Hot Topics

Skincare Science: Update on Topical Retinoids

According to the author, the single most effective component in a skincare regimen for reversal of photoaging is the use of retinoids. Here is a guide to the mechanism and application of various formulations of retinoids, and a comprehensive skin regimen incorporating tretinoin. (Aesthetic Surg J 2006;26:233-239.)

The search for the fountain of youth, beginning with Ponce de Leon in the 1400s, currently persists in the form of surgical and nonsurgical treatments to roll back the effects of time. Women's magazines devote significant editorial content and advertising space to treatments that are purported to restore, or at least maintain, a youthful appearance. Prime time television abounds in commercials about products that will “defy the effects of time” or “wipe away wrinkles.” More than 12 billion dollars were spent on cosmeceuticals in 2005; by 2010, expenditures are expected to top 15 billion dollars.

People are looking for ways to prevent or reverse the signs of aging, and the easiest and most accessible method is skincare.

Mechanisms of Photoaging

There are 2 types of skin aging: chronological aging (intrinsic aging) and photoaging (extrinsic aging). Chronological aging occurs in all skin areas; photoaging occurs in skin that has the most sun exposure, such as the face, neck, and dorsum of the hands. Photoaging, characterized by a rough texture, fine and coarse wrinkling, sallow color, and uneven skin pigmentation (Table 1), is primarily caused by ultraviolet radiation, but can also be caused by tobacco smoke and other environmental exposures, such as ozone. Immediate results of ultraviolet radiation may include sunburn, immune suppression of the skin, collagen breakdown, and decreased collagen synthesis. Exposure to ultraviolet radiation over an extended period can lead to clinically obvious skin sun damage and skin cancer.

Ultraviolet radiation causes breakdown of collagen, elastin, and ground substance, which when combined with imperfect resynthesis of these components, leads to the characteristic changes seen with photodamaged skin. The primary histological characteristics of photoaging are the accumulation of abnormal elastic material in the upper and middle dermis and loss of collagen in the dermis (Table 2). The elastin gene is overexpressed in sun-damaged cells, causing excess elastin, which is deposited in an unorganized and nonlinear fashion.

Overall loss of collagen in the dermis is due to 2 factors: (1) the increased breakdown of collagen by matrix metalloproteinases (MMPs) and (2) inhibition of collagen precursors by transcription factor activating protein 1 (AP-1). Both factors are stimulated by ultraviolet radiation.

Collagen is one of the major components of the dermis, providing strength and volume to the dermis; type I collagen is the most prevalent type of collagen in the skin. About 85% of collagen is type I; type III collagen accounts for an additional 10%. Skin that has significant photodamage may undergo a 56% reduction in type I collagen as compared with skin that has been protected from the sun.

Matrix metalloproteinases are proteolytic enzymes that degrade collagen and are downregulated by tissue inhibitor of matrix metalloproteinases (TIMP-1). The 3 MMPs responsible for the degradation of collagen are collagenase, 92 kD gelatinase, and stromelysin-1. Collagenase hydrolyzes the collagen fibrils, and then the collagen is further degraded by 92 kD gelatinase and stromelysin-1. Transcription factor AP-1 regulates transcription of the MMPs and is composed of the 2 proteins, c-Jun and Fos. C-Jun is directly upregulated when exposed to ultraviolet radiation leading to increased AP-1 activity. It takes as little as 10 to 15 minutes in the sun to upregulate AP-1 and increase the MMPs responsible for collagen breakdown. MMPs are primarily induced in the epidermis by ultraviolet radiation; however, their pro-
T eins and enzymatic activity are seen in both the epider-mis and dermis.

In addition to increasing collagen degradation, ultravi-olet radiation exposure directly inhibits types I and III procollagen production. This occurs by ultraviolet radia-tion inducing c-Jun production, leading to increased AP-1, which negatively regulates both type I and III gene tran-scription. As little as 0.5 minimal erythema dose (MED) can cause a 50% reduction in procollagen production, and 1 MED causes a 70% to 80% reduction of procolla-gen types I and III in vivo. The MED is the time that it takes to turn the skin red when exposed to sunlight. This effect lasts for up to 24 hours, so a daily exposure of 1 MED will cause a sustained decrease in procollagen.

Topical Vitamin A Analogs

The best way to a healthy skin is to prevent photo-damage with liberal use of broad-spectrum sun blocks and to limit sun exposure. When sun damage has occurred, treatment consists of skincare, chemical peels, and laser resurfacing. The single most effective compo-nent in a skincare regimen for reversal of sun damage is the use of retinoids, which are derivatives of vitamin A. Familiar examples of retinoids are retinol, retinal, retinyl palmitate, retinyl acetate, and retinoic acid. Retinoic acid was used solely for acne treatment until the late 1980s when 2 published papers suggested that this agent could reverse the effects of sun damage. Since then, retinoic acid has been more frequently prescribed for its cosmetic benefits than for its effect on acne.

All trans-retinoic acid (tretinoin) is the most bioactive form of the retinoids when topically applied to the skin (Table 3), causing thinning of the stratum corneum, which leads to a smoother skin texture and allows for better penetration of other topical agents. Initially it causes thickening of the epidermis to improve the moisture barrier, although over time, the epidermal thickness decreases to baseline. Tretinoin increases cellular turnover, which may explain the initial increase in epider-mal thickness. Increased cellular turnover also helps with reepithelialization of the skin following an injury. Tretinoin causes dispersion of the melanin granules in the epidermis, which helps reduce hyperpigmentation in treated areas. It helps reverse keratinocyte atypia and treats fine lines and wrinkles by increasing collagen pro-duction and glycosaminoglycan (hyaluronic acid) deposition in the epidermis. Continued use of tretinoin will improve the sallowness (yellow color) of the skin by neo-vascularization of the dermis.

Retinol, which is very stable in product formulations, is the alcohol formulation of vitamin A and the most fre-quently used vitamin A analog in cosmeceuticals. At equivalent doses, it is better tolerated than retinoic acid; however, retinoic acid is approximately 20 times more potent than retinol. The mechanism of action of retinol is multifactorial. There is conversion of retinol to retinoic acid through a 2-step oxidative process; it can directly bind to the retinoic acid receptors (although with a very low binding affinity, and thus weak biologic activity) and through undescribed pathways. Retinol has been shown to improve texture, dyspigmentation, dryness, and fine lines. However, the optimal concentra-tion to balance skin irritation versus effectiveness has not been determined.

Retinyl esters, such as retinyl palmitate and retinyl acetate, are frequently used in cosmeceuticals because they are very stable. However, these are the least effective of the retinoids because they first need to be con-verted to retinol by cleavage of the ester bond, and then need to be converted into retinoic acid. Retinyl esters have been shown to increase the epidermal thickness in human skin, but their results are not as impressive as those of retinoic acid.

Retinal is the aldehyde formulation of vitamin A. Similar to retinyl esters, retinal represents a stable der-ivative of vitamin A, which is used in cosmeceuticals but has limited efficacy. It mildly improves wrinkles and tex-ture and is less irritating than retinoic acid. As with the ester formulations, it causes a mild increase in epidermal thickness.
The unorganized accumulation of excess elastin that is characteristic of chronic sun damage may be improved with administration of tretinoin. In a rat model, treatment with tretinoin decreased the tortuosity of the elastic fibers and improved skin elasticity. The mechanism of action for improved linearity of the elastin is unclear.3

Retinoids and Acne

The etiology of acne is multifactorial, consisting of abnormal sebum production, overgrowth of Propionibacterium acnes, hyperkeratinization of the follicular epithelium, and inflammation. Acne may be classified into 2 types: noninflammatory, which is characterized by comedones, and inflammatory, which predominantly consists of papules and pustules. Microcomedones are the precursors of both inflammatory and noninflammatory acne. Retinoids work by decreasing microcomedones and comedones; therefore, retinoids primarily decrease noninflammatory acne, but also cause some reduction of inflammatory acne.

Tretinoin demonstrates an effect in 1 to 2 months, with the peak effect occurring after 2 to 4 months. Tretinoin does not have any effect on bacterial overgrowth, so it needs to be combined with topical or oral antibiotics to decrease Propionibacterium acnes. In addition to their antibacterial effects, tetracycline and erythromycin have anti-inflammatory properties that may improve tolerability of the retinoic acid. When antibiotics are used chronically, bacteria may develop resistance. Benzoyl peroxide reduces bacterial colonization without inducing resistance and is appropriate to use in combination with antibiotics and topical retinoids.18 Since benzoyl peroxide is known to decrease the stability of retinoic acid, benzoyl peroxide and other topical antibiotics should be applied in the morning and retinoic acid applied in the evening. Retinoic acid encapsulated in microspheres is significantly more stable than standard retinoic acid, especially in skin treated with benzoyl peroxide.19 For those with severe sebum overproduction, nodulocystic acne, or for those unresponsive to other treatments, oral isotretinoin (Accutane) (Hoffman-LaRoche, Inc., Nutley, NJ) is extremely effective.

Retinoic Acid Formulations, Use and Safety

Initiation of tretinoin treatment is frequently associated with retinoid dermatitis, characterized by erythema, pruritus, dry skin, burning sensation, and desquamation. In addition, because of thinning of the stratum corneum, tretinoin makes the skin more sensitive to the sun. The severity of retinoid dermatitis depends on skin sensitivity,
concentration and formulation of retinoic acid, and frequency of application. Retinoic acid is normally hydrophobic, with minimal penetration through the stratum corneum layer of the epidermis. As the retinoic acid is trapped in the stratum corneum, it gradually induces irritation and inflammation associated with retinoid dermatitis.

Retinoic acid is formulated in a cream (0.025%, 0.05%, 0.1%); gel (0.01%, 0.25%); solution (0.05%); microspheres (0.04%, 0.1%); and emollient (Renova 0.05%). The solution and gel products are very drying and are usually not well tolerated. The microspheres work in a time-release fashion and are more stable than an equivalent dose of tretinoin. Microspheres delay the onset of irritation, but do not reduce the cumulative irritation when compared with tretinoin. Renova causes fewer side effects than the cream-based formulation, and most of the reactions have resolved within 1 to 2 months. However, it takes longer to see a clinical effect (3 to 6 months). People with very dry skin usually tolerate Renova better than tretinoin.

Tretinoin is most commonly prescribed in the cream formulation and is usually applied at night since it is degraded with sun exposure. It is best to start with a low concentration (0.025%), using it every other day. Once the tretinoin is tolerated daily, the concentration can be increased. To achieve optimal results from retinoic acid, 0.1% retinoic acid should be used daily. Tretinoin has been used in high-strength formulations (0.25%) with histological changes occurring at a much faster rate. Patients develop tolerance to the tretinoin and see improvement of the retinoid dermatitis caused by tretinoin within 2 weeks. This is due to downregulation of the retinoic acid receptors. Tretinoin has also been combined with topical steroids to effectively decrease retinoid dermatitis. The tretinoin mitigates the dermal atrophy caused by the corticosteroid.

**Recommended Skincare Regimen**

The optimal course of action is to prevent sun damage by avoiding significant sun exposure and liberally applying broad-spectrum sun blocks. However, for most people, this is not easily achieved, making a skincare regimen designed to reverse the histological and clinical effects of sun damage a necessary cosmetic and health measure.

Tretinoin is frequently used as part of a comprehensive skincare regimen including cleansers, toners, exfoliants, antioxidants, sun blocks, and skin lightening agents. Abrasive cleansers can make the skin more sensitive by damaging the epidermal barrier and should be avoided when initiating tretinoin therapy. Patients are instructed to clean and dry the face 20 to 30 minutes before applying tretinoin, since application while the face is damp will increase sensitivity. Combination therapy with tretinoin and alpha-hydroxy acids shows more improvement in dyspigmentation and fine lines than monotherapy and is not associated with increased side effects when compared to tretinoin by itself. There have been multiple studies that show that, because of their different mechanisms of action, the combination of tretinoin and hydroquinone is much more efficacious than either drug alone at treating dyspigmentation. In addition, tretinoin causes thinning of the stratum corneum, which allows better penetration of the hydroquinone. Sun blocks are an important part of the skincare regimen to help prevent further photodamage, and they should broadly cover both the UVA and UVB spectrum.

Other than the local side effects, which are directly related to concentration and frequency of use, topical retinoic acid is well tolerated and has a good safety profile. It is considered a pregnancy category C pharmaceutical and should not be used by pregnant or nursing women. Topical retinoic acid has not been shown to be teratogenic in rats and rabbits, even when administered in doses 100 to 320 times the topical human dose. Systemic absorption of retinoic acid ranges between 1.1% to 2%. Long-term use (greater than 1 year) of retinoic acid is associated with a lower absorption. Even with maximal absorption, the systemic levels of retinoic acid and its metabolites are significantly lower than the US recommended daily allowance as set by the FDA for vitamin A supplements. This also suggests that retinoic acid has minimal systemic risks.

A comprehensive skin care regimen includes a 7-step process:

1. Cleanse the face with a low-residue cleanser each morning and evening.
2. Follow cleansing with an alcohol- and astringent-free toner (to prevent drying) to restore the pH to 5.5.
3. Apply daily an 8% to 12% alpha hydroxy acid to exfoliate the skin, help with fine lines and wrinkles, increase glycosaminoglycan deposition, and improve sallowness and texture.
4. Apply daily an antioxidant, such as topical L-ascorbic acid in a 10% to 20% formulation with a pH less than 3.5 to function as an oxygen-free radical scavenger, increase collagen deposition, and help with hyperpigmentation.
5. Apply a blending agent daily, such as hydroquinone or Kojic acid to decrease hyperpigmentation by the inhibition of melanin production.
6. Apply 0.1% tretinoin daily to improve skin texture, decrease fine wrinkles, improve hyperpigmentation, increase dermal volume and strength, and reduce sallowness.
7. Apply a sun block covering a broad spectrum of UVA and UVB waves early in the morning and then again, 4 hours later.

If you cannot convince your patients to stick with a comprehensive regimen like this, then at least convince them to use a sun block and the maximal strength of tretinoin that they can tolerate.

**Tazarotene and Adapalene: Third-Generation Retinoic Acids**

Tazarotene and adapalene are third-generation retinoic acids that work by selectively binding to the nuclear retinoic acid receptors (RARs) $\alpha$, $\beta$, $\gamma$. Adapalene has primarily been used for the treatment of acne and causes significantly less retinoid dermatitis than tretinoin and tazarotene formulations because of its direct anti-inflammatory properties. Adapalene does not induce epidermal hyperplasia, so it is not used in the treatment of sun-damaged skin.20,31

Tazarotene has been shown to have effects similar to retinoic acid and has been used to treat acne and sun-damaged skin. When used to treat photodamaged skin, tazarotene treatment demonstrates improvement in fine wrinkling, mottled hyperpigmentation, lentigines, irregular depigmentation, apparent pore size, elastosis, and tactile roughness.33 Tazarotene has been compared with tretinoin 0.5% cream, and both agents improve fine wrinkles, mottled hyperpigmentation, and demonstrate an overall improvement. Tazarotene induces similar histological and clinical changes as tretinoin; however, it is slightly more irritating for the first 1 to 3 months of treatment.33 It has been compared with different tretinoin formulations and is more effective in the treatment of acne.34,35

**New Directions**

The goal of the next generation of topical retinoids is to increase stability and histological and clinical effects, while minimizing side effects. Microsphere technology improves the stability of retinoic acid and delays the onset of skin irritation, but does not significantly decrease the irritation. Tretinoin has been combined with sun blocks and ultraviolet filters to attempt to reduce degradation by ultraviolet radiation; however, only by adding a yellow color to the tretinoin was stability improved.36 For acne treatment, tretinoin has been combined with liposomes to increase stability and anti-acne activity while minimizing local side effects.37

Nanotechnology has been combined with retinoic acid to improve penetration across the stratum corneum, causing less inflammation than a similar dose of stan-
standard retinoic acid. In addition, the epidermal thickening was more significant and occurred more quickly than with standard retinoic acid. Hyaluronic acid production was significantly elevated in the epidermis, which helps with reduction of fine lines and wrinkles.10

References


Reprint requests: C.B. Boswell, MD, Bodyaesthetic Plastic Surgery & Skincare Center, 969 North Mason Road, Suite 170, St. Louis, MO 63141. Copyright © 2006 by The American Society for Aesthetic Plastic Surgery, Inc.

1090-820X/$32.00
doi:10.1016/j.asj.2006.02.003