Topical Retinoids: the Misplaced Key to Treating Photodamaged Skin

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Compelling clinical data support the efficacy and safety of topical retinoids in the treatment of photodamaged skin. Despite these data, concerns are frequently voiced regarding retinoid tolerability in the management of patients with photodamaged skin, which is frequently self-described as sensitive. Studies of topical retinoids in combination with hydroquinone 4% and clindamycin 1%/benzoyl peroxide 5% demonstrate that retinoids are compatible in such combination regimens and enhance results with no significant increase in irritation. Retinoids are also safe and effective in combination with procedural therapies for photodamaged skin and may decrease postprocedural erythema. In a comparative study, tazarotene 0.1% cream led to more rapid improvement in photodamaged skin than tretinoin 0.05% emollient cream. Retinoid side effects can be controlled with a nonsteroidal anti-inflammatory cream, which may also enhance compliance.

With the aging of the world population, searching for treatments of photodamaged and intrinsically aged skin has become the Holy Grail of cosmeceutical, pharmacologic, and device research. Both medical literature and the media are quick to announce the newest and best treatments, particularly those that are purported to "turn back the clock" on photodamaged or aging skin. Women aged 30 to 70 years are the target population for such treatments, but men are becoming increasingly interested in treatments for photoaging.

Dermatologists have the Herculean task of sorting through the myriad of treatments available to offer safe, effective, and affordable management of photoaging. The task is daunting because of the volume of largely unsubstantiated claims with which patients are bombarded. Eager to have their appearance restored, patients are easily misled by apparently compelling in vitro studies that have few quality data. These studies are small, frequently uncontrolled, or bolstered by the claims of so-called experts.

However, compelling clinical data support the efficacy and safety of one class of topical agents—retinoids and their analogues—for the treatment of both visible and invisible effects of photodamage. Tretinoin, the first topical retinoid, was approved by the US Food and Drug Administration (FDA) in 1971 for the treatment of acne. Soon afterward, tretinoin began to be used off-label for managing the cutaneous signs of photoaging. Tretinoin in varying concentrations and formulations was later introduced; also introduced were retinoid analogues and retinoidlike molecules, including adapalene (1996) and tazarotene (1997), which were structurally different from retinoids but displayed similar activity. In 2003, an emollient-based 0.05% retinoic acid cream was approved specifically for the treatment of photodamaged skin. At

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TABLE 1

Treatment-Related Adverse Events of Tazarotene 0.1% Cream Alone Versus Tazarotene 0.1% Cream Plus Clindamycin 1%/Benzoyl Peroxide 5% Gel (N=121)[12]

Adverse Event	Tazarotene, n (%) (n=61)	Tazarotene Plus Clindamycin/Benzoyl Peroxide, n (%) (n=60)
Peeling	11 (18)	6 (10)
Burning	8 (13)	8 (13)
Redness/erythema	7 (11)	8 (13)
Dryness	7 (11)	5 (8)
Facial discomfort	2 (3)	3 (5)
Itching/pruritus	2 (3)	3 (5)
Oiliness	1 (2)	1 (2)
Facial irritation	0 (0)	1 (2)

present, only 3 retinoids or synthetic retinoid analogues are FDA approved for managing photodamaged skin: tazarotene 0.1% cream, tretinoin 0.05% emollient cream, and tretinoin 0.02% emollient cream.

Tazarotene 0.1% cream is approved as an adjunctive agent for the reduction of signs of facial photodamage, including fine wrinkling, mottled hyperpigmentation, and benign lentigines. Tretinoin 0.05% emollient cream is approved as adjunctive treatment for mitigating fine wrinkles, mottled hyperpigmentation, and tactile roughness of the facial skin in patients who do not achieve symptom palliation from a comprehensive regimen of skin care and sun avoidance. Tretinoin 0.02% emollient cream is approved only as an adjunctive agent for mitigating fine wrinkles, not hyperpigmentation or tactile roughness. The efficacy of all 3 agents in managing photodamaged skin is supported by the results of multicenter, double-blind, randomized, vehicle-controlled trials.[1-4]

RATIONALE FOR THE EFFICACY OF TOPICAL RETINOIDS IN MANAGING SYMPTOMS OF PHOTODAMAGE

Clinically, photoaging comprises wrinkles, laxity, dyspigmentation, tactile roughness, telangiectases, actinic keratoses, and skin cancers. Even more significant changes can be demonstrated histologically, including solar elastosis and collagen degeneration. The reversal and prevention of these structural changes accounts for most of the visible benefits of retinoid therapy.[5] Another important benefit of retinoids in treating photodamaged skin is their ability to restore actinically depleted Langerhans cell populations and correct dysplastic changes.[6,7]

The cosmetic benefits of retinoids are foremost in the minds of many patients and physicians, but in fact this class of drugs influences a diversity of biological processes including morphogenesis, epithelial differentiation, and carcinogenesis.[5] Histologic studies have shown that tretinoin increases epidermal and granular layer thickness, causes stratum corneum compaction, decreases melanin content,[3,8,9] increases dermal collagen production, and stimulates angiogenesis.[10] On the molecular level, results from a study by Fisher et al[11] demonstrated that retinoids prevent full induction of c-Jun expression and thus inhibit the induction of matrix metalloproteinases, which degrade collagen in human skin.

RETINOID TOLERABILITY AND COMPATIBILITY IN COMBINATION REGIMENS

Retinoids are an ideal choice for reversing and preventing many of the changes that constitute the aged-skin phenotype. Nevertheless, concerns are frequently voiced regarding retinoid dermatitis and the possibility of skin irritation in patients with photodamaged skin (frequently

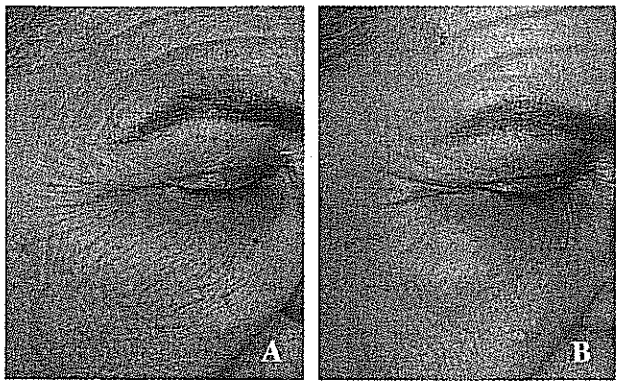

Figure 1. Patient with facial photodamage at baseline (A) and 24 weeks posttreatment with tretinoin 0.1% cream (B).

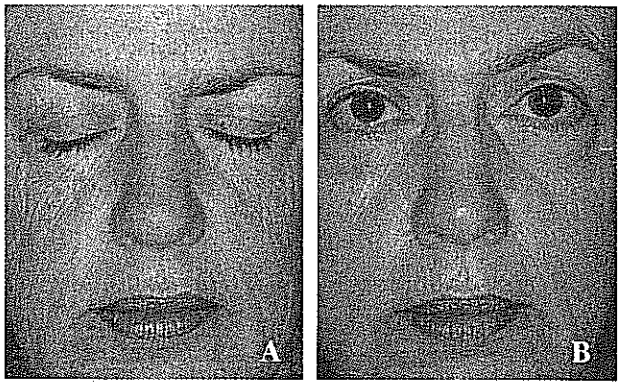

Figure 2. Patient with facial photodamage at baseline (A) and 24 weeks posttreatment with tretinoin 0.1% cream (B).

self-described as sensitive skin). Studies that have been conducted in patients with acne should allay the dermatologist's concerns regarding the use of topical retinoids, both alone and in combination with other topical agents, in managing other inflammatory skin conditions, including photodamage.

In a 12-week, double-blind, randomized, parallel-group study of 121 subjects, the safety and efficacy of tazarotene 0.1% cream alone were compared with those of tazarotene 0.1% cream combined with clindamycin 1%/benzoyl peroxide 5% gel.[12] Peeling and dryness occurred less frequently in the group receiving combination therapy, presumably because of the well-known retinoid-tolerance effect of clindamycin when used in combination with retinoids and the emollients and humectants in the vehicle of the nonretinoid product (Table 1).

Although retinoids have been shown to have some level of depigmenting activity of their own, hydroquinone 4% has long been the standard for treating hyperpigmentation associated with melasma and various inflammatory dermatoses, including acne and pseudofolliculitis barbae. A multicenter, randomized, double-blind study comparing tazarotene 0.1% cream alone and in combination with hydroquinone 4% cream to treat mottled hyperpigmentation from photodamage showed that the combination enhanced cosmetic results.[13] Patients were permitted to apply hydrocortisone before tazarotene, if they so chose, to minimize the potential for local irritation that often occurs in the early weeks of retinoid therapy prior to retinization.

TOPICAL RETINOID THERAPY IN COMBINATION WITH PROCEDURAL THERAPY FOR PHOTODAMAGED SKIN

Besides their highly effective use as pharmacotherapy for photoaged skin, recent studies have demonstrated a role for retinoids as adjuncts to cosmetic procedures.[14,15] In a split-face study of 20 women with facial photodamage, patients applied tazarotene 0.1% cream to their entire face once daily for 6 months.[16] One side of the face was randomly assigned to receive pulsed dye laser therapy (2 to 4 J/cm^2) at baseline, 1 month, and 2 months. Seventy percent of the patients (14/20) showed improvement in pigmentation, redness, fine lines, or deep lines (Figures 1 and 2). Although comparable improvement in these parameters was seen on both sides of the face, in some patients the combination of topical tazarotene and pulsed dye laser therapy minimized excessive redness (Figure 3).[16]

Retinoid treatment before wounding procedures such as chemical peels and ablative and nonablative laser resurfacing can accelerate healing by increasing the rate of reepithelialization.[17] Postlaser retinoid therapy, in addition to strict sun avoidance, is effective and warranted for the optimal maintenance of results.[14]

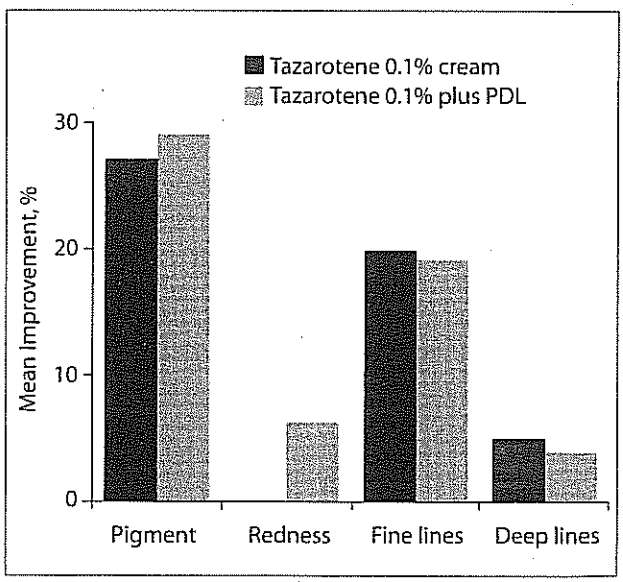

Figure 3. Mean percentage improvement from baseline with tazarotene alone versus tazarotene plus pulsed dye laser at 6 months posttreatment.

TABLE 2

Incidence of Treatment-Related Adverse Events of Tazarotene 0.1% Cream Versus Tretinoin 0.05% Cream (N=173)[18]

Adverse Event	Tazarotene, % (n=88)	Tretinoin, % (n=85)
Irritation	21	35
Retinoid dermatitis	16	11
Dryness	9	15
Peeling	12	11
Redness	10	7
Burning	15*	0
Erythema	3	4
Stinging	3	6
Dermatitis	4	2
Itching/puritis	1	4
Acne	5	0
Herpes	0	4
Scaling	3	0
Swelling	0	2

*$P \leq .001$.

EFFICACY OF TOPICAL RETINOIDS IN THE MANAGEMENT OF PHOTODAMAGE

With regard to efficacy in treating photodamage, a multicenter, double-blind, parallel-group comparison of tazarotene 0.1% cream with tretinoin 0.05% emollient cream in 173 subjects suggested that tazarotene has superior efficacy in treating fine wrinkling and mottled hyperpigmentation. Although both products were comparable in terms of tolerability, tazarotene was associated with a slight, but significantly higher, incidence of a burning sensation during the first week of treatment only ($P \leq .001$)(Table 2).[18] Initiating tazarotene therapy with alternate-day treatment or short-contact therapy with a washoff 2 to 5 minutes before cleansing is likely to prevent or reduce this symptom.[19] In addition, tazarotene showed more rapid improvement of the photodamaged skin.[18]

A triple-combination cream containing fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%, approved by the FDA for the treatment of melasma, may be another therapeutic choice for short-term management of photodamage. The author has used this cream with some success in a small subset of patients with photodamage and poikiloderma of Civatte.

CONTROL OF RETINOID SIDE EFFECTS

Studies of retinoids in acne management have demonstrated that reducing facial skin irritation and other side effects is associated with better compliance.[20] This may be particularly true in older patients with drier more sensitive skin. Recently, 2 nonsteroidal anti-inflammatory creams have been approved by the FDA for the management of atopic dermatitis. MimyX™ Cream contains ingredients that mimic stratum corneum components and may help repair and restore skin barrier function in many dermatoses, including atopic dermatitis, allergic contact dermatitis, and radiation dermatitis. Atopiclair™ Nonsteroidal Cream, which adheres to injured tissue, is designed to protect the skin and assist in healing by maintaining a moist environment. This product contains glycyrrhetinic acid and has been shown to be clinically useful

in managing experimentally induced irritant contact dermatitis.[21] In addition to its anti-inflammatory and antipruritic properties, glycyrrhetinic acid has been shown to potentiate endogenous and topical corticosteroids via inhibition of 11β-hydroxysteroid dehydrogenase.[22] Effective nonsteroidal anti-inflammatory creams are particularly desirable because of the need to minimize steroid application to facial skin and may be an important adjunct to topical retinoid therapy.

CONCLUSION

Topical retinoids have great promise in preventing and treating photodamage. They have few adverse effects; the most significant side effect—irritation early in treatment—may be minimized by using topical nonsteroidal anti-inflammatory agents, adjusting dosing regimens early in treatment, and using appropriate skin care regimens. Topical retinoids are the treatment of choice for both visible and invisible signs of photodamage.

Topical retinoids are useful adjuncts in combination with procedures including light- and laser-based therapies, dermabrasion, and chemical peels. The utility and reliability of topical retinoids in maintaining symptom remission following successful procedural therapy has been demonstrated.[15]

The advent of 2 new nonsteroidal, anti-inflammatory, topical agents will most likely facilitate the mitigation of irritation early in retinoid therapy and may therefore enhance both compliance and efficacy. These agents are an important advance over topical steroids, which should be used minimally on facial skin.

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