

Topical Tretinoin Use for Photodamage

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Skin aging is caused by intrinsic genetic determinants combined with the influence of extrinsic environmental factors. Progress has been made in understanding the mechanisms behind photodamage. UV-induced changes in the nuclear and mitochondrial DNA, oxidative stress with the generation of reactive oxygen species, and chronic subclinical inflammation from exposure to UV radiation all have been implicated as plausible etiologies.¹

Retinoids were first discovered to have antiaging effects in the mid-1980s when Kligman et al² reported that twice-daily application of tretinoin cream 0.05% to photodamaged skin partly reversed structural damage from excessive UV exposure by creating a substantial repair zone of new collagen in the papillary dermis. Additionally, the authors described a significant effacement of wrinkles compared to vehicle ($P < .05$). In essence, retinoids decelerated the photoaging process.² Since then, vitamin A and its derivatives have become popular ingredients in topical antiaging preparations. Vitamin A is available over-the-counter in some cosmeceutical formulations, but certain derivatives (ie, tretinoin, isotretinoin, alitretinoin, tazarotene, adapalene) strictly are classified as prescription medications.

Lipophilic in nature, retinoids induce their effects by diffusing through cellular membranes. Once inside the cell, they bind to active specific nuclear receptors and modulate expression of genes involved in cellular proliferation and differentiation. Specifically, signaling of retinoid receptors increases the production of procollagen, thus augmenting the formulation of types I and III collagen while inhibiting matrix metalloproteinases.³ Histologic changes observed following retinoid application include epidermal hyperplasia, angiogenesis, increased synthesis of collagen and elastin, and decreased corneocyte adhesion.² Retinoids also enhance epidermal cell turnover and promote a rapid loss of pigment through epidermopoiesis.⁴

Of all the topical retinoids, tretinoin is the most frequently investigated for efficacy and safety in the treatment of photodamage since its approval by the US Food and Drug Administration in 1971. Currently, Renova (tretinoin cream 0.02%; Valeant Dermatology) and Refissa (tretinoin cream 0.05%; Spear Dermatology/Products) are 2 topical tretinoin products that have been approved by the US Food and Drug Administration for use in the mitigation of fine facial wrinkles. Despite the beneficial effects of tretinoin on aging skin, discontinuation of treatment causes progression of photodamage. In one trial, a 6-month discontinuation of therapy led to reversal of some of the effects that were observed 1 year after continuous treatment with topical tretinoin.⁵ The clinical data indicate that initial tretinoin treatment should be followed by a long-term maintenance phase with either a lower concentration or less-frequent application.¹ Additionally, tretinoin has been demonstrated to have dose-dependent therapeutic effects. For instance, when applied once daily for 6 months, tretinoin cream 0.05% was shown to be more effective than tretinoin cream 0.01% in reducing wrinkles, skin toughness, and mottled hyperpigmentation.⁶

At the beginning of treatment with topical tretinoin, patients commonly experience localized adverse effects, such as xerosis, mild erythema, peeling, and burning (known as retinoid dermatitis), as well as exaggerated photosensitivity. These effects also are dose dependent and decrease with ongoing use. Several strategies should be recommended to diminish and/or prevent the adverse effects caused by topical tretinoin, such as less-frequent application of the product (ie, alternating days); concomitant application of emollients, indomethacin 3%, and/or hydrocortisone 1% have been shown to provide relief. Furthermore, several natural compounds such as ginkgo extracts, cola extract, and β -sitosterol might have some potential to antagonize the irritative effect of retinoids.⁷ Sunscreens also should be used during the daytime.¹

Conventional tretinoin therapy often is discouraging for patients because treatment must be continued for a long period before effects become noticeable, often leading to

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discontinuation of therapy. Additionally, the short-term effects of retinoid dermatitis often lead to noncompliance. To minimize these disadvantages, Kligman and Draelos⁸ explored the advantages of a high-strength tretinoin solution (0.25% solution in a fast-penetrating vehicle) applied nightly for 1 month in 32 females who presented with photodamage. Mild to moderate improvements in fine wrinkles, mottled hyperpigmentation, and surface texture/roughness were observed; however, the most noteworthy yet unexpected result was that the skin accommodated quickly to vitamin A-associated cutaneous side effects in just 2 weeks. The authors proposed that this accommodation stemmed from the downregulation of constantly stimulated retinoic acid receptors.⁸ Larger clinical studies hopefully will confirm these results.

Since the introduction of vitamin A as a topical drug, evidence for systemic adverse effects has been conflicting. With regards to teratogenicity, human and animal data argue against plausible effects because of minimal systemic absorption (values measured from undetectable to a small fraction of the dose, not exceeding endogenous levels).^{9,10} A recent European study evaluated the rate of congenital malformations in babies born to pregnant women who were exposed to topical retinoids during the first trimester.¹¹ A population of 235 exposed pregnant women was compared with 444 control patients. No significant differences were observed between the groups with regard to the rates of spontaneous abortion or birth defects. Additionally, no baby showed features of retinoid embryopathy.¹¹ Nevertheless, women of childbearing potential, representing the most common population to be prescribed topical retinoids for antiaging purposes, are advised to cease all retinoid treatment during pregnancy.¹

The overall safety profile of topical tretinoin came into question when Weinstock et al¹² reported the early termination of the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) trial. This 6-year, randomized, placebo-controlled study included 1131 veterans (mean age, 71 years) who used tretinoin cream 0.1% twice daily. The study was terminated early when the authors uncovered significant differences in mortality rates (14% vs 9% in the tretinoin and placebo groups, respectively) ($P=.01$), mostly attributed to pulmonary disease, non-small cell lung cancer, cardiac disease, and other cancers.¹²

A recent systematic review by Shapiro et al¹³ challenged the Weinstock et al¹² conclusion by pooling the results of various topical tretinoin acne and photodamage studies to probe for the development of noncutaneous adverse events. They concluded that there were no clinically significant noncutaneous adverse events observed among the 20 studies identified. However, one important limitation

of this systematic review should be highlighted; the dosing schedule of the 20 studies was comparable (ie, participants received low to medium, 0.02%–0.05% daily applications of tretinoin as indicated), but this treatment schedule varied greatly from the VATTC trial, which included more-frequent use of a higher concentration of topical tretinoin. Until the relationship between dosage and duration of use of tretinoin in the VATTC trial are explored, these data are still considered to be inconsistent with prior experiences reported in photodamage studies of tretinoin use.¹³

The corrective effects of tretinoin preparations on photo-damaged skin have been substantiated by many researchers since the 1980s. It is the prescribing dermatologist's responsibility to discuss the practical considerations of topical retinoid use prior to starting treatment. The need for appropriate dermal moisturization to curtail localized adverse effects and application of sunscreen are important advisory measures. Communicating the expected outcomes that have been substantiated in the literature will allow the patient to gauge his/her expectations for treatment. Future clinical trials investigating the long-term use of topical tretinoin regimens at varying doses and frequencies that are indicated for photodamage will only help to establish a systemic risk profile. Until then, low doses of topical tretinoin applied once daily appear to be the safest, most efficacious means of remedying photodamaged skin.

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