
Erythema	0.54	0.07	0.34	-0.02	.0001
Scaling	0.36	-0.03	0.41	-0.01	.0001
Burning	0.26	0.04	0.25	0.04	.0010
Stinging	0.23	0.01	0.22	0.00	.0001
Itching	0.08	0.07	0.21	-0.01	.0232

* Tolerability was graded according to a 4-point scale (0=none; 3=severe).

[†]Group 1 used tretinoin/hydroquinone-based system (Obagi Nu-Derm®); group 2, 0.1% tretinoin plus nonprescription cleanser and moisturizer; group 3, 4% hydroquinone plus nonprescription cleanser and moisturizer; group 4, nonprescription cleanser and moisturizer. Study duration was 24 weeks.

In the study, the delivery of tretinoin and hydroquinone may have been facilitated by the cleanser, toner, and exfoliant vehicle. Cleansers remove sebum lipids, as well as desquamated cells and foreign materials, from the skin. Toner removes excess cleansing residue and lowers the pH of the skin. Exfoliants remove superficial lesions of the epidermis, producing sloughing of the stratum corneum. Collectively, these agents may help improve the permeability of the epidermis and prepare the skin for subsequent application of tretinoin and hydroquinone.

CONCLUSION

The skin health system evaluated in this study significantly reduced perioral and periocular fine wrinkles, as well as mottled hyperpigmentation ($P \leq .05$), and

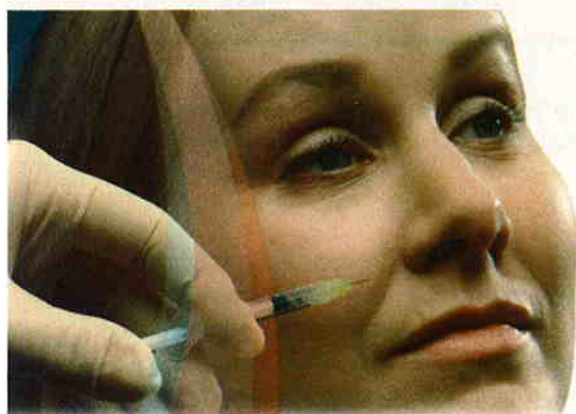
improved clarity, sallowness, laxity, and tactile roughness. Combination therapy was associated with increased dermal density, cornified layer compaction, and granular layer thickness. These features may result from the specific, sequential, combined activities of cleanser, toner, exfoliant, tretinoin, hydroquinone, and sunblock applied in a systematic dosed manner.

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