The effectiveness of topical tretinoin for treating the effects of photoaging is now unchallenged. This acceptance, however, has come more than a decade after the initial reports by Cordero1 and Kligman et al2 who described the potential utility of topical tretinoin for photoaging, and it did not occur without controversy. Although several large-scale clinical studies have consistently demonstrated the efficacy of tretinoin in treating photoaging and although basic research into its mechanism of action in human skin has greatly enhanced our understanding of its pharmacologic effects, misconceptions remain about the proper clinical use of tretinoin. In this review, we highlight pertinent data to clarify 5 commonly misunderstood aspects of tretinoin therapy for photoaging: (1) tretinoin-specific improvement in skin; (2) irritation associated with tretinoin treatment; (3) tretinoin treatment in non–white persons; (4) sunlight and tretinoin treatment; and (5) patient safety from systemic absorption.

When the original double-blind, vehicle-controlled study was published in 19883 that demonstrated that topical tretinoin improves the phenotypic features of photoaging, the report received tremendous attention from the media and the medical community around the world. Along with the excitement it generated, a certain amount of skepticism was initially expressed by many. Although several reasons may be cited for the mixed response, the most important was probably the medical community’s unfamiliarity with photoaging at the time and a consequent inability to draw clear distinctions between photoaging and natural aging of skin. After all, the clinical features of photoaging—dry, sallow skin; mottled or blotchy dyspigmentation, and wrinkles4—are what most people envision for skin of advanced age. Therefore it is easy to see how the improvements brought about by tretinoin therapy could have been misconstrued as a reversal of the aging process, a claim that was made more than once in the media and one that was understandably difficult to accept. With the realization that even in individuals with marked photoaging, their sun-protected skin was much more youthful in appearance, a clearer distinction could be drawn between photoaging and intrinsic/chronologic aging. This distinction made it easier for critics to accept that photoaged skin is treatable with pharmacologic agents. The controversy was effectively resolved when several well-controlled studies5-8 provided consistent, indiscputable evidence that tretinoin improves the effects of photoaging in human skin.

TRETINOIN SPECIFICITY OF PHOTOAGING REPAIR

Although the clinical efficacy of tretinoin for treatment of photoaged skin is now generally accepted, some critics have argued that the
improvement observed in skin cannot be credited to tretinoin per se. This skepticism stems from the fact that skin irritation, also known as “retinoid dermatitis,” frequently accompanies topical application of tretinoin. Though data were lacking to support these contentions, and some critics claimed that improvement in photoaging was secondary to nonspecific irritation associated with topical application of tretinoin and not a result of retinoid-specific action in skin.

The facts about the efficacy of tretinoin therapy were finally clarified with the publication of a large, single-center study involving nearly 100 subjects.9 Study participants were randomized into 3 treatment groups, treated with 0.1% tretinoin, 0.025% tretinoin, or vehicle cream. The results indicated that treatment with either 0.1% or 0.025% tretinoin induced statistically significant improvement in the effects of photoaging, compared with vehicle treatment. There were no significant differences in the overall clinical efficacy of treatment with 0.1% versus 0.025% concentrations of tretinoin. However, the degree of irritation, defined as erythema and scaling of mild or greater severity on 2 or more occasions during treatment, differed markedly between the 2 treatment groups: the 0.1% tretinoin-treated group exhibited an approximately threefold greater incidence of irritation than the 0.025% tretinoin-treated group.

If clinical improvement of photoaged skin was, in fact, secondary to skin irritation caused by tretinoin as some critics claimed, then the effects produced by 0.1% tretinoin treatment should have been significantly greater than those produced by 0.025% tretinoin treatment because of significantly greater irritation expected at the higher concentration. However, the absence of any correlation between clinical efficacy and level of irritation points to the conclusion that tretinoin’s irritant properties are clearly distinguishable from its beneficial effects on photoaged skin. In a separate study by Kligman et al,10 which used an animal model of photoaging, tretinoin effectively effaced wrinkles, whereas topically applied irritants had no effect, which supports the results of the study on human subjects.

The consistent results of both animal and human studies have clear implications for clinical practice, the most important being that it is unnecessary to push tretinoin use to the point that brisk retinoid dermatitis develops to achieve maximum clinical improvement of photoaged skin. On the contrary, equally impressive clinical results may be achieved with sparing but diligent use of tretinoin, an approach that minimizes retinoid dermatitis. One recent study reported that a 48-week regimen of treatment once-daily with 0.05% tretinoin emollient cream, followed by treatment 3 times weekly for an additional 24 weeks, maintained and, in some cases, even enhanced the improvements in photoaged skin.11 Treatment once-a-week with tretinoin was less effective in sustaining the clinical improvement achieved by the initial treatment regimen of tretinoin once-daily. In the same study, some reversal of the beneficial effects of tretinoin treatment was observed after discontinuation of therapy for 24 weeks, which indicates the need to continue tretinoin therapy to maintain clinical improvement.

RETINOIC ACID RECEPTORS MEDIATE THE BIOLOGIC EFFECTS OF TRETINOIN

Although improvements in photoaged skin are attributable to retinoid therapy and not a result of a nonspecific irritant reaction, it was not initially clear how tretinoin’s effects are mediated in human skin. We provide a brief overview of this avenue of research here, but readers are referred to a recent review for a more comprehensive discussion of the subject.12

The mechanism by which tretinoin (all-trans-retinoic acid) induces its biologic effects was not well understood until recently. The discovery of retinoic acid receptors (RARs) in 198713,14 was the first demonstration of the existence of a tretinoin-specific gene transcription factor, a landmark finding that lead to the realization that tretinoin is a hormone. RARs are similar to steroid/thyroid hormone receptors in terms of molecular composition and function. As such, RARs have distinct DNA and retinoid-binding domains, and they function in pairs, either pairs of identical receptors called homodimers or pairs of different receptors called heterodimers. In human skin, RARs partner with retinoid X receptors (RXRs) to form heterodimeric complexes.15,16 The RAR-γ subtype accounts for approximately 90% of RARs in human epidermis, although the RXR-α subtype accounts for roughly 90% of RXRs.15 For the most part, normal human skin is regulated by paired heterodimers composed of RAR-γ and RXR-α. In the presence of the RAR-specific retinoid (eg, all-trans-retinoic acid, or
tretinoin), the heterodimers bind to specific DNA sequences, known collectively as the retinoic acid response element (RARE), in the promoter region of genes that are regulated by tretinoin and in this manner regulate the transcriptional activity of tretinoin-responsive genes. The heterodimer requires only the RAR-specific retinoid to bind to the RARE and initiate transcriptional activity; the presence of an RXR-binding retinoid, such as 9-cis-retinoic acid, does not confer additional trans-activation induced by the RAR retinoid. However, for the (RAR/RXR) heterodimer to function, the RXR protein must be physically present to associate with the RAR protein.

Currently, it has been determined that tretinoin’s actions in the skin are primarily, and probably solely, mediated by these retinoid receptors. Because the receptors are transcription factors, tretinoin must accomplish its effects in skin through regulated gene expression. Although initially only RARE-containing genes are activated in response to tretinoin, some of the protein products of these genes are believed to activate other non-RARE-containing genes in a cascading fashion, producing the diverse array of retinoid actions in skin.

Recently we reviewed evidence that dermal collagen may be the central player in the pathogenesis of photoaging. Partial restoration of dermal collagen that had been reduced in photoaged skin is observed after topical tretinoin use, which is an example of a tretinoin-initiated cascade whose end result is wrinkle effacement at the clinical level.

PEELING COMPONENT OF TRETINOIN IRRITATION IS ALSO RECEPTOR MEDIATED

Repeated topical applications of tretinoin predictably produce a skin reaction resembling irritation. This reaction is characterized by redness and desquamation, signs that correspond histologically to alterations in the stratum corneum and epidermal hyperplasia. Similar clinical and histologic findings can be observed after 4 days of occlusive therapy with tretinoin or sodium lauryl sulfate (SLS). These histologic changes result from increased proliferation of keratinocytes, as indicated by a greater number of mitotic figures, and enhanced expression of differentiation markers. Collectively, these epidermal changes lead to clinical desquamation and peeling.

Although both tretinoin and SLS induce similar clinical and histologic changes after 4 days of continuous occlusion, there is a difference in the time of onset. Tretinoin induces these changes after 2 days; SLS takes longer. The rapid onset with tretinoin therapy suggests that tretinoin has a direct effect on cutaneous cells (ie, mediated by receptors), whereas the effects of SLS are indirect and caused by secondary phenomena. This possibility was confirmed in experiments with genetically engineered mice that expressed mutant RXR-α receptors. In these transgenic mice, the expression of dominant negative RXR-α mutant proteins was targeted to the suprabasal layers of the epidermis by the keratin 10 promoter. Because mutant RXR-α are capable of dimerizing with wild-type RARs, one consequence of mutant receptor over expression is a functional deficiency of RARs. Normal RARs are tied up with mutant RXR-α in heterodimers, with the end result that skin is deficient in functional retinoid receptors. In the skin of the transgenic mice deficient in functional RARs, topical application of tretinoin does not induce the epidermal hyperplasia and desquamation typically seen, indicating that the tretinoin-induced epidermal hyperproliferative response and peeling are indeed receptor mediated. These findings suggest that any retinoid, natural or synthetic, that can bind to and activate the RARs will induce the epidermal hyperplasia and desquamation response in skin. Claims that synthetic retinoids can provide clinical efficacy without the concomitant peeling response should therefore be viewed with extreme skepticism, because they are inherently contradictory, according to current knowledge.

The erythema component of retinoid dermatitis appears not to be receptor mediated. Topical application of all-trans retinol to human skin induces epidermal hyperplasia and expression of the RARE-containing cellular retinoic acid-binding protein-II gene mRNA. The ability of all-trans retinol to elicit histologic and molecular effects identical to those produced by tretinoin can be explained by the conversion of retinol to trace amounts of tretinoin. Despite evidence that retinol treatment activates RARs, it is unassociated with clinical erythema.

TRETINOIN THERAPY IN NON–WHITE PERSONS IS SAFE AND EFFECTIVE

It is a well-established clinical fact that individuals with greater baseline constitutive skin pig-
mentation are more prone to the development of patches of dyspigmentation (called postinflammatory hyper- or hypopigmentation) at sites of skin inflammation. Because topical tretinoin therapy is commonly associated with “retinoid dermatitis,” there has been legitimate concern about inducing postinflammatory dyspigmentation at sites of retinoid dermatitis, especially in darker-skinned individuals. However, controlled studies in which black patients and Asian patients were treated with 0.1% tretinoin cream have consistently demonstrated that such undesirable dyspigmentation does not occur. Remarkably, one study showed that topical tretinoin can be effectively used to treat postinflammatory hyperpigmentation caused by inflammatory conditions such as acne or folliculitis in black patients. In our experience, tretinoin therapy rarely causes hyperpigmentation, and when it does, the undesirable effects are treatable with continued use of tretinoin. Furthermore, the incidence of hyperpigmentation is not more prevalent in black patients and Asian patients. Indeed, these individuals tolerate topical tretinoin, even the 0.1% strength, as well as, if not better than, white patients. Given this evidence, tretinoin therapy for individuals with darker skin pigmentation can be recommended with confidence.

SUN EXPOSURE AND TRETINOIN THERAPY

Two concerns have been raised regarding sun exposure during tretinoin therapy: photosensitivity and photocarcinogenesis. Skin treated with topical tretinoin does respond differently to solar radiation than untreated skin does. However, the differences in response need to be clarified. Under controlled conditions, when human skin that has been pretreated with topical tretinoin is irradiated with UV light of a defined energy, there is no effect on the minimal erythema dose. These results clearly indicate that tretinoin has no phototoxic activity and that it does not possess sunscreen properties either. Patients undergoing topical tretinoin therapy do occasionally complain of uncomfortable sensations when their skin is exposed to sunlight. These sensations often occur within minutes of being in the sun, which suggests that the reaction is quite different from the sunburn reaction that normally occurs hours after excessive sun exposure. Furthermore, the sensations are more noticeable in hot environments than in cold ones, indicating that heat (infrared radiation), rather than UV radiation, may contribute to this response. With daily use of tretinoin, the stratum corneum becomes thinner but more compact. To what extent thinning of the stratum corneum affects photosensitivity is unknown. However, formal phototesting of individuals treated with oral isotretinoin (which must be converted to tretinoin to be effective) has failed to demonstrate any significant changes in photosensitivity (minimal erythema dose).

The only evidence that tretinoin may have photocarcinogenic potential comes from animal studies. In albino and hairless mice, the application of tretinoin has been reported to promote UVB-induced carcinogenesis. Opposite effects, demonstrating that tretinoin inhibits growth and in some cases cause regression of UVB-induced tumors, have also been reported in hairless mice. This evidence suggests that the carcinogenic effects of tretinoin may be limited to susceptible animals under laboratory conditions. The gross inadequacy of commonly used rodent models for studying photocarcinogenesis in human skin was recently demonstrated in a study in which human skin was grafted onto mice with severe combined immunodeficiency (SCID). In this study, human carcinomas developed only rarely (3.6%) and only in grafts that were first tumor initiated (with dimethyl(a)benzanthracene) before being irradiated with UVB. On the other hand, murine carcinomas were commonly observed in all UVB-irradiated SCID mice grafted with human skin, whether they were dimethyl(a)benzanthracene initiated (23%) or not (45%), before irradiation. These results indicate that UVB is much more potent in mouse skin than in human skin, either as a complete carcinogen or as a promoter. Furthermore, these findings demonstrate the tendency of rodent models to overestimate the carcinogenic potential of tested agents in human skin. In humans, there is no evidence to date that tretinoin is carcinogenic. On the contrary, topical tretinoin may provide protection against UV-induced premalignant lesions.

We have recently demonstrated that doses of UV light too low to cause visible skin reddening are still capable of activating the enzymatic machinery that leads to photoaging. Therefore minimizing sun exposure must be an important part of any photoaging treatment program, to prevent its further progression. Pretreatment with
tretinoin markedly inhibits UV induction of matrix metalloproteinases at the mRNA, protein, and enzyme activity levels. Recently, these changes were demonstrated visually by the use of riboprobe in situ hybridization, immunohistology, and in situ zymography techniques, collectively providing the first solid evidence for prevention of photoaging by tretinoin.

SYSTEMIC ABSORPTION OF TOPICAL TRETINOIN

When administered systemically, tretinoin is a potent teratogen, like isotretinoin and etretinate. Because more younger women are using topical tretinoin both for treatment and presumed prevention of photoaging, there has been great concern about whether tretinoin, topically administered, also has teratogenic potential. Existing data on teratogenicity of topical tretinoin use have, for the most part, been collected from patients who were being treated for acne. In a large population-based study, no significant increase in the rate of fetal malformation was observed in the tretinoin-treated group during the first trimester of pregnancy, as compared with those without the exposure. Consistent with this finding were results from a controlled study in which 0.025% tretinoin gel was applied daily to the face, neck, and upper part of the chest for 14 days. Fluctuations in plasma levels of endogenous retinoids were lower than those of diurnal and nutritional factors. Taken together, the data on routine clinical use of topical tretinoin indicate that there is no increased risk for pregnant women.

The cytochrome P-450 enzyme, retinoic acid 4-hydroxylase, metabolizes tretinoin to 4-hydroxy retinoic acid, which is inactive. Very recently, this enzyme was cloned and identified as a novel cytochrome P-450 (CYP26). Human skin not only expresses the enzyme but, after exposure to pharmacologic doses of tretinoin, also induces the enzyme activity. It appears likely that, with repeated topical application of tretinoin, locally induced 4-hydroxylase will remove excess tretinoin, limiting the amount available for systemic absorption. This compensatory induction of 4-hydroxylase will not serve similar functions for synthetic retinoids unless such compounds can be hydroxylated by the enzyme and their products rendered inactive by hydroxylation. Given the molecular structure of synthetic retinoids, it is unlikely that 4-hydroxylation and inactivation will occur before absorption.

SUMMARY

Photoaging is a treatable condition that responds favorably to treatment with topical tretinoin. The improvement in photoaged skin is tretinoin specific, not secondary to irritation. Indeed, marked clinical improvement can be achieved without excessive use of tretinoin, thereby minimizing the occurrence of skin irritation. However, some skin peeling, or desquamation, is unavoidable (except by dose reduction), because the epidermal hyperproliferative response is RAR-mediated. Based on evidence from controlled studies, non-white patients tolerate topical tretinoin treatment well. Postinflammatory dyspigmentations are only rarely observed. Increased “photosensitivity” during tretinoin use appears to be an enhanced neurosensory response to infrared irradiation, rather than a phototoxic or an accelerated sunburn response. No increased risk of photocarcinogenesis has been detected in humans with tretinoin treatment. Finally, according to published epidemiologic data, tretinoin therapy involves no increased risk of teratogenicity at the typical dose used to treat photoaging. Nevertheless, because spontaneous malformation of the fetus occasionally occurs in “normal” pregnancies, it is probably prudent to postpone tretinoin therapy for patients who are actively trying to conceive, to avoid wrongful blame for congenital defects that may occur by chance. In summary, topical tretinoin is an effective agent that can be used safely and wisely to treat photoaging when the clinical approach is based on existing scientific knowledge.

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