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Retinoids in Acne Management: Review of Current Understanding, Future Considerations, and Focus on Topical Treatments

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ABSTRACT

Acne vulgaris is the most common skin condition affecting adolescents and young adults with a tremendous psychosocial impact. Its pathogenic hallmarks include follicular dyskeratosis, increased sebum production, and inflammation induced by *Cutibacterium* (formerly *Propionibacterium*) *acnes* within the follicle. Retinoids, derived from vitamin A, are the mainstays of acne treatment given they address the key pathogenic pathways of acne. Retinoids exert their effects through the binding of their nuclear receptors leading to downstream biological effects. The understanding of retinoid pharmacology has increased the diversity of retinoids with now both natural and synthetic retinoids available for use. For acne, retinoids can be administered both topically in a variety of formulations and combinations as well as systemically. With judicious use, this class of medication is well tolerated and very efficacious in managing acne. Furthermore, there is evidence showing its role in improving and preventing one of the most challenging post-acne changes, atrophic acne scarring. With a promising topical retinoid, trifarotene, on the horizon, the acne armamentarium will be further broadened to better manage acne and its related sequelae.

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INTRODUCTION

Acne vulgaris affects approximately 85% of youths and can persist into adulthood.[1-4] It is an inflammatory disease of the pilosebaceous unit and brought about by follicular hyperkeratinization, increased sebum production, and *Cutibacterium* (formerly *Propionibacterium*) *acnes*. Follicular dyskeratosis leading to formation of the microcomedo is believed to be central to the development of acne. The activation of innate and cellular immune responses subsequently occurs with genetics, androgens, diet, and stress also playing a role. Clinically, acne presents with open and closed comedones, inflammatory papules, pustules as well as nodules. It typically affects areas with greater density of sebaceous glands such as face, neck, chest, upper back, and upper arms.[5-9]

Although there are many treatment modalities for acne, scarring is an unfortunately common clinical outcome.[10] Acne scars, which range from hypertrophic and keloidal to atrophic, arise due to delayed or inadequate treatment and healing of acne lesions.[11-14] Atrophic scars are arguably the most frequently seen and can have significant impact on patients' quality of life.[15] The severity of scars is correlated with the extent of acne and the delay between disease onset and treatment initiation. Thus, one of the primary goals in acne treatment is adequately addressing the active disease in an effort to minimize potential permanent scarring.

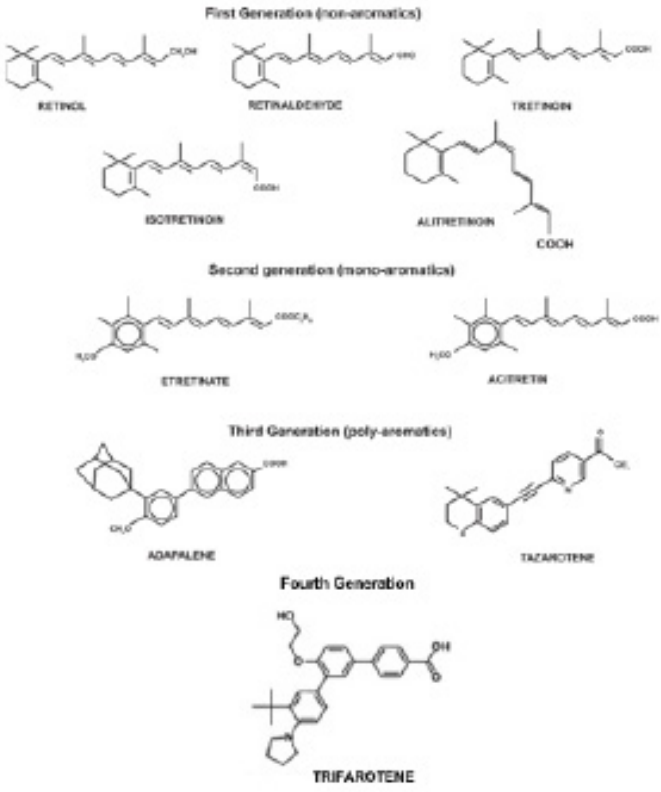
Retinoids are widely used in the management of acne. This class of medication targets the follicular dyskeratosis central to acne pathogenesis and also possesses anti-inflammatory properties. It has also been studied in the context of hyperpigmentation and scarring associated with acne. Here, we review the mechanism of action of retinoids, their topical and systemic use in acne vulgaris, their role in the management of acne scars, and early data on a new fourth generation retinoid, trifarotene.

Retinoid Mechanism of Action

Retinoids are structural and functional analogues of vitamin A that exert multiple biological effects. The key to their efficacy is their ability to mediate their effects through their intranuclear retinoid receptors. Thus, a retinoid is defined as any molecule that, by itself or through metabolic conversion, binds to and activates the retinoic acid receptors, leading to activation of retinoic acid-responsive genes resulting in specific skin responses.[16,17]

Currently, retinoids are classified as first, second, and third generation retinoids. First generation retinoids include all-*trans*-retinoic acid (tretinoin), 13-*cis*-retinoic acid (isotretinoin), and 9-*cis*-retinoic acid (alitretinoin). Through replacement of the β-ionone ring in all-*trans*-retinoic acid with an aromatic structure, newer retinoids (or second-generation retinoids), were introduced, which include etretinate and acitretin. With the discovery of retinoic acid receptors, receptor-specific, third-generation retinoids such as adapalene and tazarotene were developed. As discussed below, a fourth-generation retinoid, trifarotene, is also on the horizon[18] (Figure 1). The second, third, and fourth-generation retinoids are also known as synthetic retinoids as they bear no structural similarities to all-*trans*-retinol or retinoic acid yet are still considered

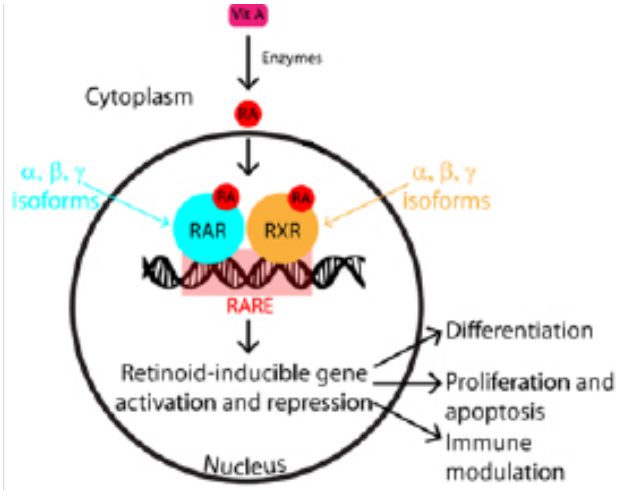
FIGURE 1. Chemistry of retinoids. *(Adapted from Mukherjee S, Date A, Patravale V, et al. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging.2006;1(4):327-348 and Thoreau E, Arlabosse JM, Bouix-Peter C, et al. Structure-based design of trifarotene (CD5789), a potent and selective RARγ agonist for the treatment of acne. Bioorg Med Chem Lett. 2018;28(10):1736-1741.)*



retinoids given their ability to activate the receptor(s) and mediate the retinoid effect.[19]

Major breakthrough in the understanding of retinoid action came with discovery of the nuclear receptors for retinoids. Retinoids exert physiological effects on DNA transcription through the binding of two receptors, retinoic acid receptors (RAR) and retinoid X receptors (RXR). Each receptor has three isotypes (α, β, and γ) and different retinoids have distinct binding properties to these receptors. For instance, tretinoin binds to RAR-γ and RXR-α heterodimer whereas the newer retinoids adapalene and tazarotene are selective agonists of RARβ and RARγ. Trifarotene, on the other hand, has selective RARγ agonist activity with minimal effect on RARβ and RARα. It is also inactive on the RXR receptor.[20] Dimer of the retinoid receptors along with their retinoid ligand binds to specific DNA regulatory sequences named hormone response elements in the promoter regions of retinoid-responsible genes (retinoic acid response elements = RARE). This leads to the downstream biologic effects seen with retinoids (Figure 2).[21-24] Each retinoid's unique receptor activity translates to specific clinical effects, although it is currently unclear how the retinoid's selective binding directly impacts these endpoints.

FIGURE 2. Mode of action of retinoids. *(Adapted from Topical trifarotene: a new retinoid, 179(2):231-232, First published: 24 August 2018.)*



A key retinoid effect important for acne includes normalization of abnormal follicular differentiation. This leads to loosening of microcomedones, allowing sebum to reach the skin surface to prevent pilosebaceous unit obstruction. Moreover, retinoids can also decrease the expression of Toll-like receptor (TLR)-2, which is elevated in acne lesions, partially activated by *C. acnes*.[25-26] Retinoids also cause sebaceous gland atrophy and a decrease in sebum production, which inhibits inflammation induced by sebum-dependent *Cutibacterium*.[27]

Topical Retinoids in Acne

It is commonly accepted that topical retinoids are extremely effective for acne treatment, especially for comedonal lesions.[28-29] Of the different anti-acne medications, retinoids are considered the first-line and arguably the only agents to normalize the abnormal follicular differentiation seen in acne. By targeting microcomedones, retinoids not only treat, but can also prevent the development of new lesions.[28-29]This prophylactic property is the basis for including topical retinoid as the foundation in almost all acne regimens. Moreover, in an era in which providers are called upon to exercise antibiotic stewardship, retinoids are playing an even more crucial role in acne treatment in place of antibiotics.

Tretinoin was the first topical retinoid for clinical use and over time, new retinoids have also become available for acne, specifically adapalene and tazarotene. Adapalene is now also sold over the counter. Combination medications with either clindamycin or benzoyl peroxide coupled with a retinoid have also been introduced (Table 1). Unlike other topical retinoids, adapalene's unique structure renders it resistant to oxidation thus allowing for its combination with benzoyl peroxide. Different formulations and combination therapies allow for flexibility in tailoring the

treatment to an individual's skin dryness or oiliness as well as increased compliance.

The most critical aspect of topical retinoid therapy is patient education. Patients must be counseled on local skin irritation, characterized by redness and peeling. Furthermore, contrary to common belief, clinical improvement does not correlate with the degree of irritation. A large, controlled clinical study in which 0.025% and 0.1% tretinoin were used showed both formulations to be equally efficacious, but the former was significantly less irritating than the latter.[30] Therefore, unlike most medications for which the dosing schedule is regimented, the use of a topical retinoid should be individualized and titrated depending on the skin reaction. Typically, retinoids are applied in the evening given it is inactivated by ultraviolet exposure. Patients are advised to apply the medication initially every other night or a few nights a week, titrating upwards as tolerated.[31]

The most common adverse effect associated with topical retinoid use is local skin irritation as discussed. This expected response is temporary, but troubling, for many patients leading to decreased compliance. This effect peaks within the first month of treatment and improves thereafter. This can be managed with a temporary reduction in the frequency or amount of retinoid application as well as the liberal use of emollients. There is evidence demonstrating that these measures enhance topical retinoid tolerability without compromising treatment efficacy.[32]

Systemic retinoid use, as discussed below, is well established as a cause of embryonic death and congenital malformation, and understandably, there is concern regarding potential teratogenicity from long-term topical retinoid use. Studies have shown that systemic absorption of retinoids and changes in retinoic acid in the blood from topical application are negligible. Furthermore, topical administration of tretinoin at doses used for acne has less impact on plasma levels of endogenous retinoids than diurnal and dietary factors.[33] As expected, a large, population-based study demonstrated no excess risk of birth defects in offspring born to mothers who were exposed to topical tretinoin during pregnancy.[34] While no evidence exists for teratogenicity of topical retinoids in humans, most practitioners delay their use for acne in pregnancy due to medical-legal reasons.

Systemic Retinoid in Acne

Isotretinoin is extremely effective in treating acne given it addresses the primary etiologic factors associated with acne. It decreases sebum production, targets comedogenesis, and minimizes colonization with *Cutibacterium acnes*.[35] Its use over time has expanded from treating only patients with severe nodulocystic disease in the early 1980s to now patients with less severe disease who fail conventional therapies, exhibit extensive scarring, suffer from significant psychosocial distress, and those with acne fulminans.[36]

TABLE 1.

Topical Retinoids and Preparations	
Topical Retinoid	**Preparation**
Tretinoin	Creams: 0.025%, 0.0375%, 0.05%, 0.1% Gels: 0.01%, 0.025% Microsphere gels: 0.04%, 0.08%, 0.1% Polyolprepolymer-2 cream: 0.025% Polyolprepolymer-2 gel: 0.025% Gel (micronized): 0.05%
Adapalene	Cream: 0.1% Gels: 0.1% (available over the counter), 0.3% Lotion: 0.1%
Tazarotene	Creams: 0.05%, 0.1% Gels: 0.05%, 0.1% Foam: 0.1%
Clindamycin 1.2% Tretinoin 0.025%	Gel
Benzoyl peroxide 2.5%/ Adapalene 0.1%	Gel
Benzoyl peroxide 2.5% Adapalene 0.3%	Gel

The daily dose of isotretinoin is approximately 0.5-1 mg/kg of body weight per day taken with food to maximize absorption.[35] However, low dose regimen (ie, 0.25-0.4 mg/kg/day) has been shown to be equally efficacious, similar in inducing remission, with fewer adverse events.[37] Previously, it was believed that post-therapy relapse is minimized by administering a cumulative dose of at least 120 mg/kg, which typically results in 6–8 months of therapy.[38] This paradigm has shifted and the current recommendations emphasize tailoring the dosing and treatment length to each individual, factoring in demographics, clinical presentation, and comorbidities to maximize success.[39] A lag period of 1–3 months may occur before the onset of the therapeutic effect and a flare of acne during the first month may be observed. Continued healing of acne after the discontinuation of therapy is frequently seen. Approximately one-third of patients with acne require a second course of therapy for either persistent disease or relapse. During isotretinoin therapy, other acne treatments, both topical and systemic, are discontinued to avoid enhancing any potential side effects.

The most important adverse effect of isotretinoin is teratogenesis. Retinoid-induced birth defects include auditory, cardiovascular, craniofacial, ocular, axial and acral skeletal, central nervous system (hydrocephalus, microcephaly), and thymus gland abnormalities.[40] In men, retinoid therapy does not appear to produce abnormalities in spermatogenesis, sperm morphology, or sperm motility.[41] However, the recommendation is for men who are actively trying to father children to avoid systemic retinoid therapy.

Most patients receiving oral retinoids will develop dryness of the lips, skin, and mucous membranes. More severe cases can lead to retinoid dermatitis. *Staphylococcus aureus* colonization can also occur due to disruption of the skin barrier caused by isotretinoin-

induced reduction in sebum production.[42] Diffuse or localized hair loss, nail thinning, and paronychia-like changes may also occur.[43]

Central nervous system side effects are rare. Although signs of increased intracranial pressure are observed occasionally, pseudotumor cerebri is extremely infrequent oftentimes occurring in the setting of concomitant use of isotretinoin and tetracyclines.[44] Anecdotal reports suggest a causal association between isotretinoin therapy and severe depression with suicide attempts. However, large-scale epidemiologic studies provide no evidence that isotretinoin exposure is associated with any greater risk of psychiatric disorders than is antibiotic use in patients with acne.[45] Nevertheless, patients should be counselled on this possible link and followed for the development of depression or suicidal ideation.

The association of isotretinoin with inflammatory bowel disease is conflicting. Multiple case-control studies did not observe statistically significant relationship between isotretinoin therapy and inflammatory bowel disease. One recent case control study found a small increase in risk for ulcerative colitis among patients who had received isotretinoin, but no association between isotretinoin and Crohn's disease. More studies are needed to clarify this association thus patients should be monitored and counselled regarding this possible link.[46]

Blepharoconjunctivitis occurs with varying severity in about one-third of patients treated with isotretinoin. This is generally alleviated by artificial tears with ophthalmologic consultation infrequently required. Alterations in visual function, mainly poor night vision, excessive glare sensitivity, and changes in color perception, have also been reported.[47]

Musculoskeletal side effects can also occur. Bone pain without objective evidence of any abnormalities and without sequelae can be seen in patients. Diffuse idiopathic skeletal hyperostosis (DISH) syndrome-like bone changes and calcification of tendons and ligaments are rare.[48] Myalgias may occasionally occur in patients taking isotretinoin, particularly in individuals involved in vigorous physical activity.[49]

Laboratory changes can be associated with isotretinoin therapy. Serum lipid changes are the most frequent abnormalities seen with retinoid treatment. Transient abnormal elevations in serum transaminase can also occur and increase in serum alkaline phosphatase levels have also been infrequently reported. Hematologic abnormalities are uncommon with isotretinoin therapy.[50]

Most adverse effects associated with isotretinoin are preventable and manageable with judicious patient selection, dosage adjustments, discontinuation of treatment when indicated, and routine monitoring for potential adverse effects. With isotretinoin, women with childbearing potential must have two negative results on a pregnancy test spaced thirty days apart and must practice effective contraception during treatment and for one month after the completion of therapy.[51] The iPLEDGE program (http://www.ipledgeprogram.com) has been put into effect by the Food and Drug Administration and the manufacturer to minimize the risk of isotretinoin-associated teratogenicity. Additional precautions before and during therapy include measurement of serum lipids, complete blood count, and liver enzyme levels. Providers should also assess for any personal and family history of psychiatric conditions, gastrointestinal diseases, and skeletal abnormalities.

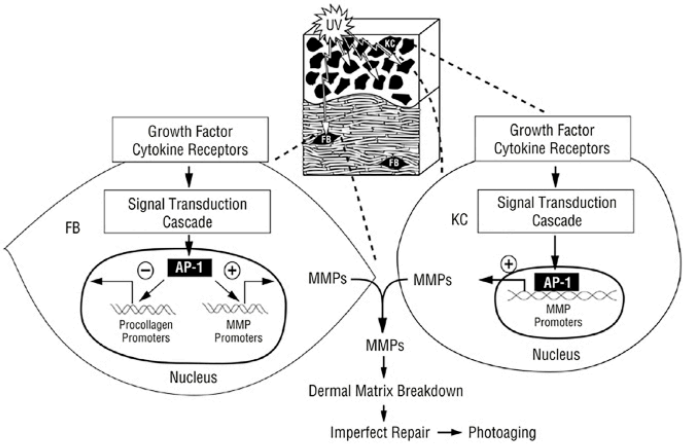
Retinoids and Acne Scars

As discussed previously, one of the major impetus for early and adequate acne treatment is the prevention of scarring. Atrophic acne scarring is one of the most common and difficult to treat sequelae of acne. Loss of dermal matrix is believed to be the main contributing factor, which involves the degradation of collagen that occurs during the inflammatory phase of acne. Activation of transcription factor AP-1 stimulates the production of matrix-degrading metalloproteinases (MMPs), which degrade the extracellular matrix. Studies have shown that MMP-1, MMP-3, and MMP-9 are increased in inflammatory acne lesions.[52] Of note, a similar phenomenon is seen in photoaging, which is also characterized by loss of dermal collagen, resulting from the same MMPs shown to play a role in inflammatory acne lesions (Figure 3).[53]

In photoaging, topical retinoids have been shown to improve fine wrinkles through the partial restoration of reduced levels of collagen seen in sun-exposed skin. It is well established that topical retinoids can stimulate dermal fibroblasts and increase the production of procollagen in photoaged skin. Furthermore, topical tretinoin has a protective effect against ultraviolet radiation-induced loss of procollagen by blocking transcription factor AP-1, thus preventing the increase in MMP synthesis.[53] Patients also note an improvement in skin texture, which is partly due to the enhanced deposition of hyaluronic acid brought about by topical retinoids.[54]

These observations can be applied in the setting of acne scarring in which scarring is improved and potentially prevented with topical retinoid via similar mechanisms. Indeed, a recent study evaluating patients with moderate to severe facial atrophic acne scars found an improvement in skin and scar texture with adapalene 0.3% gel.[55] Moreover, a multicenter, randomized, investigator-blinded, vehicle controlled, split-face study found that adapalene 0.1%/benzoyl peroxide 2.5% gel reduced the risk of atrophic acne scars and led to improved scar counts and global severity grading in the retinoid group.[56] A separate trial with adapalene 0.3%/benzoyl peroxide 2.5% gel yielded similar results.[57] Topical retinoid is an important tool to incorporate in the management and prevention of acne scars. Current treatment options for atrophic acne scars consist of primarily procedure-based modalities.[58] However, these invasive procedures may not be suitable or affordable to all patients. They also do not prevent the formation of acne scars

FIGURE 3. Pathogenesis of photoaging. This diagram depicts the effects of solar ultraviolet irradiation on the dermal matrix. Ultraviolet irradiation (jagged arrows) activates growth factor and cytokine receptors on keratinocytes (KC) and fibroblasts (FB). Activated receptors stimulate signal transduction cascades that induce transcription factor AP-1, which stimulates transcription of matrix metalloproteinase (MMP) genes. In fibroblasts, AP-1 also inhibits procollagen gene expression. Matrix metalloproteinases break down collagen and other proteins in the dermal matrix. Imperfect repair of the dermal damage impairs the integrity of the extracellular matrix. Repeated sun exposure causes accumulation of dermal damage that eventually results in wrinkling of photodamaged skin. *(From Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol 2002;138:1462.)*



and can only be employed once scarring has occurred. A topical retinoid offers an easier to use and more economical approach in acne scar treatment while preventing and targeting the persistent dermal tissue loss not addressed by many of the non-pharmacological treatments.

Future Directions

The area of retinoid research remains robust with the development of a new retinoid, trifarotene, on the horizon. This medication is the first fourth generation topical retinoid with potent and selective RARγ agonist activity with minimal RARβ-mediated effects, thus lending it greater efficacy with potentially decreased side effect of skin irritation. Furthermore, trifarotene has also been shown to possess increased hepatic instability compared to first and third generation retinoids, thus theoretically giving it a more tolerable systemic safety profile. This is an important consideration with more extensive topical use. In early studies, this medication demonstrated significant comedolytic and anti-inflammatory activities. Trifarotene was also shown to regulate many of the traditional retinoid-induced pathways. Its role in that regard along with its depigmenting properties can potentially expand its use in acne-related post-inflammatory hyperpigmentation and scarring.[20]

CONCLUSIONS

Acne vulgaris affects 85% of individuals 12-24 years of age and persistence into adulthood is not uncommon. Its pathogenesis centers around follicular dyskeratosis, increased sebum production, and *Cutibacterium* (formerly *Propionibacterium*) *acnes*. Acne can have tremendous psychosocial impact on the patient and can lead to permanent post-acne changes such as atrophic scarring. Retinoid is the cornerstone of acne treatment given it addresses the key pathogenic pathways in acne, which enables it to both treat and prevent acne. Furthermore, given its ability to down-regulate MMPs seen with acne inflammation and restore dermal collagen, retinoid can also improve and prevent acne scars. Trifarotene is a new fourth generation topical retinoid with significant comedolytic, anti-inflammatory, and depigmenting properties. Its introduction to the acne therapeutic ladder will expand options for patients and further treatment success.

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