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Issues and Considerations for Optimal Outcomes in Acne Management

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Issues and Considerations for Optimal Outcomes in Acne Management

INTRODUCTION

ORIGINAL ARTICLES

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PHYSICIANS' CONTINUING EDUCATION PCE

ISSUES AND CONSIDERATIONS FOR OPTIMAL OUTCOMES IN ACNE MANAGEMENT

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Termination Date: November 30, 2019
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Medium or combination of media used: Written article
Method of physical participation: Journal article, journal post-test, web-based post-test, and evaluation
Hardware/software requirements: High speed internet connection, any web browser

Statement of Need

Acne affects more than 85% of the general population at some point during the average lifespan and up to 95% of all acne patients have some degree of scarring; acne scarring is not well studied despite the high incidence. Scientific evidence leads to prevention as the main step toward eliminating scarring. Approximately 50% of patients with facial acne will experience truncal acne (61% experience lesions on the back; 45% on the chest); truncal acne may be underdiagnosed and undertreated. Advances in scientific understanding of acne pathogenesis are leading to new and innovative treatment options and standards of care include both evidence-based guidelines and clinical consensus recommendations. Medical interventions include topical and systemic retinoids, azelaic acid, benzoyl peroxide, and salicylic acid with combination therapy targeting multiple pathogenic factors becoming common. Treatment strategies for truncal acne are derived from those used for facial acne and challenges exist due to involvement of extensive body surface area with some treatment vehicles being more preferable for application on the back and chest.

Educational Objectives

The overall information and educational goals of this enduring activity are to summarize recent advances in the scientific understanding of acne pathogenesis as it relates to effective treatment acne in patients of all skin types; describe the role of retinoids in the management of acne; develop effective treatment and prevention strategies for hypertrophic and atrophic acne scarring in all skin types; and identify patient-specific issues impacting effective acne scar prevention and treatment. Upon completion of this continuing education activity, participants should be able to:

- Summarize the impact of acne on the practice of dermatology including issues associated with the identification of acne scars in patients at greatest risk
- Classify forms of acne scars
- Discuss measures to prevent formation and progression of acne scars
- Classify acne treatment strategies as they relate to disease pathogenesis
- Explain the role of topical and systemic retinoids in acne management

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants, nurse practitioners, and other healthcare providers with an interest in cutaneous diseases and disorders affecting patients of all skin types.

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Acne and Scarring: Facing the Issue to Optimize Outcomes

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The scourge and stigma of acne is only completely evident to those afflicted. The cruel reality for many, even when acne eventually abates, is the facial disfigurement of acne scars. And so, the stigma continues. Others perceive those with facial acne scars as insecure and shy and as being less attractive, confident, happy, healthy, and successful.[1] It is unsurprising then that acne scarring is associated with embarrassment, self-consciousness, anxiety, and depression. This issue aims to address this aspect of acne management to optimize outcomes.

Acne scarring can affect patients across the spectrum of acne severity. Of multiple potential risk factors, the most important is acne severity followed by time to effective treatment, manipulation of lesions, and a family history of acne scarring.[2] These factors reflect the intensity and duration of inflammation as well as an intrinsic tendency to scar.

There are 3 conceptual dimensions relevant to interventions in reducing atrophic acne scarring. First, timely and effective therapy of active acne. This requires management to reduce the folliculocentric inflammation so characteristic of acne that leads to atrophic scars. This is the subject of multiple evidence-based acne guidelines currently available throughout the dermatological literature. Secondly, increasing the proportion of newly formed scars that resolve or normalize. Recent studies have found that newly formed atrophic acne scars may not be permanent. In a six-month observational study of patients with moderate inflammatory facial acne, one third of scars forming during that time resolved spontaneously.[3] Matrix repair is ongoing during scar formation leading some scars to normalize. The therapeutic challenge then is to increase the proportion of scars that resolve by enhancing matrix repair. This potential was recently evaluated in 2 recent vehicle-controlled, rater blinded, half face studies using adapalene 0.1%/benzoyl peroxide 2.5% gel and adapalene 0.3%/benzoyl peroxide 2.5 gel, respectively. While both demonstrated mitigation in atrophic acne scar formation and improvement in global acne scar grades over 6 months, adapalene 0.3%/benzoyl peroxide 2.5 gel also demonstrated a reduction in scar numbers from baseline and compared to vehicle.[4,5] The likely underlying mechanism is stimulation of collagen production by the retinoid adapalene.[6] Thirdly, the correction of persistent scars. Repair procedures have progressively advanced beyond peels and dermabrasion with the advent fractionated ablative and non-ablative lasers, micro-needling with or without radiofrequency, trichloroacetic acid cross technique, subcision, and fillers. Nevertheless, such procedures are often costly, discomforting, and incompletely effective. Furthermore, there is little high-quality evidence to help direct patients and providers to best corrective options.[7] More evidence-based research is an unmet need in this context.

In summary, timely and effective therapy for active acne, use of interventions that address acne and enhance matrix repair, and selection of appropriate scar repair procedures, can reduce impact and optimize patient outcomes.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Evaluation, Prevention, and Management of Acne Scars: Issues, Strategies, and Enhanced Outcomes

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ABSTRACT

Acne is a common disease affecting a high percentage of the younger population. Without appropriate and effective primary prevention of scarring, post-acne scars occur in about 80-95% of all patients. Acne scarring is the result of an alteration of the healing process and it can have deep psychosocial implications for patients. Scars can involve textural change in the superficial and deep dermis and it can also be associated with erythema or pigmentation. While the most effective strategy to reduce acne scarring is to prevent its formation, over the past decades, numerous aesthetic and surgical techniques have been proposed to improve the appearance of acne scarring. However, scar treatment still remains suboptimal; indeed, acne scarring management is a difficult therapeutic challenge for dermatologists. Several treatment options have been described to treat various acne scar types and clinical responses may differ from various factors, such as skin types. Treatment approaches for acne scarring should be individualized and primarily determined by the morphological features of each patient's scars. Dermatologists need to better organize their assessment of acne scarring and develop a multistep treatment plans tailored to address patients' individual needs.

J Drugs Dermatol. 2018;17(12 Suppl):s44-48

INTRODUCTION

Evaluation of Acne Scars

Although several grading scales exist for acne scarring, there are many limitations in their application in daily clinical practice. Scars classifications is difficult even for acne experts, sometimes.

To simplify, there are two basic types of acne scars depending on whether there is a loss or gain of skin volume: 80–90% of patients having scars associated with a loss of collagen (atrophic scars) compared to a minority of subjects showing hypertrophic scars and keloids (with a ratio atrophic/hypertrophic scars 3:1).

Atrophic Scars

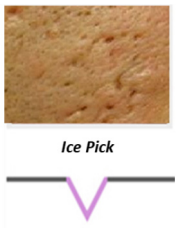
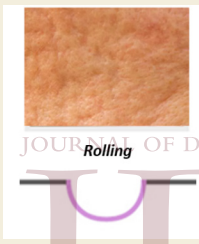
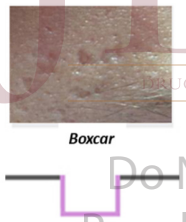
Atrophic scars can be sub-classified into ice-pick (60%–70% of total scars), boxcar (20%–30%), and rolling scars (15%–25%).[1] In Table 1 we summarize morphological features and corresponding clinical aspect of different type of atrophic scars. Among classifications and scales proposed by several authors, the qualitative scarring grading system proposed by Goodman and Baron[2] is simple and universally applicable (Table 2). The qualitative approach is useful in mild post acne scarring, but the main limitation of these scales is the subjectivity of the assessment. In the observation of severe cases, different patterns are simultaneously present and may be difficult to differentiate. For these cases, Goodman developed a quantitative global acne scarring assessment tool[3] based on the type of scar and the number of scars. This system assigns fewer points to macular and mild atrophic scars, and highest score to moderate and severe atrophic scars (macular or mildly atrophic: 1 point; moderately atrophic: 2 points; punched out or linear-troughed severe scars: 3 points; hyperplastic papular scars: 4 points). The multiplication factor for these lesion types is based on the numerical range: for 1-10 scars, the multiplier is 1; for 11–20 scars, the multiplier is 2; for more than 20 scars, the multiplier is 3. Other systems have been proposed to improve the approach to the classification of acne scars. In 2017, the Global Alliance to Improve Outcomes in Acne presented a system based on the global grading scale.[4] Tan et al proposed a six-category global severity scale (SCAR-S) for assessment of acne scarring at each of the face, chest, and back.[5]

The ECCA (Echelle d'Evaluation clinique des Cicatrices d'acn´e)[6] for facial acne scarring is also a quantitative scale, designed for use in clinical practice with the aim of standardizing discussion on scar treatment and is based on the sum of individual types of scars and their numerical extent. The potential advantages of this system include independent accounting of specific scar types, thereby providing for separate atrophic and hypertrophic sub-scores in addition to total scores. Potential shortcomings include restriction to facial involvement, time intensity, and undetermined clinical relevance of score ranges.

Hypertrophic and Keloidal Scars

Keloids and hypertrophic scars are caused by cutaneous injury and inflammation. Notably, superficial injuries that do not reach the reticular dermis never cause keloidal and hypertrophic

TABLE 1.

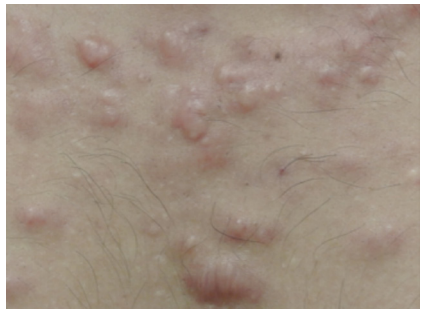
Acne Scars Morphological Description and Clinical Aspect		
Acne Scars Subtype	**Morphological Features**	**Clinical Aspect**
Icepick	Ice-pick scars are narrow (<2 mm), deep, sharply marginated epithelial tracts that extend vertically to the deep dermis or subcutaneous tissue.	
Rolling	Rolling scars occur from dermal tethering of otherwise relatively normal-appearing skin and are usually wider than 4 to 5 mm. Abnormal fibrous anchoring of the dermis to the subcutis leads to superficial shadowing and a rolling or undulating appearance to the overlying skin.	
Boxcar Shallow <3mm diameter >3mm diameter Deep <3mm diameter >3mm diameter	Boxcar scars are round to oval depressions with sharply demarcated vertical edges, similar to varicella scars. They are clinically wider at the surface than ice-pick scars and do not taper to a point at the base. They may be shallow (0.1–0.5mm) or deep (≥0.5mm) and are most often 1.5 to 4.0 mm in diameter.	

scarring. This suggests that these pathological scars are due to injury of this skin layer and the subsequent aberrant wound healing therein by persistent inflammation. The reticular layer of keloids and hypertrophic scars contains inflammatory cells, increased numbers of fibroblasts, and newly formed blood vessels. Hypertrophic scars are typically pink, raised, and firm, with thick hyalinised collagen bundles that remain within the borders of the original site of injury and collagen deposits (Figure 1). Hypertrophic and keloidal scars are more common in darker-skinned individuals and occur predominantly on the trunk.

Prevention of Acne Scars

Prevention of acne scar development can be lead by controlling skin inflammation during acne treatment. Inflammation plays a crucial role in acne scars formation. By examining biopsy specimens of acne lesions from the back of patients with severe scars and without scars, Holland et al found that the inflammatory reaction at the pilosebaceous gland was stronger and had a longer duration in patients with scars versus those without;

FIGURE 1. Hypertrophic acne scars in a 24-year-old female.



in addition, the inflammatory reaction was slower in those with scars versus patients who did not develop scars. They showed a strong relationship between severity and duration of inflammation and the development of scarring, suggesting that treating early inflammation in acne lesions may be the best approach to prevent acne scarring.[7] Among therapeutic options to control the inflammatory process in acne are topical retinoids that have shown high efficacy. Several clinical trials have demonstrated the efficacy of topical retinoids to prevent acne scars.[8-9] Direct and indirect anti-inflammatory properties of topical retinoids are the molecular principle by which their activity is based on.

Different authors focused on the molecular events involved in the scar formation, explaining the activity of topical retinoids in acne scarring prevention.[10] They described the inflammatory pathways active in vivo in acne lesions, showing the hyperactivation of two important transcriptional factors: NFK-B e AP-1. In particular, NFK-B activation increases the expression of various cytokines (especially TNF alpha and IL-1) that are able to break out the inflammatory cascade with different mechanisms, especially through the recruitment of circulating inflammatory cells. These cells, when "attracted" by these mediators, migrate from the circulation through the vessel wall reaching the inflammatory site. All these events contribute significantly to the histological damage occurring in the pilo-sebaceous unit, contributing to the appearance of disfiguring scars in patients suffering from acne (Figure 2).

AP-1 is a transcriptional factor able to modulate different genes and activate the expression of different Metalloproteinases (MMPs) such as MMP-1, MMP-3, MMP-9. These types of MMPs seem to be particular represented in the dermis and they are involved in extracellular matrix degradation, a crucial event in acne scars formation. The activities of NFK-B and AP-1 on molecular pathways involved in scarring events explain why the anti-inflammatory effect of retinoids is so important for their efficacy in acne scars prevention.[11] It has also been demonstrated that retinoids are able to reduce free fatty acids amounts in microcomedones, promoting the correct barrier function of infundibular wall by an indirect antinflammatory activity. Retinoic

TABLE 2.

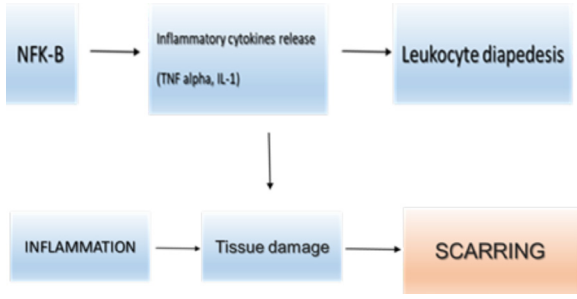
Qualitative Scarring Grading System *(adapted from Goodman and Baron, 2006)*		
Grades of Post Acne Scarring	**Level of Disease**	**Clinical Features**
1	Macular	These scars can be erythematous, hyper-, or hypopigmented flat marks. They do not represent a problem of contour like other scar grades but of color.
2	Mild	Mild atrophy or hypertrophy scars that may not be obvious at social distances of 50 cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair if extrafacial.
3	Moderate	Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial, but is still able to be flattened by manual stretching of the skin (if atrophic).
4	Severe	Severe atrophic or hypertrophic scarring that is evident at social distances greater than 50 cm and is not covered easily by makeup or the normal able to be flattened by manual stretching of the skin.

acid is able to increase fibroblast proliferation and extracellular matrix components synthesis in vitro.[12-14] All these biological properties make retinoids a very useful tool for dermatologists in the prevention and treatment of acne scarring.

Management of Acne Scars

Anecdotal experience and medical investigations have shown that most cases of acne scarring cannot be solved by a single "best" treatment. Acne scars can vary for type and depths and each of the currently available treatments is ideally suited to address a subset of this spectrum. Below, we summarize the most used therapeutic techniques available for acne scars management, their indications/contraindications, evidence for efficacy, and potential adverse effects.

FIGURE 2. NFK-B dependent inflammatory pathway involved in acne scars formation.



Chemical Exfoliation

Chemical exfoliation is obtained by applying chemicals to the skin to destroy the outer damaged layers and accelerate the repair process. Active inflammation, dermatitis or infection of the area to be treated, isotretinoin therapy within 6 months before peeling procedure, pregnancy, and delayed or abnormal wound healing are general contraindications for all types of chemical exfoliations. Different agents have different depths of penetration and therefore, chemical peels can be divided into four different groups based on the histologic level of necrosis that they cause (Table 3).

Glycolic acid (GA): GA is the most commonly used alpha hydroxyl acid as a peeling agent. GA acts by thinning the stratum corneum, promoting epidermolysis, and dispersing basal layer melanin. It increases dermal hyaluronic acid and collagen

TABLE 3.

Classification of Peeling Agents		
Depth of Penetration	**Histologic Level**	**Peeling Agents**
Very superficial	Destruction of the stratum corneum without creating a wound below the stratum granulosum	• Glycolic acid, 30% to 50%, applied briefly (1 to 2 minutes) • Jessner solution, applied in 1 to 3 coats • TCA 10%, applied in 1 coat
Superficial	Destruction of part or all of the epidermis, anywhere from the stratum granulosum to the basal cell layer	• Glycolic acid, 50% to 70%, applied for a variable time (2 to 20 minutes) • Jessner solution, applied in 4 to 10 coats • TCA, 10% to 30%
Medium Depth	Destruction of the epidermis and part or all of the papillary dermis	• Glycolic acid 70%, applied for a variable time (3 to 30 minutes) • TCA, 35% to 50% • Augmented TCA (CO2 plus TCA 35%; Jessner solution plus TCA 35%; glycolic acid 70% plus TCA 35%)
Deep	Destruction of the epidermis and papillary dermis, extending into the reticular dermis	• Phenol 88% • Baker-Gordon phenol formula

gene expression by increasing secretion of IL-6. The best results achieved for acne scars include five sequential sessions of 70% glycolic acid every two weeks. The disadvantages of GA are penetration often not uniform, mandatory neutralization, and high risk of overpeel if the time of application is too long or if the skin is inflamed. Persistent hyperpigmentation and irritation are the most common side effect of this chemical agent.

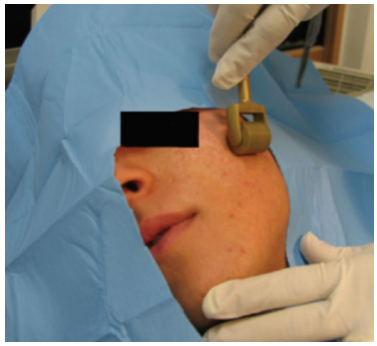
Jessner's solution (JS): JS is a combination of salicylic acid, resorcinol, and lactic acid in 95% ethanol, able to induce corneocyte detachment and subsequent desquamation of the stratum corneum, enhancing penetration of other agents. The depth of the peel depends on the number of coats of solution applied. Different patients may require different number of coats to achieve the same level of peel. This is because the penetration of the solution depends on a number of factors, including the preparation of the skin, the thickness of the corneum, and the sensitivity of the skin. The advantages of JS are that the peel is very superficial and safe, and rarely goes deeper than one would expect. Scaling, irritation, burning sensation, and persistent hyperpigmentation are the most frequent side effects of this chemical agent.

Pyruvic acid (PA): PA presents keratolytic, antimicrobial, and sebostatic properties, as well as the ability to stimulate new collagen production and the formation of elastic fibers. The use of 40 to 70% pyruvic acid has been proposed for the treatment of moderate acne scars. The advantages of pyruvic acid are the homogeneous penetration with uniform erythema, mild desquamation, short postoperative period, and the possibility of use for all skin types. Disadvantages include intense stinging and burning sensation, mandatory neutralization, and irritating vapors for the upper respiratory mucosa.

Salicylic acid (SA): SA is one of the best peeling agents for the treatment of acne scars. It is a beta hydroxy acid. SA removes intercellular lipids that are covalently linked to the envelope surrounding cornified epithelioid cells. The most efficacious concentration for acne scars is 30% in multiple sessions, 3 through 5 times, every 3 through 4 weeks.[15] The side effects of salicylic acid peeling are mild and transient. The advantages of salicylic acid are an established safety profile in all skin types, post-inflammatory hyperpigmentation or scarring are very rare, and for this reason it is used to treat dark skin. The disadvantage of salicylic acid is the intense stinging and burning sensation.

Trichloroacetic acid (TCA): TCA causes protein denaturation, the so-called keratocoagulation, resulting in a readily observed white frost. The degree of the frosting correlates with the depth of solution penetration on the basis of different concentrations. TCA in a percentage of 10%–20% results in a very light superficial peel with no penetration below the stratum granulosum; a concentration of 25%–35% produces a light superficial peel with diffusion encompassing the full thickness of the epidermis; 40%–50% can produce injury to the papillary dermis, and finally, greater than 50% results in injury extending to the reticular dermis. The use of TCA in concentrations greater than 35% should be avoided. It can be preferred in some cases of isolated lesions or for treatment of isolated ice-pick scars (TCA CROSS).[16] The advantages of TCA are low cost, uniformity of application, and the ability to evaluate the penetration by the color of frost. The disadvantages include stinging and burning sensation during the application. High concentrations are not recommended in skin types V to VI due to the potential for hypo/hyperpigmentation.

FIGURE 3. Skin needling procedure.



Phenol: Phenol is a deep peel that can improve atrophic acne scars. However, it requires sedation and cardiovascular monitoring and it is not recommended in skin types IV to VI. Deep peels as phenol are more rarely used because of the downtime required for healing and the potential for complications and adverse events.

Skin Microneedling or Percutaneous Collagen Induction

Skin needling is a dermatologic treatment procedure performed to achieve percutaneous collagen induction (PCI), which is effective in improving depressed acne scarring. At first, facial skin must be cleansed, then a topical anaesthetic is applied and left for 60 minutes. The skin needling procedure is achieved by rolling a preformed tool comprising multiple thin microneedles on the cutaneous areas affected by acne scars: the skin is punctured in multiple directions, applying constant pressure (Figure 3).

The needles penetrate from 1.5 to 2 mm into the dermis. As expected, the skin bleeds for a short time. The skin develops multiple microbruises in the dermis. This damage induces the release of growth factors that stimulate the production of new collagen and elastin in the upper dermis. Several studies report that 6 months after collagen-induction therapy, histology shows a dramatic increase of new collagen and elastin fibers.[17-18] Aust et al showed a considerable increase in collagen and elastin

TABLE 4.

Absolute Contraindications to a Skin Needling Procedure
Presence of open wounds, cuts, or abrasions to the skin
Radiation treatment within the last year
A current outbreak of herpes simplex or any other infection or chronic skin condition in the area to be treated
Areas of the skin that are numb or lack sensation
Pregnancy or breast feeding
A history of keloid or hypertrophic scars or poor wound healing

TABLE 5.

Post-operative Precautions after Skin Needling Procedure
Prevent hyperpigmentation by avoiding direct sunlight after treatment for 1 week
Apply SPF50+ sunscreen
Avoid topical product containing irritating ingredients such as glycolic/salicylic/TCA
Avoid invasive treatment (laser/chemical peel/microdermabrasion) until the skin is recovered.

deposition at 6 months' post-operation. The epidermis demonstrated a 40% thickening of stratum spinosum and normal rate ridges at 1-year post-operation.[19]

Results generally start to be seen after about 6 weeks, but complete improvement can take at least 3 months to occur, and, as the deposition of new collagen takes place slowly, the skin texture will continue to improve over a 12-month period.[18] Most individuals will require around three treatments approximately 4 weeks apart. Some clinical conditions can be considered as absolute contraindications for a skin-needling procedure (Table 4). Several early reports suggested that performance of dermatosurgical procedures in patients on oral isotretinoin is associated with abnormal skin healing, keloid, or hypertrophic scar formation. However, a task force of experts from the American Society for Dermatologic Surgery concluded that there is insufficient evidence to justify delaying treatment with superficial and focal dermoabrasion and nonablative lasers for patients recently exposed to isotretinoin.[20]

Complications are very rare, and when they occur, are represented by post-inflammatory hyperpigmentation, erythema, acne, and herpes flares superinfection. Allergic contact dermatitis from materials used in the needles has also been observed. Complications risk can be reduced following some simple post-operative precautions (Table 5). The management of these complications are different for different patients. In case hyperpigmentation occurs, it should be treated with a solution of glycolic acid (50%) or hydroquinone creams combined with sunscreen or laser therapy. In the case of infection, an antibiotic therapy has to be prescribed: either topical therapy with mupirocin 2% ointment, three-times daily for 10 days, alternatively, fusidic acid, and, in severe cases, systemic therapy with amoxicillin and clavulanic acid, twice daily for 6 days. If aggravation of acne occurs, it is possible to consider local or systemic antibiotic therapy, depending on the gravity of the condition. The observation of all the pre- and post-operative precautions and respect of contraindications may reduce the risk of adverse effects, which are minimal with this type of treatment and typically include minor flaking or dryness of the skin, milia, and hyperpigmentation, which can occur only very rarely and usually resolves after a month. Edema and erythema are the most frequent sequelae. Recovery may take 24 hours or up to a few days. Most patients are able to return to work the following day.

Skin needling provides good outcomes with negligible risks and can be safely performed on all skin colors and types. There is a lower risk of postinflammatory hyperpigmentation than other procedures such as dermabrasion, chemical peels, and laser resurfacing. A peculiar type of microneedling is fractional radiofrequency microneedling (FMR) in which insulated needles release radiofrequency waves to act deeper in the dermis, thus preventing epidermal damages. After damage to the reticular dermis, long-term dermal remodelling, neoelastogenesis, and neocollagenogenesis results in dermal thickening. The treatment is generally well tolerated with transient side effects such as mild erythema, post-inflammatory hyperpigmentation, and track marks of the device.[21]

Lasers

The efficacy of lasers and radiofrequency in atrophic acne scarring is confirmed by many comparative and observational studies. Different types of laser, including the nonablative and ablative lasers, are very useful in treating acne scars. Ablative lasers achieve removal of the damaged scar tissue through melting, evaporation, or vaporization. Carbon dioxide laser and Erbium YAG laser are the most commonly used ablative lasers for the treatment of acne scars. Nonablative lasers do not remove the tissue but stimulate new collagen formation and cause tightening of the skin resulting in the scar being raised to the surface. Among the nonablative lasers, the most commonly used are the Nd:YAG and diode lasers.[22] In Table 6, we summarize some characteristics of the most used ablative and nonablative lasers. Ideal candidates for laser treatment must present a skin disease with acne of at least 1 year; they should have stopped taking oral isotretinoin for at least 1 year; they should not have presented skin infections by herpes virus during the six months prior to treatment; they must not have a history of keloids or hypertrophic scarring. All ablative lasers showed high risk of complications and side effects. Nonablative skin remodeling systems have become increasingly popular for the treatment of acne scars because they decrease

TABLE 6.

Wavelength and Effects in Tissues of the Most Used Ablative and Nonablative Lasers

Type of laser	Wavelength	Effects on Tissues
Carbon dioxide (CO2) laser	10.600nm	Rapid heating and vaporization of tissue, which causes collagen remodelling and heat-mediated tissue contraction
Erbium:yttrium-aluminum-garnet (Er:YAG)	2940nm	Has a more superficial ablation profile and a smaller zone of thermal damage beneath the ablated layer leading to shorter healing time
Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser	1 064 nm	Stimulates inflammatory mediator release, fibroblast activation, neocollagenesis, and dermal remodelling
Diode laser	*Diode laser*	Targets the water in the upper dermis, remodels the skin's underlying collagen, and promotes formation of new collagen.

the risk of side effects and the need for postoperative care. Although improvement was noted with these nonablative lasers, the results obtained were not as impressive as the results from those using laser resurfacing. For this reason, a new concept in skin laser therapy called fractional photothermolysis (FP) has been designed to create microscopic thermal wounds to achieve homogeneous thermal damage at a particular depth within the skin, a method that differs from chemical peeling and laser resurfacing. The benefits of this system are less downtime and side effects compared to the conventional ablative laser, and an increased efficacy of tissue regeneration compared to the nonablative methods. Skin resurfacing is a new technology that delivers heat energy directly to the skin. After treatment, fibroblasts depositing new collagen and elastin fibers can be seen. Side effects are rare and can include temporary hyperpigmentation, erythema, edema, epidermal de-epithelialization, and infection.

Subcision

Subcision is a stand-alone treatment for depressed scars and wrinkles designed to address the underlying pathophysiology of rolling acne scars.[23] Despite their superficial appearance, rolling scars result from deep fibrous attachments gathering the epidermis to the subcutis. Subcision is designed to cut these fibrous bands while causing minimal damage to the overlying skin. Typically, this technique results in elevation of the depressed scar to the level of the surrounding skin. In the weeks following subcision, additional augmentation of the depressed defect is typically observed. This subsequent elevation is thought to result from trauma caused during the procedure, which initiates a wound-healing response culminating in the deposition of new connective tissue beneath the scar surface. The main advantage of subcision is that it has the potential to produce long-term improvement in the appearance of rolling acne scars while causing minimal injury to overlying skin. The procedure is easy to perform and it is generally safe and well tolerated. One disadvantage of subcision is that a single treatment is not guaranteed to produce substantial improvement. The final result of the procedure depends on the individual wound-healing response, and it is often difficult to predict the outcome of an initial treatment. Subcision may be readily combined with other treatments such as filler injection, laser resurfacing, needling, or trichloroacetic acid peeling.

Excision, Punch Elevation, and Punch Grafting

Excision and punch techniques have been used for several decades in the treatment of deep, atrophic acne scars.[24] These techniques remain indispensable for the correction of acne scars whose depth precludes correction by resurfacing and whose irregular scar bases and sharply defined walls make them unsuitable candidates for filler correction. Elliptical or punch excision should be used when one's aesthetic goal is to replace a prominent scar with a less conspicuous linear, superficial scar. Punch excision is indicated for the treatment of ice-pick and deep boxcar scars that are <3.5 mm in diameter. Excision is also often the best option for the treatment of acne scars with cutaneous bridges or persistent cysts and tunnels. Excision and punch techniques have a distinct advantage over nonsurgical scar revision techniques in their capability to substantially improve the appearance of ice-pick and deep boxcar scarring. The primary disadvantage of all excision and punch techniques is that they necessitate an injury that can stimulate an abnormal healing process.

Additional Modalities and Future Developments

Although many of the surgical treatments for acne scarring have been used for decades, there has been a limited amount of evidence evaluating the long-term response to these treatments, comparing outcomes from different modalities. While some modalities, novel treatments, newer protocols, and more comparative studies continue to be reported. Recent work in stem-cell biology and regenerative medicine suggests that novel approaches to scar revision may be available in the future. Great strides have been made in elucidating the differences between the process of fibrotic wound healing that leads to scarring and the pathways of regeneration of injured tissues.[22] A recently described therapeutic intervention study involves the use of stem cells for visual improvement of scars. Ibrahim et al found a significant qualitative and quantitative improvement in 14 patients where acne scars were directly injected with autologous bone marrow stem cells.[25] The use of stem cells may be considered as a single treatment or in conjunction with surgical management for potentially improved outcomes.

Autologous fat transplantation, or fat grafting, is another treatment option that has been more recently explored for its use in acne scarring. An additional potential adjunctive treatment that has undergone investigation is the use of low-level light therapy (LLLT). Although additional research is necessary, LLLT is thought to possibly decrease IL-6 and modulate TGF-B, which are associated with abnormal wound healing. The clinician should consider the combination of the traditional surgical modalities with non-surgical and resurfacing procedures together with some innovative treatments options, which potentially may act synergistically in order to achieve better result.

CONCLUSION

Various modalities have been used to treat scars, but limited efficacy and problematic side effects have restricted their application. In order to optimize the best treatment, we need to consider which option offers the most satisfactory result. There are also promising procedures for the future, such as stem cell therapy. A deep knowledge of the therapeutic options is mandatory for correct selection of the best therapeutic strategy for treatment of acne scars, whether it may be unique or combined, and for reducing or avoiding side effects and complications. Because severe acne scars are frequently the source of profound social and emotional distress for patients, the knowledge of all available techniques is essential for the cosmetic dermatologist.

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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.)*

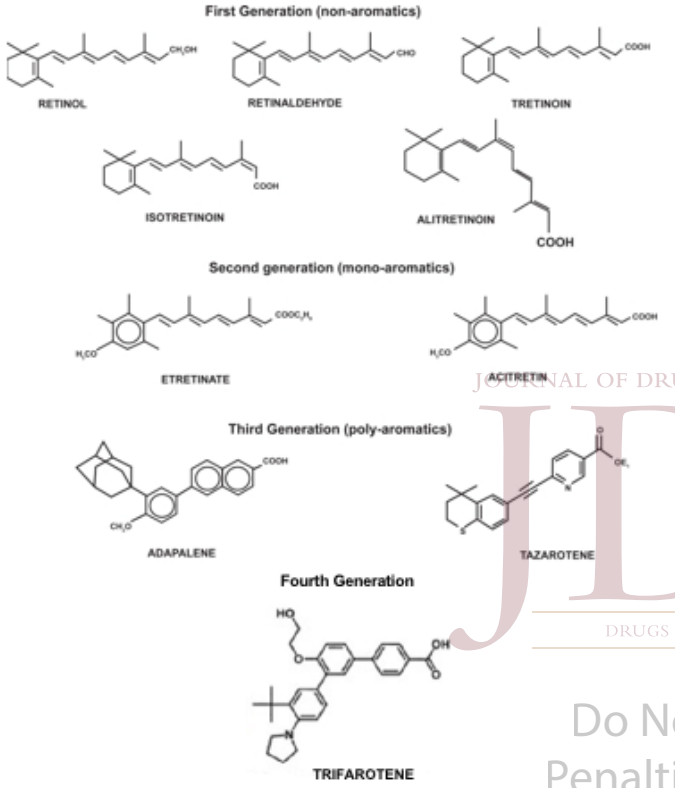
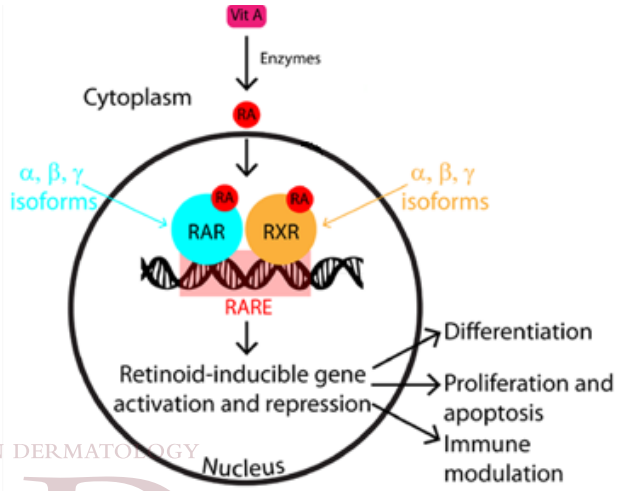


FIGURE 2. Mode of action of retinoids. *(Adapted from Topical trifarotene: a new retinoid, 179(2):231-232, First published: 24 August 2018.)*



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.

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.

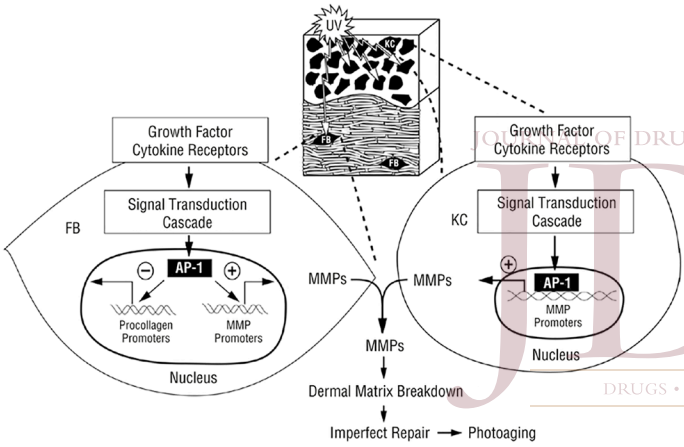
Retinoids and Acne Scars

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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1. How do we classify acne scars?
   a. Atrophic and hypertrophic
   b. Ice-pick and atrophic
   c. Boxcar and hypertrophic
   d. Hypertrophic and atrophic (sub-classified into ice-pick, boxcar, and rolling scars)

2. Why are retinoids useful in acne scarring prevention?
   a. For the direct and indirect anti-inflammatory properties of topical retinoids
   b. There are no studies that confirm this hypothesis
   c. For the direct anti-inflammatory properties of topical retinoids
   d. For the indirect anti-inflammatory properties of topical retinoids

3. How do we classify chemical peels?
   a. Superficial and deep
   b. Very superficial, superficial, medium depth, deep
   c. Light and strong
   d. None of the above

4. What is the skin needling mechanism of action?
   a. Skin needling induced dermal damage prompts the release of growth factors that stimulate the production of new collagen and elastin in the upper dermis
   b. Skin needling induced dermal damage prompts the release of growth factors that stimulate the production of new collagen and elastin in the lower dermis
   c. Skin needling induced epidermal damage prompts the release of cytokines that stimulate the production of new collagen and elastin in the upper dermis
   d. Skin needling induced dermal damage prompts the release of growth factors that inhibit the production of new collagen and elastin in the upper dermis

5. What is fractional photothermolysis?
   a. An innovative technique in phototherapy
   b. An innovative technique in skin laser therapy
   c. An innovative technique in skin laser therapy designed to create microscopic thermal wounds to achieve homogeneous thermal damage
   d. It doesn't exist

6. Which of the following statements most accurately define a retinoid?
   a. It is a reduced molecule of vitamin K
   b. It is converted to vitamin D through hydroxylation
   c. It or its metabolite binds to and activates retinoic acid receptor
   d. Its structure must include a side chain of 4 double bonds
   e. It is synthesized from cholesterol

7. Which of the following accurately describes retinoid receptors in human skin?
   a. Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) are present in equal amounts since they must pair up for proper functioning
   b. Only naturally occurring retinoids, such as all-trans retinoic acid, can bind to RARs. In the presence of their ligands, retinoid receptor dimers interfere with protein synthesis
   c. When ligand is bound to RARs, appropriate dimers bind to specific stretch of DNA called response elements
   d. In the presence of their ligands, retinoid receptor dimers interfere with protein synthesis
   e. Ligands for RARs and RXRs are the same

8. Which of the following retinoid effect(s) is/are important for acne?
   a. Normalization of abnormal follicular differentiation
   b. Loosening of microcomedones
   c. Sebaceous gland atrophy
   d. Inhibition of inflammation induced by Cutibacterium
   e. All of the above

9. The most common side effect of topical retinoids is:
   a. Hair loss
   b. Exacerbation of acne
   c. Increased sensitivity to UV
   d. Increased risk of inflammatory bowel diseases
   e. Skin irritation

10. Which of the following should not be taken concomitantly with oral retinoid?
    a. Vitamin C
    b. Minocycline
    c. Cephalexin
    d. Etanercept
    e. Atorvastatin

11. The proposed mechanism by which topical retinoid can treat and potentially prevent acne scars is:
    a. Increase in matrix metalloproteinases
    b. Reduction in Cutibacterium
    c. Alteration of skin barrier
    d. Formation of procollagen
    e. Normalize sebaceous gland dysfunction

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1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

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1 2 3 4 5

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1 2 3 4 5

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