Use of Topical Retinoids for the Treatment of Nonmalignant Photodamage in Clinical Practice, Part 2

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Photodamage is primarily an aesthetic issue for patients but also can lead to malignant skin changes. Moreover, clinical and histologic evidence show that the skin changes attributable to photodamage are not necessarily irreversible, and there are now a number of nonsurgical approaches to this problem.

Topical therapies are simple to use but require proper adherence to treatment for some months before measurable improvement is seen. Of all topical therapies available to date, the retinoids can be prescribed with most confidence, as the clinical evidence underpinning their use far outweighs that available for other compounds such as antioxidants and α-hydroxy acids. Retinoid therapy consistently has been shown to attenuate and reverse the signs of photodamage, including coarse wrinkling, in controlled trials. Tretinoin has been the most extensively studied retinoid in trials of up to 4 years' duration, and a systematic analysis demonstrated that the evidence of benefit for tretinoin at concentrations of at least 0.02% is greater than for other agents. Moreover, the clinical changes achieved with tretinoin are accompanied by histologic evidence of benefit. Among the tretinoin formulations available in the United States, only Renova (tretinoin 0.02%) is indicated for use in photodamage. The main drawback of retinoid use is local irritation and erythema, but this is manageable in most patients. Overall, patients with realistic expectations who receive appropriately individualized therapy can achieve good results with topical retinoid therapy. All patients should receive thorough education and information about how to use retinoid therapy, sun avoidance, appropriate skin care during use, and the likely outcomes of treatment.

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Over the course of a lifetime, skin is exposed to a range of unavoidable and avoidable factors that result in visible signs of damage, such as wrinkles, irregular pigmentation, atrophy, or keratosis.[1] For some individuals, these signs of skin aging can negatively impact self-esteem, relationships, and employment opportunities.[2] Therefore, it is not surprising that the combination of an aging population and increasing emphasis on youthful looks has led to a growing number of dermatologic consultations for the treatment of age-related and sun-related skin damage.

Although previously it was thought that the changes associated with intrinsic or extrinsic skin aging were irreversible, clinical advances in recent decades have indicated that this is not necessarily the case. Various topical therapies and in-office procedures are now available to alleviate age-related and sun-related skin damage, and among the topical therapies, there is most evidence to support a benefit for topical retinoids.[3] In a previous article,[4] we have described the mechanisms by which photodamage occurs, the treatment options available, and the mechanism by which retinoids reduce the severity of signs of photodamage. In this article, we use an illustrative case study to examine more closely the use of topical retinoids in the treatment of photodamage in clinical practice and describe the evidence for the benefit of these agents in the context of other topical therapies and the patient education required for the successful use of retinoids in clinical practice.

TOPICAL RETINOIDS IN CLINICAL PRACTICE

A number of topical retinoids are available in the United States, mostly for the treatment of acne (Table 1). However, only 2 are specifically indicated for the mitigation of signs of photodamage: tretinoin cream 0.02% (Renova) and tazarotene cream 0.1% (Avage). All act to improve the appearance of photodamaged skin via effects on cellular differentiation and growth, immune modulation, and cell-surface alterations.[5]

CASE REPORT

A 66-year-old white woman presented with concerns over her appearance. She had noticed an increase in the amount of discoloration, wrinkles, and sagging on her face. Dermatologic examination revealed persistent rhytides at rest, moderate elastosis, and several lentigines, telangiectasias, and actinic keratoses on her face (Figure 1A). Her medical history was characterized by hypertension, hyperlipidemia, and hypothyroidism, and she had no known drug allergies. Clinical treatment options discussed with the patient included topical treatments, chemical peels, and light and laser treatments. Topical treatment was selected, which included a cleanser, a moisturizer with sunscreen in the morning, and tretinoin cream 0.02% (Renova) at night. After 13 weeks, the patient's own evaluation showed a significant improvement in fine lines, tone, and texture of her face and a decrease in lentigines (Figure 1B). The tretinoin cream was well tolerated, and the patient reported that she was very satisfied with the results.

EVIDENCE FROM CLINICAL TRIALS

Tretinoin

Despite the large number of retinoid compounds now available, only a small number have been studied in detail in individuals with photodamaged skin. The best documented retinoid compound is tretinoin, and in 1986 the first definitive report on the beneficial effects of this agent in photoaging was published.[6] In this vehicle-controlled study in which tretinoin cream 0.05% was applied daily to facial and forearm skin of white participants, marked clinical and histologic changes indicated partial reversal of photodamage.[6]

The effects of tretinoin at various concentrations have been extensively studied. A recent comprehensive meta-analysis of 12 studies compared this topical agent with placebo.[3] Overall assessment of facial photodamage (investigator assessment) across these trials showed that topical formulations with concentrations of tretinoin ranging from 0.02% to 0.1% used for up to 48 weeks were significantly better than placebo ($P<.05$); lower concentrations had no significant effect overall.[3] In this meta-analysis, the 0.02% concentration (as was used in our clinical case) produced significant improvements in all assessed parameters ($P<.05$), with the exception of mottled hyperpigmentation ($P=.17$)(Figure 2).[3]

Although not approved for treatment of photodamage in the United States, other concentrations of tretinoin have been studied. The Cochrane collaboration demonstrated that only concentrations of tretinoin 0.02% and higher have proved to be significantly more effective than placebo ($P<.05$).[3] In randomized, placebo-controlled, double-blind studies, tretinoin cream 0.02% (Renova) significantly reduced all signs of photodamage ($P<.05$) except tactile roughness and laxity compared with vehicle over 24 weeks in 360 participants (predominantly women) with moderate to severe photodamage.[7] At concentrations shown to have a clinical benefit, tretinoin also has been demonstrated to have a positive histologic impact on photodamaged skin, including thicker epidermal layers, reduced melanin content, more compact stratum corneum, and increased levels of collagen and procollagen I.[8-11] Since there is a dose-dependent effect of tretinoin for both efficacy and irritation,[3] the 0.02% concentration represents the best balance of efficacy and tolerability.

Double-blind and vehicle-controlled trials have shown benefit of topical tretinoin at concentrations ranging from 0.05% to 0.1% for periods of up to 4 years. For example, tretinoin cream 0.1% for 4 months improved fine wrinkles ($P<.0001$) and to a lesser extent coarse wrinkles ($P<.01$) and skin texture ($P<.02$), and induced a pink hue in the skin (rosy glow) in a study of

Table 1

Topical Retinoid Agents Available in the United States

Product	Brand	Formulation/Concentration	Indication
Tretinoin	Altinac	cream 0.05% cream 0.025% gel 0.025%	Acne vulgaris
	Atralin	gel 0.05%	Acne vulgaris
	Avita	gel 0.025%	Acne vulgaris
	Renova	cream 0.02%	Palliation of fine facial wrinkles in combination with skin care and sun protection
	Retin-A Micro	gel 0.1% gel 0.04%	Acne vulgaris
	Retin-A	cream 0.1% cream 0.05% cream 0.025% gel 0.025% gel 0.01% liquid 0.05%	Acne vulgaris
	Tretin-X	cream 0.1% cream 0.05% cream 0.025% gel 0.025% gel 0.01%	Acne vulgaris
Tazarotene	Avage	cream 0.1%	Palliation of photodamage in combination with skin care and sun protection
	Tazorac	cream 0.1% cream 0.05% gel 0.1% gel 0.05%	Plaque psoriasis or acne vulgaris Plaque psoriasis Stable plaque psoriasis with ≤20% body surface area involvement or mild to moderate facial acne Stable plaque psoriasis with ≤20% body surface area involvement
Adapalene	Differin	cream 0.1% gel 0.1% gel 0.3%	Acne vulgaris Acne vulgaris Acne vulgaris in individuals aged ≥12 y

30 white participants.[12] The improvement in skin hue is concordant with the increased skin brightness seen in our patient reported herein. Fourteen of 15 participants who applied tretinoin to the face showed reduced photoaging, whereas none of the vehicle-treated participants' faces showed improvement ($P<.0001$). Statistically significant histologic changes (including epidermal thickness and stratum corneum compaction) were seen in forearm skin

Table 2

Practical Points for Retinoid Use[5,31-34]

Issue	Recommendations/Precautions
Application	Apply lightly in evening before bedtime to clean, dry skin, ≥20–30 min after washing
	Cover entire affected area lightly and evenly
	Transitory warmth or stinging may be felt
	Avoid sensitive areas such as eyes, nose, mouth
	Avoid spot treatment; can reduce efficacy, lead to blotchiness
	Discontinue in the event of sensitivity, irritation, or systemic reactions
Sunscreen/moisturizer	Moisturizers and broad-spectrum sunscreens (SPF ≥15) recommended to decrease irritation and counteract partial loss of sun protection due to retinoid use
	Apply moisturizer in morning after washing off retinoid
	Apply sunscreen even on cloudy days, avoid peak sunlight hours (10:00 AM–4:00 PM), and do not use sunbeds
Cosmetics	May be used, but only after cleansing
	Avoid agents with irritant effects (eg, keratolytics, abrasives, astringents, drying agents, products containing high proportions of alcohol, spices, or lime)
Contraindications/precautions	Pregnancy or risk for pregnancy
	Sunburn or eczema/other chronic skin conditions
	Photosensitivity
	Concurrent use of photosensitizing drugs (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides)

Abbreviation: SPF, sun protection factor.

treated with tretinoin compared with vehicle ($P<.001$).[12] Double-blind trials of tretinoin cream 0.05% showed significant improvements in wrinkling and skin structure over periods of 12 to 24 weeks in participants with evidence of photoaging ($P<.05$ versus vehicle),[13,14] and a double-blind trial of tretinoin cream 0.025% or 0.1% showed significant improvements at 48 weeks in 99 participants with photoaged skin ($P<.001$).[15]

Topical tretinoin therapy 0.05% or 0.1% also has been evaluated in long-term studies.[16,17] Most improvement seems to be observed over the first 6 to 12 months. Ellis and colleagues[16] invited participants who had completed a 4-month double-blind study to continue treatment with tretinoin 0.05% or 0.1% on an open-label basis for a total of 10 (n=21) or 22 (n=16) months. They noted that improvements gained during the initial double-blind trial were maintained, with a 71% decrease in number of discrete facial lentigines.[16] In another study in which tretinoin 0.05% was used for up to 4 years in 27 participants, improvements in skin histology and structure gained during the first 12 months of therapy were maintained or improved.[17]

Other Topical Retinoids

The efficacy of topical isotretinoin in participants with photodamaged skin has been shown in 2 large double-blind studies of a total of 1576 individuals.[18,19] Significant improvements in overall appearance, wrinkling, pigmentation, and texture ($P\leq.02$),[18,19] together with histologic improvement in epidermal thickness ($P<.01$),[19] were noted in participants receiving treatment for 36 weeks, mostly with isotretinoin cream 0.1% (participants used cream 0.05% for the first 12 weeks in the study by Sendagorta et al[18]). No topical formulation of isotretinoin is available in the United States.

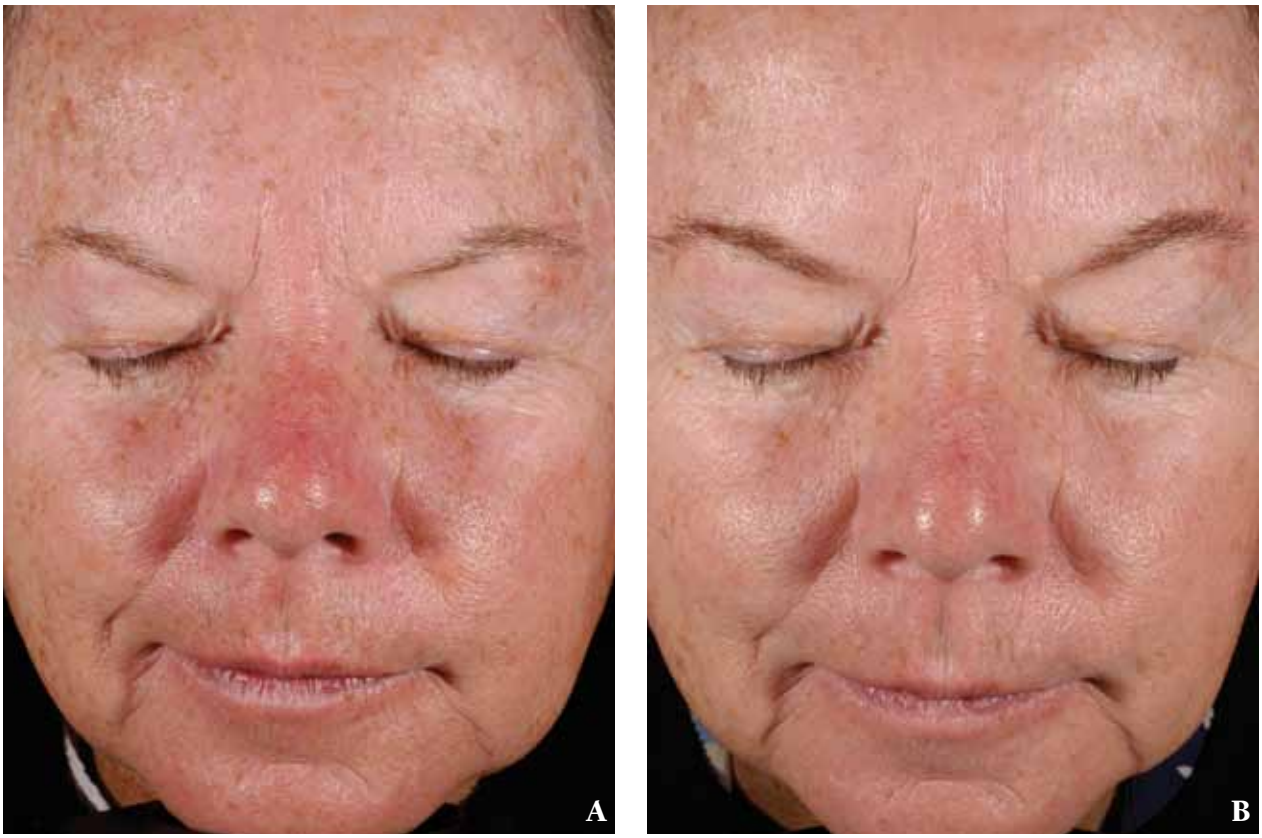

Figure 1. Appearance of the skin and severity of photodamage before (A) and after (B) 13 weeks of treatment with tretinoin cream 0.02% (Renova) in a 66-year-old white woman.

Tazarotene has also been shown to be useful in persons with photodamaged skin, with one 24-week study showing similar improvements in wrinkling and hyperpigmentation for tazarotene cream 0.1% and tretinoin cream 0.05%.[20] The longest reported treatment study with tazarotene is a 24-week double-blind trial with a 28-week open-label extension in 563 participants.[21] Tazarotene 0.1% cream or nonmedicated vehicle cream was applied to the face once daily during the double-blind phase, and all participants received active cream during the extension.[21] During the double-blind phase, a significantly greater percentage of participants using tazarotene than vehicle achieved treatment success (≥50% global improvement) and improvement of at least 1 grade in signs of photodamage (including fine and coarse wrinkling, mottled hyperpigmentation, and roughness) and in the overall integrated assessment of photodamage ($P \leq .05$). Open-label treatment resulted in additional clinical improvement.

Even less is known about the effects of adapalene for photodamage. However, a double-blind study of 90 participants showed significant improvements relative to placebo in solar lentigines and actinic keratoses with adapalene 0.1% or 0.3% gel for up to 9 months ($P < .05$).[22]

RETINOIDS IN COSMECEUTICAL PREPARATIONS

A number of cosmeceuticals contain retinoids, including retinaldehyde, retinyl esters, and retinols, although the data to support their use are limited. Retinaldehyde is biologically active in the skin,[23] but few studies have investigated its efficacy for amelioration of photodamage. However, optical profilometry was used in a study in 125 participants (40 treated with tretinoin cream 0.05%, 40 with retinaldehyde cream 0.05%, and 45 with placebo vehicle) to show significant reduction of wrinkling and skin roughness with both active treatments after 18 weeks ($P < .01$).[24] The benefits were maintained at week 44, although they were less pronounced than at week 18.

In a small comparative study (n=9), a cosmetic antiaging cream containing 6% total active complex (including retinyl palmitate <0.2%, along with lipopentapeptide, white lupin peptides, and antioxidants) was found to have significant beneficial effects on fibrillin ($P < .01$) and procollagen I levels ($P < .05$) in photoaged skin, similar to the effects achieved with topical tretinoin (Retin-A).[25] However, a larger double-blind, placebo-controlled trial was unable to demonstrate any significant difference between a retinyl propionate cream or placebo in signs or

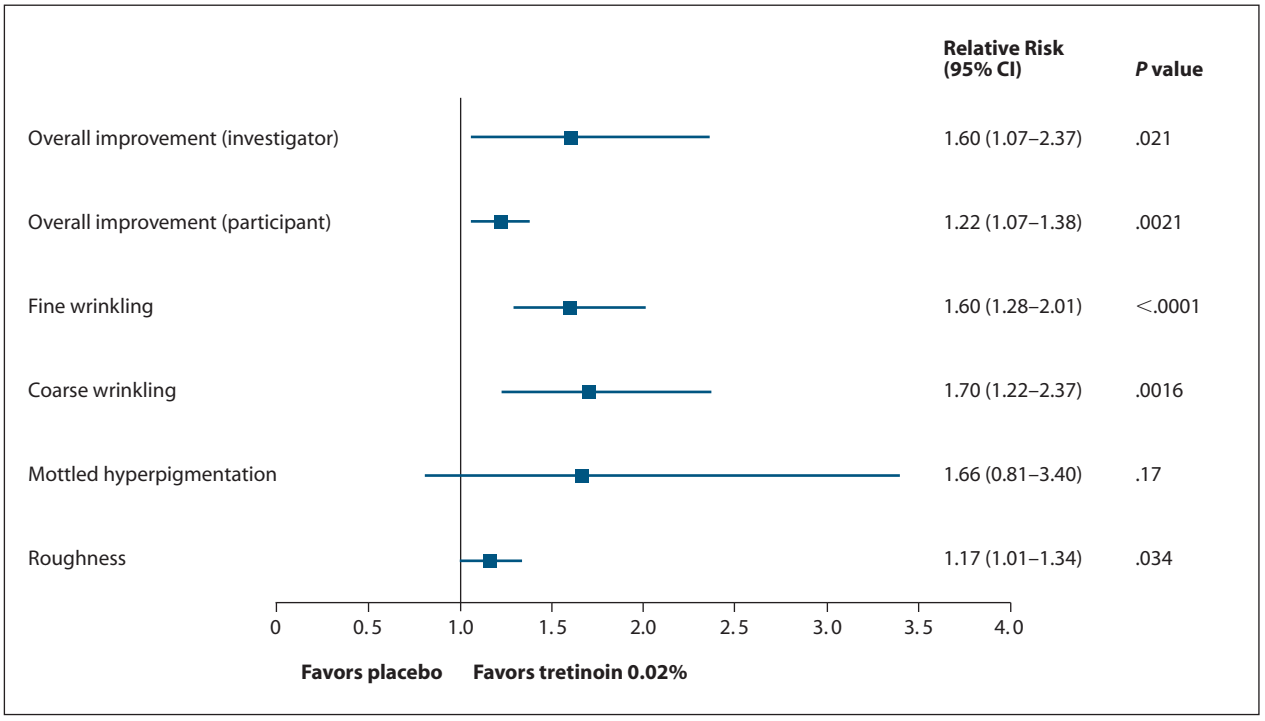

Figure 2. Relative risk with 95% confidence interval (CI) of various end points in a meta-analysis of randomized trials with tretinoin 0.02% for the treatment of photodamage. Data from Samuel et al.[3]

symptoms of photoaging after 48 weeks of treatment.[26] Of note, however, is that actinic keratoses virtually disappeared in the 4 participants (of 34) who were receiving active treatment and had such lesions at baseline.[26]

Topical retinol 0.4% in a vehicle composed of polysorbate and moisturizer has been shown to significantly mitigate fine wrinkling and tactile roughness associated with intrinsic aging ($P<.001$) in a 24-week study of elderly women residing at a rest home (mean age, 87 years).[27] In this study, the participants applied active cream to the inside of their upper arms (an area unaffected by photodamage) and vehicle to the other arm. The improvements in fine wrinkling were observed as early as week 4. Biopsy data showed a significant increase in glycosaminoglycan expression ($P=.02$) and procollagen I immunostaining ($P=.049$) after 24 weeks, suggesting that the wrinkle effacement may have been mediated by upregulation of collagen and glycosaminoglycan synthesis.[27] Although these results are promising, it should be noted that they were not demonstrated in photoaged skin, which shares some of the features of intrinsically aged skin but also is characterized by deep wrinkling, areas of hypertrophy (keratosis), and lentigines.[4] A cosmetic preparation containing retinol, lactose, and glycolic acid was compared with placebo in a randomized, double-blind, split-face study in 40 fair skinned women aged 30 to 50 years with moderate to severe photoaging.[28] The cosmetic was significantly better than placebo at reducing the total surface area with wrinkles, depth of wrinkles, and skin roughness at 12 weeks ($P<.05$) and in improving skin moisturization at 2, 4, and 8 weeks.[28] However, skin microrelief on biopsy specimens and viscoelastic properties were similar in the active-treated and placebo-treated areas. The percentage of participants reporting improvement in response to active treatment was higher than with placebo treatment, but these differences did not reach statistical significance.[28]

Stabilized retinol also has been included in a cream with hydroquinone 4% and examined in participants with pigmentary changes. Two strengths of retinol (0.15% and 0.3%) have been tested with this concentration of hydroquinone. In a randomized, double-blind study of 40 women with mild to moderate periocular fine lines and dyspigmentation, the combination including retinol 0.3% was significantly more effective than treti-noin cream 0.05% for reducing the severity of fine lines ($P\leq.04$) and tactile roughness ($P=.02$) and the extent and severity of pigmentary changes ($P=.001$) during 16 weeks.[29] However, some of the benefits of the retinol plus hydroquinone cream (eg, roughness improvement and appearance of fine lines) may be partly

attributable to the moisturizing effect of the product's vehicle. Retinol 0.3% plus hydroquinone also was better tolerated than tretinoin, with significantly less erythema, scaling, and dryness ($P<.02$).[29] In a separate open-label study, a cream containing hydroquinone 4% plus retinol 0.15%, along with antioxidants, proved to be effective in reducing the number, size, and darkness of hyperpigmented lesions and overall disease severity ($P\leq.05$).[30] However, participants in this study had melasma or postinflammatory hyperpigmentation,[30] so the efficacy of creams containing this dose of retinol plus hydroquinone in participants with photodamage is not established.

PRACTICAL ISSUES

Treatment with topical retinoids should be individualized, with factors such as patient age, skin type, degree of photodamage, and presence of other skin conditions taken into consideration. Therapy should start with a low concentration to minimize irritation and erythema, and formulations should be applied in the evening to clean, dry skin after washing. The patient should also be told to expect a temporary irritation phase with peeling that usually lasts around 6 weeks. A 1-night or 2-night break from treatment can be prescribed if the irritation is excessively bothersome. Concurrent use of moisturizers and sunscreen is essential. In Table 2, other points and precautions are summarized.[5,31,32]

Patients should be told that treatment should reverse some but not all signs of photodamage, with greatest benefit on the mitigation of fine wrinkles, and that some time on treatment will be needed before improvement is visible. Maximum effects will be seen after 6 to 12 months, although the duration of benefit is not known. Topical retinoids also have a prophylactic effect against photoaging, and maintenance application 2 or 3 times per week is recommended to prolong the effects of initial therapy. Patients should also be warned that persistence of harmful behaviors such as smoking and excessive or aggressive washing or scrubbing of the skin will negate some of the benefits of treatment.

SUMMARY

Although a number of topical therapies are now available for the treatment of photodamaged skin, many remain unproven or are supported by only limited clinical evidence. The greatest weight of evidence is available for topical retinoids, and in particular tretinoin at concentrations of 0.02% and higher. Among available tretinoin formulations, only Renova (tretinoin cream 0.02%) is specifically approved for use in the alleviation of photodamage and is supported by an extensive range of controlled clinical studies in large numbers of participants, as well as histologic confirmation of benefit. Appropriate individualization of therapy and effective counseling, together with high levels of adherence and realistic expectations on the part of the patient are essential, but clinical data show that correct use with effective follow-up can be very successful.

***Acknowledgement*—**Editorial services provided by Catherine Rees and Medisys Health Communications, LLC.

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