Non-Prescription Retinoid Alternatives: Can Vitamin A Offer Gentle Efficacy?

Numerous compounds in OTC products promise to erase wrinkles with a mechanism similar to prescription retinoids. But they may not deliver.

By Dee Anna Glaser, MD

When it comes to topical treatments for photodamage, prescription retinoids are and have been the most reliably effective and well-documented options. Riding the coattails of the topical retinoids, numerous other vitamin A-derived compounds have emerged in OTC moisturizers, creams, and spot treatments, promising to offer wrinkle reduction without a prescription and presumably with less expense.

In a previous column, I’ve outlined effective approaches to the use of prescription retinoids to treat and prevent photodamage. I’ll review some of the basics below and address the appropriate role, if any, for alternative vitamin A derivatives.

Prescription Topical Retinoids

Several double-blind, placebo-controlled trials document improvement in global appearance, fine and coarse wrinkling, roughness, pigmentation and sallowness associated with daily application of topical tretinoin (retinoic acid). The effects, which are dose-dependent, increase with the duration of therapy for at least 12 months. In addition to clinical improvement, tretinoin has been shown histologically to reverse changes associated with intrinsic aging both in vivo and in vitro. We know that retinoids regulate gene transcription and affect activities such as cellular differentiation and proliferation.

The first of the marketed retinoids, Retin-A (tretinoin, Ortho-Neutrogena), revolutionized acne care and has since been tried in various disease states. Currently, it is available in several formulations, including a cream (0.025%, 0.05%, 0.1%), gel (0.01%, 0.025%), and solution (0.05%). Higher concentrations generally induce greater irritation. Renova (tretinoin 0.05% or 0.02%, Ortho-Neotrogena)—specially formulated in a water in oil emulsion vehicle with light mineral oil—is more moisturizing and more tolerable for many patients, especially those with fair or dry skin, and may be associated with a decreased incidence of irritant dermatitis. It is specifically approved for the treatment of signs and symptoms of photodamage. Numerous other brands and generic formulations of tretinoin are now marketed.

A third generation retinoid, adapalene (Differin gel, Gladerma Laboratories) is a naphthoic acid derivative approved for the treatment of acne. It is reported to have a much
lower irritation potential, no phototoxicity, and fewer issues of sensitization. While there is no published data on its use in photoaging, it is expected to provide benefit similar to other retinoids and is reportedly used by some.

If and how selectivity of retinoid receptors influences disease treatment is unclear. Tazarotene selectively binds to retinoic acid receptors RAR-β (which account for about 90 percent of the RARs in the skin) and RAR-β. Nonselective tretinoin, by comparison, directly activates all RAR pathways (RAR-α, RAR-β, and RAR-γ) and indirectly activates the retinoid X receptor (RXR). Tazorac (tazarotene, Allergan) is FDA-approved to treat acne vulgaris and psoriasis. Avage (tazarotene, Allergan), is FDA-approved to treat photoaging. Compared to vehicle, tazarotene 0.1% gel has been shown to reduce skin roughness and fine wrinkling.

**Vitamin A and Related Compounds**

Retinoic acid (RA) provides notable benefits in treatment of photoaging, but its irritating effects on the skin can limit its usefulness in this and other indications, such as acne and skin cancer. Therefore, interest has shifted to Vitamin A or retinol (ROL), an RA precursor, and other similar compounds as gentler yet potentially effective alternatives. Among the other compounds of interest are retinaldehyde (RAL), an intermediate compound in the conversion of ROL to RA, retinyl propionate (RP), and retinyl palmitate (ROL Palm).

The published data supporting the activity of these agents is limited, and manufacturers frequently cite proprietary data when marketing products formulated with these agents. Based on available data, ROL and RAL do indeed seem to be significantly less irritating than RA. Studies involving repeated patch testing for 14 days show that RA was more irritating than ROL or RAL; ROL produced less scaling than RA or RAL. After 44 weeks of use, RAL was associated with a significantly lower incidence of erythema, scaling, and burning/pruritus compared to RA.

Studies also confirm that ROL, RAL, and ROL Palm have effects similar to RA. The extent of irritant effect may not correlate with the level of activity on a cellular level. None of the three vitamin A derivatives produced the irritant effect (as measured by erythema) of RA, but they did induce increased epidermal thickness and RA 4-hydroxylase activity. ROL demonstrated better skin penetration than RA or ROL Palm. Although ROL is a weaker retinoid than RA, its increased penetration, less irritating side effects, and similar cellular activity may allow retinol to become clinically very useful.

Compared with placebo, ROL Palm produced no significant difference in any of the clinical, histologic, or profilometric parameters of photoaging in one study. In another study, improvement in the appearance of skin wrinkles and hyperpigmentation for topical retinyl propionate was comparable to those of retinol, but retinyl palmitate did not produce any observable skin benefit.

At this time, I do not recommend these types of vitamin A products.

**Tried and True**

Findings suggest that topical vitamin A-based ingredients available over-the-counter, especially retinol, may hold potential to treat photodamage. However, there is insufficient evidence to support their use as the basis of a topical antiaging regimen. Instead, patients interested in a topical approach to management of photodamage should concentrate on tretinoin or tazarotene.

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**What About Systemic Retinoids?**

Oral isotretinoin, commonly used to treat acne, psoriasis, and other systemic diseases, has yet to emerge as a viable therapy for aging skin despite significant interest. One study observed individuals who underwent rejuvenation treatments followed by oral isotretinoin 10-20mg three times a week for six months and compared them to patients who received the same rejuvenation treatments with no isotretinoin post-treatment. Although isotretinoin-treated patients demonstrated greater improvement in wrinkles, thickness and color of skin, size of pores, “general” skin improvement, and elasticity, the difference compared to controls was not statistically significant. Side effects were minimal and included dryness of the lips. No studies compare topical retinoids to systemic retinoids for photoaging.

The limited available data suggest that the benefits of isotretinoin do not outweigh the well-known risks—especially to women of childbearing age. Especially in light of increased efforts to monitor access to the drug, isotretinoin is not suitable for general use to treat photoaging.