Tretinoin for the Treatment of Photodamaged Skin

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Interest in and interventions for photodamaged skin have dramatically increased over the last few years. Although a number of topical therapies have been used for the treatment of photodamaged skin, many therapies remain unproven in efficacy, unapproved, or only supported with limited clinical evidence. Topical retinoids, particularly tretinoin, are the most extensively studied. They have been shown to attenuate and reverse the signs of photodamage, such as coarse wrinkling. In addition, the clinical changes achieved with tretinoin are accompanied by histologic evidence of benefit. The main drawbacks to retinoid use are local irritation and erythema that can limit utility in some patients. New retinoids and formulations specifically optimized to improve cutaneous tolerability have been introduced. Two case reports of patients using low-concentration tretinoin gel 0.05% for the treatment of photodamaged skin are discussed. Over a relatively short treatment period of 4 weeks, tretinoin gel 0.05% was shown to provide both chemoprevention and reversal of photodamage.

Cutis. 2010;86:47-52.

The dermatologist's role in addressing the signs of aging and photodamage is increasing, with a focus on achieving cosmetic benefits and preventing photocarcinogenesis. Dermatology visits for the prevention and treatment of aging skin are rapidly increasing. The cutaneous effects of skin aging are a combination of both intrinsic (associated with the natural aging process and genetically determined) and extrinsic (associated predominantly with exposure to sunlight, a process called *photodamage*) factors. From 1997 to 2007, the number of cosmetic procedures performed in the United States has increased 457%, with a 114% increase in surgical procedures and a 754% increase in nonsurgical procedures.[1]

Extrinsic factors such as photodamage and environmental factors (eg, smoking) serve to accelerate the course of intrinsic skin aging. In addition, sunlight suppresses the immune function of the skin with medical consequences including actinic keratoses, invasive squamous cell carcinoma, basal cell carcinoma, and malignant melanoma.

The clinical sequelae of photodamage, including wrinkles, pigmentary alterations, roughness, laxity, and telangiectasia, can all result in the appearance of aging skin, which can have a negative impact on quality of life including social interactions, occupational functioning, and the psychological state of the individual. Decreased self-esteem and an adjustment disorder may occur.[2]

Treatment of Photodamaged Skin With Tretinoin

Tretinoin was first reported to reverse photodamage to facial skin in 1986.[3] The first double-blind, vehicle-controlled study of tretinoin was reported 2 years later.[4] In this 16-week trial, 30 participants used tretinoin cream 0.1% on one forearm and vehicle cream on the other once daily for 4 months. Half of the participants also applied tretinoin to the face, and the other half applied vehicle cream to the face. All 30 participants showed a statistically significant improvement in photodamage on the forearm treated with tretinoin ($P<.0001$), and 14 of 15 participants who received tretinoin on the face reported improvement in photoaging (coarse wrinkles, $P<.01$; roughness, $P<.02$; and fine wrinkling, $P<.0001$ [all versus vehicle]).

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Irritation related to tretinoin application was reported by 93% (28/30) of participants.[4]

The efficacy of tretinoin cream 0.05% to reverse photodamage and improve the clinical appearance of the skin has since been demonstrated in numerous long-term, large-scale, double-blind clinical studies.[5-12] Reduction of fine wrinkles, mottled hyperpigmentation, and roughness occur as soon as 2 weeks after initiation of treatment.[4] These effects can be sustained with continued use.[12] Histologically, long-term treatment (mean duration, 2.3 years) with tretinoin emollient cream 0.05% has been shown to reduce epidermal cellular atypia and thicken the collagen band in the papillary dermis.[13] Reducing the application frequency of tretinoin cream 0.05% from once daily to 3 times per week maintained and, in some cases, further enhanced the reduction of photodamage. Cessation of therapy for 6 months, however, resulted in some reversal of the beneficial effects seen after 48 weeks of treatment.[12]

The 2 most common barriers to using topical antiaging products are local irritation and the lack of patient motivation. The erythema and desquamation experienced by most patients when they initiate tretinoin therapy can make compliance difficult. Although these reactions subside after a few weeks,[13] many patients cannot tolerate the peeling and redness. Irritation can be ameliorated by short-contact or alternate-day application and by avoiding abrasive cleansers. Patient education regarding the proper use of topical retinoids cannot be overemphasized. If the dermatologist and staff are enthusiastic about the use of tretinoin and the results they have seen, patients will be more likely to be motivated to continue use. Serial photography is invaluable for showing patients how their skin has improved over time, as patients may not notice subtle improvements, especially in the first few weeks of treatment, and their assessment can differ from the dermatologist's assessment.[14]

Improved appearance is associated with reduced levels of collagen-degrading matrix metalloproteinases (MMPs)[15,16] and increased collagen synthesis.[17,18] More recently, it has been shown that retinoids function to reverse the adverse consequences of the chronological aging process in the skin.[19] Specifically, retinoid treatment stimulates fibroblast proliferation and new collagen synthesis while reducing MMP production in aging skin, which is accompanied by an increase in epidermal thickness that reflects increased keratinocyte proliferation.

In addition to the improved appearance that tretinoin provides photodamaged skin, histologic evidence demonstrates that tretinoin works both on the epidermis and dermis. Tretinoin increases epidermal thickness and granular layer thickness, decreases epidermal melanin content, and promotes stratum corneum compaction.[20] A deficiency of superficial dermal collagen is a key contributing factor and tretinoin increases collagen synthesis.[21] Topical tretinoin increases the number of collagenous anchoring fibrils within the papillary dermis and thereby improves the dermoepidermal junction.[22] Tretinoin also is associated with an increased number of blood vessels in the skin, which is believed to be responsible for the "rosy glow" that is characteristic of its use.

Studies have shown that a reduction in the cutaneous stigmata of photodamage with topical tretinoin is associated with an improvement in quality of life.[2]

Chemoprevention

The application of tretinoin to the skin initiates a series of events that can both prevent and repair photodamage.[23] Tretinoin facilitates the ability to prevent collagen loss and stimulate new collagen formation within the papillary dermis of sun-exposed skin.[24] Applied to human skin before UV irradiation, tretinoin inhibits induction of activator protein–1 as well as MMPs.[25] This action down-regulates production of enzymes that degrade collagen and thus preserves dermal collagen.

Because of their role in the regulation of cell growth, differentiation, and apoptosis, retinoids have undergone extensive investigation over the last 3 decades as chemopreventive agents. Indeed the concept of clinical cancer chemoprevention is largely based on preclinical and early clinical studies in which retinoids suppressed epithelial carcinogenesis.[26-29] Retinoids can suppress tumor promotion and modify some properties of fully transformed malignant cells by activating and/or repressing specific genes.[30] In addition to nuclear receptors and retinoic acid–responding elements, specific cellular retinoid-binding proteins bind retinoids with high affinity and regulate their metabolism, though their role in retinoid signaling remains unclear.[31]

Comprehensive reviews of preclinical and clinical work have been published and cover most organ sites in detail, including the lungs, cervix, intestine, prostate, and bladder.[31-36] Within preneoplastic diseases, retinoids have demonstrated efficacy in treating cervical dysplasia, xeroderma pigmentosum, and oral leukoplakia.[37] Providing a direct therapeutic role, retinoids have been used for treating hematologic malignancies (ie, acute

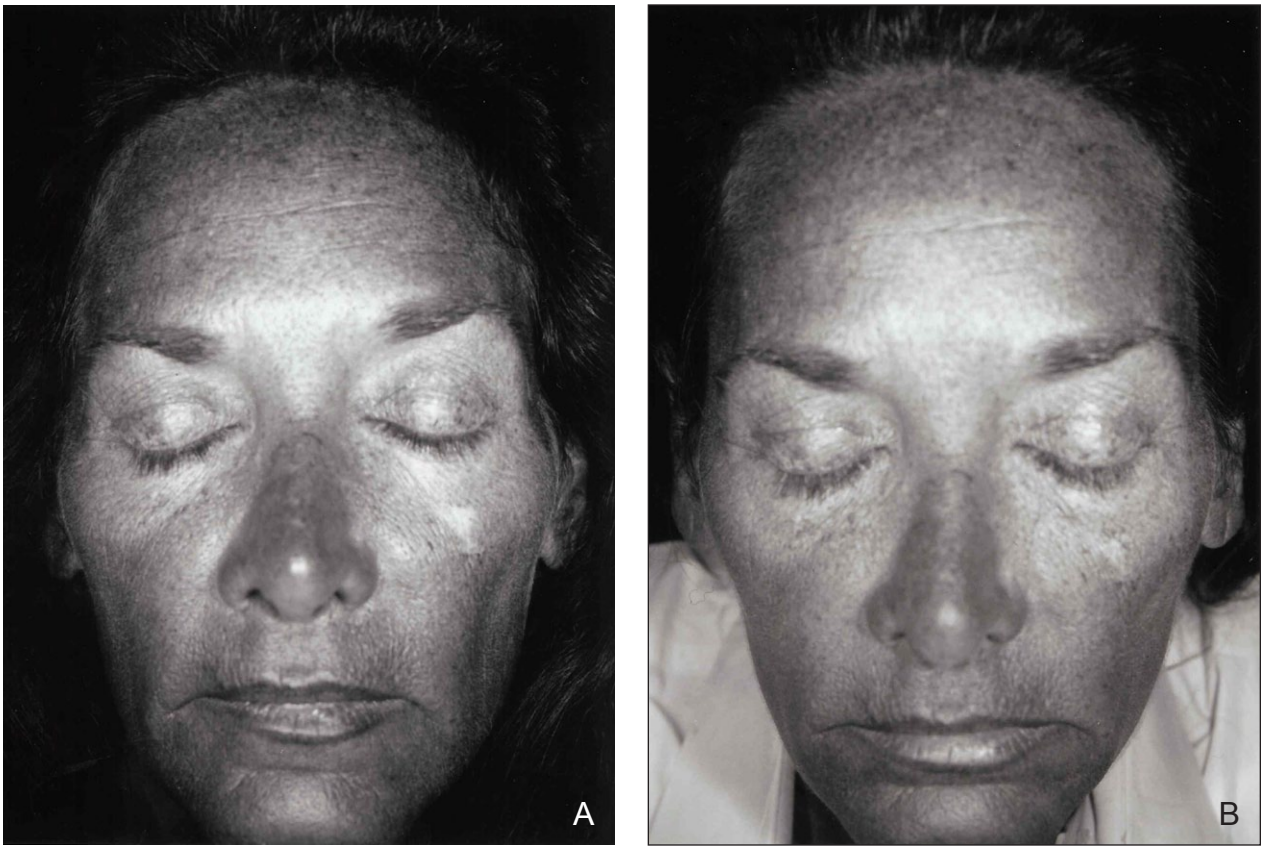

Figure 1. Patient undergoing chemoprevention before (A) and 4 weeks after application of tretinoin gel 0.05% prior to fractional CO_2 laser resurfacing (B), which resulted in moderate improvement of the skin texture with fewer fine lines and reduction of lentigines.

promyelocytic leukemia, mycosis fungoides, Kaposi sarcoma, juvenile chronic myelogenous leukemia) as well as solid tumors (ie, advanced kidney cancer, neuroblastoma, squamous cell carcinoma in combination with interferon alfa-2a).[38-41]

Micronized Tretinoin: A New Generation of Tretinoin Balancing Efficacy and Safety

A major drawback to retinoid therapy is its potential to cause irritation of the treatment area, a side effect that is generally dose dependent. Retinoid therapy has been associated with irritation, exfoliation, dryness, and scaling, especially during the first 3 to 4 weeks of treatment, which can be a limiting factor for treatment adherence in many patients.[42] Factors that influence irritant reactions have been shown to include individual skin sensitivity, the particular retinoid and concentration used, and the vehicle formulation.[43] Since its introduction, various concentrations of tretinoin have been approved in the United States and several formulations introduced, each designed to reduce irritation and provide flexibility in dosing.[44]

An aqueous gel formulation containing a 0.05% concentration of tretinoin has been developed and introduced. It is indicated for the topical treatment of acne vulgaris. Tretinoin gel 0.05% is uniquely formulated as micronized particles; 85% of the particles are less than 10 μm in size, which is important because raw tretinoin particles are approximately 200 to 300 μm and the skin follicles have an average diameter of 11 to 66 μm. The micronized particles are stabilized in suspension in an aqueous gel for targeted controlled release into the skin follicle to optimize tolerability and efficacy. The gel also contains ingredients that are commonly found in moisturizers (ie, soluble collagen, sodium hyaluronate) and skin hydration products (ie, glycerin). These moisturizing ingredients coupled with micronized tretinoin particles likely play a key role in enhancing the tolerability of tretinoin gel 0.05%.

The results of the combined analysis of pooled data in 1537 participants with mild to moderate acne demonstrated that tretinoin gel 0.05% administered once daily is an effective, safe, well-tolerated

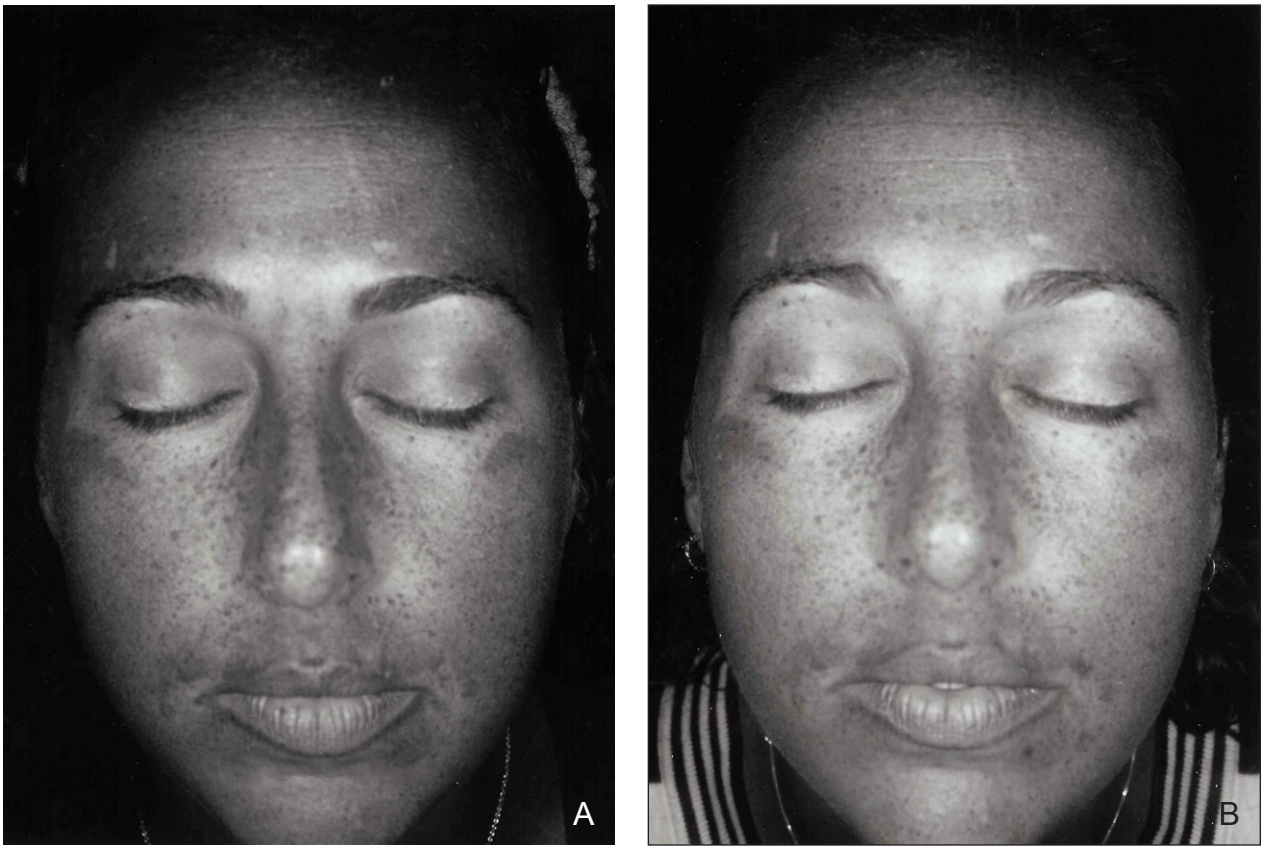

Figure 2. Patient with photodamage before (A) and 4 weeks after application of tretinoin gel 0.05% to the right side of the face (B), which demonstrated both chemopreventive and photodamage reversal effects.

therapy exhibiting a favorable irritation profile.[45] Overall efficacy of tretinoin gel 0.05% was significantly greater than vehicle ($P<.001$) and comparable to tretinoin gel microsphere 0.1%. Cutaneous tolerability of tretinoin gel 0.05% was significantly better than tretinoin gel microsphere 0.1% ($P<.001$). The overall incidence of skin-related adverse events was 52% (196/376) with tretinoin gel microsphere 0.1% versus 31% (208/674) with tretinoin gel 0.05% ($P<.001$), and dry skin occurred in 30% (112/376) and 16% (109/674) of participants, respectively ($P<.001$). In addition, exfoliative dermatitis and scaly rash were reported by 29% (109/376) of participants treated with tretinoin gel microsphere 0.1% compared to 8% (51/674) treated with tretinoin gel 0.05%, and erythema was reported in 18% (67/376) and 7% (47/674) of participants, respectively.[45]

Case Reports: Use of Tretinoin Gel 0.05% in Chemoprevention

Patient 1—A 56-year-old white (Fitzpatrick skin type II) woman with a history of actinic damage and prior nonmelanoma skin cancer on the face was evaluated for chemoprevention. She was recommended to undergo fractional CO_2 laser resurfacing for the treatment of photodamage. She was instructed to apply tretinoin gel 0.05% nightly (pea-sized amount dabbed 2–3 inches apart and spread thin) and adhere to strict sun protection for a month prior to the laser treatment.

Photodamage was assessed with UV photography, which takes advantage of selective absorption of UV light by epidermal melanin and highlights the amount of damage lying beneath the surface of the skin, such as the mottled hyperpigmentation that is characteristic of photodamage. The baseline UV photograph and a subsequent photograph taken 4 weeks later (prior to fractional CO_2 laser resurfacing) are shown in Figure 1. Comparison of the UV photographs revealed moderate improvement of the skin texture with fewer fine lines and reduction of lentigines (Figure 1). In keeping with the extensive clinical data reported above, the patient reported minimal irritation and a smoother complexion.

Patient 2—A 28-year-old white (Fitzpatrick skin type II) woman who worked as a sales representative

and drove frequently was constantly exposed to the sun and had photodamage despite using strict daily sunscreen application (Figure 2A). A split-face study was conducted over 4 weeks with tretinoin gel 0.05% applied nightly to the right side of the face. After 4 weeks there was a reduction of wrinkles on the right lower eyelid but not the left (Figure 2B). More lentigines and mottled pigmentation were present on the left upper cutaneous lip, while most of the right side showed some improvement, suggesting both chemopreventive and photodamage reversal effects with tretinoin gel 0.05%.

Comment

Literature abounds regarding the efficacy of topical tretinoin in the reduction of photoaging. The relatively immediate clinical benefit of tretinoin gel 0.05% was shown in before and after UV photographs and split-face techniques after 4 weeks of nightly application. The results are encouraging, especially as tretinoin gel 0.05% was well-tolerated, and larger studies are to be encouraged.

Acknowledgments—The author thanks Brian Bulley, MSc, Lindfield, West Sussex, United Kingdom, for editorial assistance.

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