REVIEW ARTICLE

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Topical Retinoids in Acne Vulgaris

Update on Efficacy and Safety

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Abstract

Topical retinoids represent a mainstay of acne treatment because they expel mature comedones, reduce microcomedone formation, and exert anti-inflammatory effects. The first-generation retinoid tretinoin (all-trans retinoic acid) and the synthetic third-generation polyaromatics adapalene and tazarotene are approved for acne treatment by the US FDA, whereas topical tretinoin, isotretinoin (13-cis retinoic acid), and adapalene are accredited in Canada and Europe. Topical retinoids have a favorable safety profile distinct from the toxicity of their systemic counterparts. Local adverse effects, including erythema, dryness, itching, and stinging, occur frequently during the early treatment phase. Their impact varies with the vehicle formation, skin type, frequency and mode of application, use of moisturizers, and environmental factors such as sun exposure or temperature. The broad anti-acne activity and safety profile of topical retinoids justifies their use as first-line treatment in most types of non-inflammatory and inflammatory acne. They are also suitable as long-term medications, with no risk of inducing bacterial resistance, for maintenance of remission after cessation of initial combination therapy.

The sequence of events leading to acne initiation is still incompletely understood and the subject of controversial discussion;[1-3] however, the most notable pathophysiologic factors are sebaceous gland hyperplasia with hyperseborrhea, alterations in the growth and differentiation of follicular keratinocytes, *Propionibacterium acnes* colonization of the follicle, and inflammation and immune

reactions. Clinical experience and evidence from various studies have shown that parallel targeting of these major pathogenetic factors represents the most effective approach in the treatment of acne.[4,5]

The primary acne lesions are the microcomedones, which are invisible to the naked eye but require special attention with regard to the development of therapeutic strategies because they represent the central precursor lesions evolving into either non-inflammatory comedones or inflammatory papules and pustules. The pathogenetic factors that induce microcomedones are hyperseborrhea and hyperproliferation and aberrant differentiation of the follicular epithelium; however, on a microscopic level, the beginning of microcomedone formation is also associated with vascular endothelial cell activation and inflammatory events.[6] Targeting microcomedone formation is not only essential in the prevention and therapeutic control of acne but also a prerequisite to maintenance of long-term remission of this chronic disease.

Retinoids play a crucial role in the treatment of acne because they inhibit the formation of and reduce the number of both non-inflammatory microcomedones[7-9] and inflammatory acne lesions, with several retinoids having been shown to exert direct anti-inflammatory activity.[10] These agents are synthetic derivatives of retinol (vitamin A) and those used in topical form for the treatment of acne include tretinoin (all-trans retinoic acid), isotretinoin (13-cis retinoic acid), adapalene (derived from naphthoic acid), and tazarotene (acetylenic retinoid), whereas retinaldehyde, retinol, and retinyl esters are used in cosmetic preparations for acne skin.[11] Motretinide is a topical retinoid in an aromatic ester form available in Switzerland only. Tazarotene is not approved for acne treatment in Europe, and topical isotretinoin is not US FDA approved (table I).

The aim of the article is to provide a systematic review of the available evidence of the efficacy and safety of topical retinoids used as monotherapy or as part of combination therapies in the treatment of acne vulgaris.

Table I. Overview of available topical retinoids/combination products in different countries

US/Canada	Europe	Japan
Tretinoin	Tretinoin	Adapalene[c]
Adapalene	Adapalene	
Tazarotene	Isotretinoin	
Retinaldehyde	Retinaldehyde	
Tretinoin + clindamycin	Isotretinoin + erythromycin	
Tretinoin + erythromycin	Adapalene + benzoyl peroxide[a]	
	Tretinoin + erythromycin	
	Motretinide[b]	

a Available in most European countries.

b Available in Switzerland only.

c Will be introduced in December 2008.

A MEDLINE database search was performed via PubMed to extract all topics dealing with topical retinoids using the search term 'topical retinoids and acne'. The search period was 1963 to January 2008. After reviewing the titles and abstracts, articles were excluded if they addressed an excluded topic (chloracne, rosacea, acne venenata, acne fulminans, acne necrotica), were not in English or German, or contained news, letters, or citations without an abstract.

1. Mode of Action of Topical Retinoids

1.1 Pharmacology

The biologic effects of topical retinoids are mediated and regulated by nuclear hormone receptors (retinoic acid receptors [RARs] and retinoid X receptors [RXRs]) and cytosolic binding proteins.[12] A retinoid is currently defined as a molecule that binds to and activates RARs either directly or by metabolic conversion and thereby elicits transcription of retinoic acid-responsive genes.[13] This clear definition overcomes previous limitations related to the fact that some molecules structurally similar to retinol had no biologic effects, whereas other synthetic compounds with no resemblance to retinol had retinol-like activity. Each receptor family includes three subtypes (α, β, γ) that form homo- or heterodimers that bind to a DNA stretch called a 'responsive element' (RARE and RXRE) and induce the expression or downregulation of target genes in a ligand-dependent manner. The most frequently distributed receptors in human skin are RARγ and RXRα, and a heterodimer formed by the two transduces the retinoid effects in human skin.[14,15] The discovery of nuclear RARs provided clues to a rational design of new synthetic receptor-selective agonists with different or improved physiochemical profiles and tolerability.[12] Tretinoin, the first topical retinoid approved for acne, binds with equal affinity to all RARs, and its metabolite 9-cis retinoic acid binds to RXRs. Furthermore, tretinoin upregulates and binds to the cellular retinoic acid binding protein II (CRABP II), the predominant intracellular binding protein in skin. This non-selective action and binding to CRABP II has been proposed as the reason for the high irritative potential of tretinoin. Another drawback of tretinoin is its high instability when exposed to light and oxygen.[16]

This limitation of tretinoin was overcome by the development of new synthetic third-generation retinoids. The three aromatic rings of adapalene, which was approved for acne treatment in 1996, render this molecule more stable to light and oxygen.[16] Its lipophilic structure and low solubility enable penetration into the sebaceous follicle rather than through the skin, which may contribute to better tolerability. Adapalene binds selectively to RARβ and

RARγ and activates gene expression through all RARs but not RXRs.[17] Despite being a strong inducer of CRABP II messenger RNA, adapalene does not bind to this protein, which might also help explain its improved tolerability.[18]

Tazarotene, which was approved for treatment of acne in 1997, was designed as a polyaromatic molecule with higher conformational rigidity than tretinoin as a means of reducing unwanted side effects. Tazarotene is RAR selective and activates gene expression through RARβ and RARγ, but antagonizes the activity of the nuclear transcription factor activator protein (AP)-1[19,20] through all RARs; this action is believed to mediate anti-inflammatory and anti-proliferative effects in psoriasis.

Retinaldehyde is a natural metabolite of retinol that does not bind to RARs; its biologic activity results from conversion to tretinoin by epidermal keratinocytes.[11,21] The same holds true for retinol and retinyl esters, which are used in cosmetic preparations.

1.2 Biologic Effects

Retinoids influence proliferation and differentiation of cells[12,22,23] and reverse abnormal desquamation by increasing follicular epithelial turnover and accelerating the shedding of corneocytes, resulting in expulsion of mature comedones (open and close type) and suppression of microcomedone formation.[7-9] RARγ in particular has been shown to mediate both the efficacy and irritation potential of retinoids,[15] whereas RARα agonist activity has no impact on irritation. Furthermore, retinoids modulate the expression of the transcription factors, such as AP-1,[19] which regulate the genetic expression of growth factors (e.g. vascular endothelial growth factor) and degradative enzymes (e.g. matrix metalloproteases) involved in inflammatory responses. Moreover, retinoids stimulate collagen synthesis[24,25] and prevent oxidative stress and thereby exert an anti-aging effect.[11] They are also involved in the induction of apoptosis by a variety of mechanisms either associated with binding of retinoid receptors or independent of receptor binding.[26]

The change in the microclimate of the pilosebaceous follicle by prevention of hypercornification promotes an inhospitable aerobic environment for *P. acnes* and is likely to enhance the penetration of other topical drugs. A specific direct antibacterial effect against *P. acnes* has been shown for retinaldehyde only.[27]

In addition to an indirect anti-inflammatory effect resulting from changes in the follicular environment, various *in vitro* and *in vivo* studies have demonstrated a direct immunomodulatory activity for topical retinoids.[10,17,28-30] *In vitro* assays have revealed that adapalene is associated with greater inhibition of lipoxygenase pathways and leukotriene production than tretinoin, isotretinoin, and etretinate.[17,28] Furthermore, adapalene and tretinoin, and to a lesser extent isotretinoin, inhibited release of oxygen free radicals from polymorphonuclear leukocytes derived from rabbits.[17] However, adapalene was less effective than tretinoin and isotretinoin in inhibiting human polymorphonuclear leukocyte chemotaxis.[17] Both adapalene[10,30] and tretinoin[29] modulate the innate immune response by inhibiting expression of toll-like receptor-2 on monocytes and keratinocytes, respectively.

In vivo, tretinoin, isotretinoin, and adapalene significantly decreased UV-induced erythema, whereas in other *in vivo* models of inflammation including croton oil, arachidonic acid ear edema (mouse), and carrageenan-induced paw edema (rat), the anti-inflammatory effect of adapalene was superior to that observed with tretinoin.[10,28] However, a recent study performed in rats demonstrated a significant anti-inflammatory effect in carrageenan-induced rat paw edema in favor of tretinoin.[31] These results support and provide an additional theoretic background for the significant reduction in inflammatory lesions that has been observed in well controlled clinical trials of various formulations of adapalene, tretinoin, and tazarotene (see following sections).

2. Tretinoin

2.1 Monotherapy

Tretinoin was the first topical retinoid to be described in reports by Stüttgen and Beer in 1962.[32] It has been a mainstay of acne therapy for more than 35 years and was approved by the FDA in 1971. Numerous trials have demonstrated that tretinoin is effective as a single-agent therapy in patients with mild-to-moderate comedonal or inflammatory acne,[33-35] in whom it significantly reduces the numbers of both comedones and inflammatory acne lesions. Tretinoin has shown in several trials that treatment for at least 12 weeks results in reductions in lesion counts ranging between 32% and 81% for non-inflammatory lesions and between 17% and 71% for inflammatory lesions, i.e. 22–83% of the total lesion count.[36] Bikowski[37] recently proposed a simple way of comparing the efficacy of different acne treatments by calculating the mean percentage reductions in lesion counts extracted from two well controlled, phase III trials published in the prescription information and adjusting for the vehicle effect. Using this method, the reported absolute mean percentage reductions for 0.1% and 0.04% tretinoin microsphere gel were 38.5% and 37.5%, respectively. The initial response to topical tretinoin may be observed after 2–3 weeks, but substantial clinical improvement can be achieved after 4–6 weeks of continuous therapy, and maximum improvement occurs after 3–4 months.[38] An ultrastructural study demonstrated significant reductions in microcomedones of 50% after 6 weeks and 80% after 12 weeks of treatment with 0.1% tretinoin cream,[7] while another study showed a 35% reduction in microcomedones[8] after 12 weeks of treatment with 0.025% tretinoin gel. These findings emphasize the need for long-term adherence to obtain complete remission.

Tretinoin is available as a gel (0.01%, 0.025%, and 0.05%), cream (0.025%, 0.05%, 0.1%, and 0.4%), liquid (0.025%, 0.05%, and 0.1%), lotion (0.1%), ointment (0.05%), compress (0.05%), microsphere gel (0.04% and 0.1%), and prepolyolprepolymer-2 gel or cream (0.025%). Use of tretinoin has been limited by cutaneous irritation, including erythema, desquamation, burning, and pruritus, particularly in patients with sensitive skin. To overcome such tolerability problems, tretinoin has been reformulated. New preparations with similar effectiveness but improved cutaneous tolerability[39-42] include tretinoin trapped within copolymer microspheres (Retin-A Micro®, OrthoNeutrogena)[1] or prepolyolprepolymer-2 gel or cream (Avita®, Bertek Pharmaceuticals), which gradually release the active ingredient over time. Furthermore, the microsphere formulation offers marked protection against tretinoin photodegradation, even in the presence of a strong oxidizing agent such as benzoyl peroxide.[43,44] After 12 weeks of treatment, 0.04% tretinoin microsphere gel was no better tolerated than the 0.1% formulation, but was less effective against inflammatory lesions at week 2.[45]

Two studies have reported that liposomal encapsulation of tretinoin allows a reduction in the concentration of the active agent without decline in efficacy for acne vulgaris compared with 0.025% or 0.05% tretinoin gel after once-daily topical application for 10 (or 12) weeks, but has a much better cutaneous tolerability and improved efficacy with respect to reduction in comedones.[46,47] However, liposomal preparations of tretinoin are not yet commercially available. Furthermore, a recent study demonstrated improved efficacy and tolerability of a new topical retinoid acid/cyclodextrin complex formulation (0.025%) compared with the double-strength conventional preparation (0.05%).[48]

2.2 Combination Therapy

Because of the multi-factorial nature of acne pathogenesis, combination therapies have been developed to target two or more causative elements of the disease, for example, a retinoid with comedolytic and anti-inflammatory potential combined with an antibacterial to arrest *P. acnes* growth and related immune response.[5,49] An early trial published in 1978 reported that a twice-daily application of 2% erythromycin base in a hydroalcoholic solution accompanied by once-daily use of 0.05% tretinoin solution was substantially more effective than tretinoin or erythromycin alone for treatment of moderate inflammatory acne.[50] Subsequently, the high efficacy and tolerability of a fixed gel preparation containing 0.025% tretinoin and 4% erythromycin for acne vulgaris was confirmed in an open-label multicenter study of 1337 patients,[51] and a combined alcoholic erythromycin/tretinoin solution showed good efficacy and tolerability in a multicenter study that included >6500 patients.[52] In a comparative study of combination treatments, 3% erythromycin/5% benzoyl peroxide achieved a significantly greater reduction in both physician- and patient-rated severity of acne symptoms than 0.025% tretinoin/4% erythromycin after 2 weeks of treatment.[53]

The improved efficacy of tretinoin in combination with benzoyl peroxide compared with either ingredient alone has been shown in several trials.[54-56] Both substances must be applied alternately (e.g. tretinoin in the morning and benzoyl peroxide in the evening) to avoid oxidative degradation of tretinoin. Tretinoin microsphere gel has been shown to have improved stability towards UV- and oxidative-induced degradation.[44] Its combination with a 6% benzoyl peroxide cleanser resulted in a greater reduction in inflammatory acne lesions than monotherapy with 0.1% tretinoin microsphere gel, without increased skin irritation.[56]

The combinations of 1% clindamycin and 0.025% tretinoin hydrogel (Velac®, Connetics) and 1.2% clindamycin and 0.025% tretinoin gel (Ziana®, Medicis) were well tolerated and significantly more effective than clindamycin, tretinoin, or its vehicle for the treatment of acne vulgaris in large trials involving 2219[57] and >4500[58] patients, respectively. A previous study reported that a fixed formulation of 1.2% clindamycin and 0.025% tretinoin in a gel base (a different formulation of 'Velac®' than that currently marketed by Connetics) was statistically significantly more effective than tretinoin in reducing mean papular and total inflammatory lesion counts as well as mean overall acne severity score, with no difference in tolerability.[59]

A combination of clindamycin and benzoyl peroxide with tretinoin was reported to be well tolerated and showed improved efficacy compared with tretinoin combined with clindamycin; however, in this study, addition of tretinoin to the combination of clindamycin and benzoyl peroxide had no additional benefit in terms of efficacy.[60] A study investigating a 1% clindamycin/5% benzoyl peroxide topical gel in combination with either tretinoin microsphere gel at concentrations of 0.04% or 0.1%, or 0.1% adapalene gel, revealed good tolerability and a trend toward better resolution of hyperpigmentation in individuals with dark ethnic skin receiving the clindamycin/benzoyl peroxide topical gel in combination with the 0.04% tretinoin microsphere gel.[61] The good tolerability and safety of triple combination regimens of clindamycin/benzoyl peroxide topical gel and tretinoin microsphere gel 0.1% or 0.04% (or 0.1% adapalene) were confirmed in another community-based, 12-week, investigator-blinded, parallel-group, multicenter study involving 353 subjects.[62] The combination regimens with tretinoin microsphere gels were equally effective and well tolerated.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2.3 Safety and Tolerability

The major adverse effect of tretinoin and other topical retinoids is local skin irritation,[63] including erythema, peeling, dryness, burning, and itching. Some individuals might also experience a pustular flare. The irritative potential depends on the concentration and formulation of the product. A study comparing the tolerability of adapalene gel with six different formulations of tretinoin reported three groups of descending order of irritancy: 0.1% tretinoin cream and 0.05% tretinoin cream; 0.025% tretinoin gel, 0.01% tretinoin gel, and 0.025% tretinoin cream; and 0.1% adapalene gel and petrolatum (control).[41,64] The irritative potential of 0.1% tretinoin microsphere gel and 0.05% tretinoin emollient cream was similar to that of 0.025% tretinoin cream.[65] Another study comparing 0.1% tretinoin microsphere gel with 0.1% adapalene gel found similar erythema and peeling rates slightly in favor of adapalene.[66] Retinoid-induced skin irritation can be relieved by regular use of a gentle moisturizing cream as an adjunctive treatment.[67] It is advisable to decrease sun exposure and avoid weather extremes such as cold wind and hot humidity during retinoid treatment. When exposed to light, 50% degradation of tretinoin was observed after 2 hours and 95% after 24 hours.[16] Therefore, tretinoin should be applied once daily at bedtime. In contrast, 89% of tretinoin microsphere gel remained stable after 2 hours of simulated solar radiation, even in combination with clindamycin and benzoyl peroxide, rendering 86% undegraded tretinoin after 2 hours.[43]

The percutaneous absorption of topical 0.05% tretinoin applied as emollient cream or cream is low and ranges between 1% and 2%, even after long-term application.[68] Topical administration of tretinoin acid did not significantly increase systemic retinoid plasma concentrations, which remained in the range of natural endogenous levels and were more influenced by nutritional and diurnal factors.[68-70] In terms of risk assessment, a pharmacokinetic model predicts that topical application of tretinoin results in an internal exposure that is four to six orders of magnitude lower than a minimally teratogenic dose.[71] Conversely, several case reports have suggested that fetal congenital abnormalities consistent with retinoid embryopathy following topical application of tretinoin in the first trimester are possible.[72,73] However, in a study evaluating the risks of birth defects in mothers exposed to topical tretinoin during early pregnancy, 215 exposed women were compared with 430 age-matched control individuals.[74] A relative risk of 0.7 (95% CI 0.2, 2.3) for a major congenital anomaly after topical tretinoin exposure was estimated, a finding that excluded any increased risk and rather suggested a protective effect of topical tretinoin. The results of this study were confirmed by those of another study in which 106 pregnant women with first-trimester exposure to topical tretinoin were prospectively identified and followed up with regard to birth outcomes, including pregnancy loss, major structural defects, and pre- and postnatal growth, compared with 389 similarly and prospectively identified women with no topical tretinoin exposure during pregnancy.[75] The study supported the notion that topical tretinoin is not associated with an increased risk of minor malformations consistent with retinoic acid embryopathy.

Topical tretinoin is an FDA pregnancy category C drug, which means that a risk cannot be ruled out because data in humans are lacking and animal studies are either positive or data are also lacking. Topical tretinoin may be prescribed when the benefits outweigh the risks; however, administration during pregnancy is difficult to justify because safer treatments are available and acne is not a life-threatening disease. During lactation, avoidance of topical tretinoin is advised because excretion via breast milk has not been studied and adverse reactions in nursing infants have not been ruled out. The safety and effectiveness of topical tretinoin in children aged <12 years have not been established.

3. Isotretinoin

3.1 Monotherapy

Isotretinoin is the 13-cis isomer of retinoic acid and is available in topical formulations (0.05% gel or cream, 0.1% cream) in countries outside the US. Its binding activity to RAR is low and isotretinoin does not bind to RXRs or CRABP. Some of the effects seen with isotretinoin in sebocytes might be related to its isomerization to tretinoin.[76,77] Topical 0.05% isotretinoin gel was effective compared with its vehicle in 268 patients with mild-to-moderate acne.[78] A significant anti-acne efficacy was observed after 8–12 weeks. In comparative trials, 0.05% isotretinoin gel was as effective as 0.05% tretinoin cream,[79] and slightly less effective than 0.1% adapalene gel,[80] although the differences were not statistically significant. Benzoyl peroxide had a superior effect compared with isotretinoin on inflamed lesions in the sense that improvement occurred earlier.[81]

3.2 Combination Therapy

A study of 160 patients with mild-to-moderate acne revealed that a fixed combination of 0.05% isotretinoin and 2% erythromycin (Isotrexin®, Stiefel) was significantly better in terms of reducing inflammatory lesions than isotretinoin alone at week 4 and than erythromycin alone at week 12.[82] Isotretinoin/erythromycin ('double-strength Isotrexin®') gel applied only once daily showed comparable efficacy to benzoyl peroxide/erythromycin applied twice daily in the treatment of mild-to-moderate acne vulgaris of the face.[83]

3.3 Safety and Tolerability

0.05% isotretinoin produces symptoms of irritative dermatitis, including erythema, scaling, burning, and dryness, in a range

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