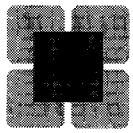

Topical tretinoin no panacea for photodamaged skin

The use of topical tretinoin in the treatment of skin diseases began with the work of Stüttgen in the 1950s. He reasoned that, since retinol and retinyl palmitate were effective in treating a variety of disorders when given orally but not when applied to skin, a metabolite such as the acid form (tretinoin) might be the effector molecule.[1] Subsequently his group reported therapeutic benefit in a variety of conditions, such as actinic keratoses, seborrheic keratoses, viral warts, and basal cell carcinomas.[2]

■ *See Andreano, p. 49*

In 1969, Kligman et al reported benefit in the treatment of acne vulgaris. In 1974, at an international congress on the use of tretinoin, investigators from many countries reported the benefit of this molecule in the treatment of a wide variety of skin diseases, including acne, ichthyosis, Darier's disease, psoriasis, lichen planus, and precancerous lesions and nonmelanomatous forms of skin cancer.

At that time, the reason that a single agent such as tretinoin could be useful in a wide variety of skin diseases was not apparent. It is now clear that the common link between so many clinically different disorders is abnormal cell differentiation. The well-recognized modulating effects of tretinoin and other "retinoids" on cell differentiation accounts at least in part for therapeutic usefulness.[5]

Perhaps the most important clinical extension of this general concept is the use of tretinoin in treating cervical dysplasia and precancerous skin lesions (actinic keratoses).[4,6,7] More recently, introduction of systemic retinoids such as isotretinoin (the 13-*cis* isomer of tretinoin) for severe acne and epidermal disorders of keratinization and etretinate for psoriasis have been major advances in dermatological therapy.[8,9] The paper by Andreano et al in this issue represents another demonstration of the most recent use of topical tretinoin—namely, for the treatment of photodamaged skin.

It is now generally agreed that chronic cumulative damage by ultraviolet light results in a variety of changes in skin that have significant clinical consequences. In the epidermis, these changes include surface roughness, epidermal dysplasia, benign hyperplasia of keratinocytes (seborrheic keratoses) and melanocytes (lentigines), epidermal dysplasia (actinic keratoses), and skin cancer. In the dermis, proliferation of superficial venules results in telangiectasias, and replacement of collagen and elastin with abnormal elastic-like material (elastosis) results in sagging and premature wrinkling.

All of these changes involve abnormalities of cell differentiation, and it is therefore reasonable that topical tretinoin might be of some benefit. The first demonstration of potential benefit in photodamaged skin was reported by Kligman et al in uncontrolled open studies.[10] In addition to clinical benefit, these studies demonstrated a variety of pharmacologic and histologic effects which supported the clinical findings. Further supportive evidence came from the elegant studies in the photodamaged mouse model reported by the Kligmans.[12] Subsequently, Weiss et al reported clinical benefit in a double-blind vehicle-controlled study.[13] In addition, blinded histologic studies demonstrated changes similar to those reported in the previous uncontrolled studies—namely, thinning and compaction of the stratum corneum, epidermal hyperplasia, thickening of the granular layer, decrease in melanocyte activity with decreased melanin production, increased anchoring fibrils and filaments, and some decrease in abnormal collagen.

Multicenter clinical trials have confirmed these results[14,15] and formed the basis of a New Drug Applica-

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tion to the US Food and Drug Administration (FDA) for the indication of treatment of photodamaged skin. While the Dermatology Advisory Panel has recommended approval of this application, the final decision by the FDA has not yet been announced.

The lay press has made much of the use of tretinoin in treating photodamaged skin. As a result, many nondermatologists are asked to prescribe this drug. Topical tretinoin should be prescribed only after consultation with those who are very familiar with its use and side effects. Local irritation and increased sensitivity to ultraviolet light are the major side effects; patients need to be counseled on how to avoid these problems.

More importantly, topical tretinoin is not a panacea. Most patients can achieve a smoother, less rough, less pigmented skin; however, jet black areas of melanocytic hyperplasia will not disappear, nor will deep wrinkling and sagging skin be reversed. On the other hand, fine lines and wrinkling may be lessened. Patients must accept conscientious sun protection as part of an overall strategy. The benefits in terms of normalization of abnormal cell differentiation are real. The degree of clinical improvement is variable but usually sufficient to warrant continued use.

The use of topical tretinoin for treating photodamaged skin is an interesting development in dermatologic therapy. While skin cancer as a consequence of ultraviolet damage makes photodamage a medically important issue, most of the changes being treated are mainly of cosmetic significance. A consensus panel of the American Academy of Dermatology concluded that the "cosmetic" aspects of photodamage are of real importance in terms of self-image and psychological implications.[16] If tretinoin is approved by the FDA for treatment of photodamaged skin, increased patient awareness of this potential treatment undoubtedly will occur. It behooves all of us involved in clinical medicine to be aware of this development in view of the interest by the lay public.

JAMES J. LEYDEN, MD
Hospital of the University of Pennsylvania
Philadelphia

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