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The Use of Topical Retinoids in Acne

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Abstract

Acne vulgaris is the most common skin disease in adolescents and young adults and has serious influence on quality of life of the patients. Acne vulgaris is the most common skin disease in adolescents and young adults and has serious influence on quality of life of the patients. The initial lesions of acne are the microcomedones that can be observed histologically in normal-appearing skin. The first step in the treatment of acne is to understand the pathophysiology of disease and to act on the factors involved in the development of acne. Increased sebum secretion from sebaceous glands, secretion of inflammatory mediators, altered keratinization and follicular plugging, and follicular colonization of Propionibacterium acnes are major four steps of acne pathogenesis. Topical retinoids have multiple effects in the treatment of acne and act on more than one factor implicated in the etiology of acne. They prevent the formation of microcomedones and reduce their number, reduce macrocomedones, promote the normal desquamation of follicular epithelium, exert anti-inflammatory effects, enhance the penetration of other topical acne drugs, and prolong the remission periods of acne by inhibiting the formation of microcomedone formation and preventing the development of new lesions and bacterial resistance. Therefore, topical retinoids have been the first-line treatment for most forms of acne vulgaris either alone or together with other agents.

Keywords: acne, retinoids, topical treatment

1. Acne

1.1. Introduction

Acne vulgaris is the most common skin disease in adolescents and young adults with 70–95% prevalence rate. Adult or postadolescent acne occurs in 12–14% of this population and is seen as the continuation of acne from adolescence into adulthood or starts in the adult life [1, 2].
Acne has a serious influence on quality of life of the patients. The negative impact of acne on behavioral and social functions has found to be greater than medical conditions such as asthma and epilepsy. Additionally, compared to unemployment, acne has been shown to be more highly associated with anxiety and depression [2, 3]. Fortunately, it is possible to improve the quality of life of patients with successful treatment. Over the past few decades, a large spectrum of local and systemic drugs has been introduced and a lot of efforts have been devoted to reach a consensus on the treatment approach of acne. As new drugs are constantly being added to the list, it is critical to update the current recommendations.

1.2. The global alliance to improve outcomes in acne

The Global Alliance to Improve Outcomes in Acne Group (“Global Alliance”) is an international group of dermatologists with clinical and research expertise in acne vulgaris. The first consensus guidelines were published in 2003 in JAAD and were very well received as an evidence-based and thoughtful document [1]. In the 2009 and 2016 guidelines updated information on pathogenesis, mechanism of action of therapies, and clinical results are presented [2, 4].

For this purpose, Global Alliance to Improve Outcomes in Acne Group (“Global Alliance”) was formed and the recommendations of the group have been published in 2003 as a supplement in the Journal of the Academy of Dermatology [2]. In the light of novel evidence-based studies, these recommendations have been updated recently [4]. On the other hand, racial and regional differences may affect the therapeutic approach to acne. Accordingly, in this ongoing process regional treatment guidelines are also being published [1, 2, 5–10].

1.3. Clinical features of acne vulgaris

Acne vulgaris is characterized by the presence of comedones and suggested to be a chronic disease. It has been traditionally thought that comedones are the noninflammatory lesions which present as either open or closed form. Inflammatory lesions of acne are papules, pustules, and nodules. In the previous guidelines, acne was graded into four levels as follows “Comedonal acne, mild to moderate papulopustular acne, severe papulopustular/moderate nodular acne, severe nodular acne/acne conglobata” [1, 7].

In the last guideline [4], acne has been divided simply as “Mild, moderate, and severe”.

1.4. Pathophysiology of acne

The first step in the treatment of acne is to understand the pathophysiology of disease and to act on all factors involved in the development of acne. The initial lesions of acne are the microcomedones that already exist in normal-appearing skin. These microcomedones can only be observed histologically [1–3, 8]. Additionally, the role of inflammatory cytokine such as interleukin-1 (IL-1), relative deficiency of linoleic acid, and hormonal and genetic factors has been reported [7].

Four major steps that have been hypothesized in the pathogenesis of acne are outlined in Table 1. Although the inflammatory step was previously believed to occur at the end of these stages, now it is thought to occur after the increased sebum secretion from sebaceous glands
because of the proinflammatory properties of lipids of hyperseborrhea as well as some other factors including excess androgen and smoking [1–4, 11].

1.5. Topical treatment of acne

Reviewing the guidelines on the treatment of acne, a recommended common approach is outlined in Table 2 [1–4].

Start with topical treatment, if appropriate
Give systemic treatment when necessary
Limit the use of local and systemic antibiotic concomitantly OR add topical BPO*

*BPO: Benzoyl peroxide

Table 2. Recommended general approach for the treatment of acne.

There is a large spectrum of topical agents for the treatment of acne (Table 3).

1.6. The importance of topical retinoids in the treatment of acne

Topical retinoids have multiple effects in the treatment of acne and act on more than one factor implicated in the etiology of acne (Table 4) [1–4, 12–14].

Topical retinoids have been the first-line treatment for most forms of acne vulgaris. They are used either alone or together with other agents as a first-line treatment in the treatment of acne forms other than severe nodular acne and acne conglobata. Alternative retinoids are included in alternative treatment options as well. In maintenance treatment, topical retinoids are used alone or in combination with BPO [1–4].

Table 3. Topical agents for the treatment of acne.

- Increased sebum secretion from sebaceous glands
- Secretion of inflammatory mediators
- Altered keratinization and follicular plugging
- Follicular colonization of *P. acnes*

Table 1. Four major steps in the pathogenesis of acne.

The Use of Topical Retinoids in Acne

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2. Topical retinoids

2.1. Introduction

Retinoids are vitamin A (retinol) or functional analogs with vitamin A activity. The abnormal keratinization in animals with vitamin A deficiency has exposed the importance of vitamin A in antikeratinization. As the systemic retinols given in effective dose have resulted in severe side effects, synthetic retinoids and their topical forms have been developed with similar clinical effect and fewer side effects. The first retinoid synthesized is all-trans-retinoic acid (ATRA, tretinoin) but as it has no significant advantages over retinol, it is used generally in topical form. ATRA is the natural metabolite of retinol. Isotretinoin has both systemic and topical forms. Today various topical retinoids are available for different purposes [14–16]. Human skin has retinoid receptors, belonging to thyroid receptor family, which have the capacity to store and metabolize retinoids [17]. The biologic effects of topical retinoids are mediated through nuclear hormone receptors and cytosolic binding proteins because human skin expresses RAR (RAR-γ > RAR-α) and RXR (RXR-α > RXR-β) [14–16]. Table 5 outlines retinoid receptors and their main endogenous ligands.

2.2. Topical retinoids used in the treatment of acne

Tretinoin and isotretinoin are the first-generation retinoids whereas adapalene and tazarotene are the third-generation retinoids. Retinaldehyde and retinol are found in cosmetic formulations [5]. Commercially available topical retinoids for acne treatment are presented in Table 6.

1. Prevent the formation of microcomedones and reduce their number
2. Reduce macrocomedones
3. Promote the normal desquamation of follicular epithelium
4. Exert anti-inflammatory effects
5. Enhance the penetration of other drugs
6. Prolong the remission periods of acne by inhibiting the formation of microcomedone and preventing the development of new lesions
7. Prevents bacterial resistance

Table 4. Multiple effects of topical retinoids in the treatment of acne.
2.2.1. Tretinoin
Tretinoin is the first retinoid studied and has been used more than 30 years in the treatment of acne. It induces the breakage of bonds between keratinized cells and enables the disintegration and the removal of the keratin plug. Besides comedolytic effect, it exerts anti-inflammatory effect; however, it does not have an effect on sebaceous gland activity. It binds to RARs on cytosol and regulates the expression of genes after moving to nucleus. It can bind all three types of RARs, namely, α, β, and γ [13–15]. Tretinoin can be used alone or in combination with other agents. As it enhances the penetration of other drugs, it creates a synergistic effect in combined use. Different formulations of tretinoin molecule have been introduced including 0.025, 0.05, and 0.1% cream, 0.025 and 0.1 gel, 0.05% solution, microsphere gel, and polymer cream [13–16].

2.2.2. Adapalene
Adapalene is a third-generation retinoid. It is available in 0.1 and 0.3 % gel and 0.1% cream form [1–4, 13–15, 18].

2.2.3. Isotretinoin
13-cis retinoic acid is produced from the isomerization of retinoic acid. The effects and efficacy are similar to retinoic acids. Other than oral form, it is available in 0.05% gel, and 0.05 and 0.1% cream form [1–4, 13–15].

2.2.4. Tazarotene
Tazarotene is a third-generation retinoid and its active metabolite is tazarotenic acid and it can bind all three types of RARs. It has not only anti-inflammatory effect like other retinoids, but also antiproliferative properties and normalizes the Filaggrin expression. Therefore, it is used also in the treatment of psoriasis. It is available in 0.05 and 0.1% cream form [1–4, 13–15].

2.2.5. Others
Retinaldehyde has a pivotal role in the natural vitamin A metabolism of keratinocytes. It is converted into all-trans retinoic acid and acts as topical retinoic acid in lower concentrations and generally found in cosmetic formulations. It has a mild comedolytic effect and has an antibacterial activity against Gram-positive bacteria including P. acnes due to its aldehyde group [19]. It is generally used in cosmetic formulations. Retinol and retinoic acid are metabolized into retinoyl beta-glucuronide. Motretinid is a second-generation monoaromatic retinoid. The clinical and side effects of motretinid are less than tretinoin [1–4].
2.2.6. Combination formulations

After the superiority of combining erythromycin 2% solution with 0.05% tretinoin to the monotherapy of each had been shown, fixed combination formulations of topical retinoids have been in production since 1978. Then, 0.025% tretinoid-4% erythromycin and 0.005% isotretinoin-2% erythromycin fixed combination formulations have been introduced [5]. It was reported that the usage of combination products were associated with better patient compliance. Recently, adapalene 0.1% and BPO 2.5% combination has been introduced. Theoretically, retinoid and BPO combination has been suggested to be advantageous due to the lack of bacterial resistance [1, 4, 13, 14].

2.2.7. The evaluation of comparative studies

Nast et al. conducted an evidence-based guideline for the treatment of acne in 2012 [7]. In this study, previous treatments were compared; superior efficacy was defined as a difference of more than 10% reduction of lesions in head-to-head comparisons.

2.2.7.1. Comedonal acne

Topical retinoids were found to show comparable-to-superior efficacy on noninflammatory lesions when compared to benzoyl peroxide [7].

Adapalene has shown comparable efficacy against noninflammatory lesions compared with tretinoin. Isotretinoin was effective as adapalene in the treatment of noninflammatory lesions, whereas it was found to be superior to tretinoin. Combination of adapalene and BPO shows a comparable-to-superior efficacy compared with BPO or adapalene alone. There was no trial comparing fixed-dose combinations of erythromycin and isotretinoin; however, using both erythromycin and isotretinoin was found to show comparable efficacy compared to erythromycin or isotretinoin alone [7].

Fixed-dose combination of adapalene-BPO has shown comparable-to-superior efficacy compared to adapalene or BPO alone, however, it was associated with lower patient tolerance [7].

2.2.7.2. Papulopustular acne

The efficacy of adapalene against inflammatory lesions was comparable to azelaic acid, BPO, tretinoin, and isotretinoin. Tretinoin was found to show comparable efficacy compared to isotretinoin. Fixed-dose combination of adapalene-BPO was superior to adapalene alone and was effective as BPO or clindamycin-BPO combination [7].

Combination of erythromycin and isotretinoin was superior to isotretinoin alone and was effective as erythromycin alone [7].

2.2.8. Patient tolerability and safety

Adapalene was found to display the best tolerability and safety among the topical retinoids followed by isotretinoin and tretinoin [7]. The tolerability and safety profile of fixed-dose adapalene-BPO preparation was lower than adapalene or BPO alone. The tolerability and
safety of erythromycin-isotretinoin combination was comparable to erythromycin or isotretinoin alone [7].

2.2.8.1. Factors affecting therapeutic compliance of patients

Treatment with less irritant topical retinoids was associated with better patient tolerance. To increase tolerance, it is advised to increase the dose gradually [5]. The carrier is also important as the active ingredient in topical formulation. Drugs with same active ingredient but different carriers were reported to show different tolerability profile [6, 13]. As these factors affect patient compliance they even influence the efficacy of the drug. Therefore, preparations with less irritant properties are more effective due to increased patient adherence. The other factors involved in treatment compliance are cosmetic products and skin cleaning habits. Application of drying agents was associated with the increased side effects of topical products. Also, racial differences were reported to affect the tolerance to topical retinoids. Asians are more prone to the irritation effect of topical retinoids compared to Caucasians [1, 3, 6].

2.2.9. The safety profile of topical retinoids

The major side effects of topical retinoids are local skin reactions such as erythema, scaling, dryness, burning, and stinging; rarely, they can cause pustular eruption. In comparative studies, adapalene with lower irritation rates has showed better tolerability profile compared to tretinoin or isotretinoin. Patient preferred adapalene over tretinoin [1, 7, 13].

2.2.9.1. Safety in pregnancy and systemic absorption

Even in long-term usage local retinoids were absorbed percutaneously only 1–2% and found in the range of natural endogenous levels in plasma [13]. However, congenital anomalies have been reported after the usage of local retinoids in the first trimester [20]. On the other hand, according to two retrospective cohort study topical retinoic acids were found not to associate with minor malformations in first trimester [21, 22]. According to many studies, systemic absorption of 0.05 and 1% isotretinoin gel is negligible even in 12 times greater than the normal dose. Adapalene is a derivative of naphthoic acid. It contains methoxyphenyl adamantyl chain and is stable against oxygen and light. Its cutaneous absorption is low due to its chemical structure. It could not be found in plasma after the application of 0.1% gel form [13]. In animal experiments, only systemic and high dose adapalene was reported to induce teratogenicity. However, as no studies have been carried out in pregnant subjects, potential risk cannot be excluded. In the literature, anophthalmia and abortion on 22nd week have been reported in a pregnant woman who used adapalene in 13th week of pregnancy [23]. Percutaneous absorption of tazarotene is less than 6%. No teratogenicity has been reported so far. Pregnancy category of tretinoin and adapalene is C, so they should be prescribed during pregnancy only if the potential benefit justifies potential risk to the fetus. On the other hand, erythromycin, azelaic acid, and BPO can be used during pregnancy, and retinoids are not recommended during pregnancy [13, 14, 24]. As no studies have been conducted on breastfeeding women, they should be avoided during lactation period. The pregnancy category of oral isotretinoin and tazarotene is X and their topical formulations are contraindicated [21, 22].
2.2.10. Practical applications

According to an investigation, dermatologists prescribe topical retinoids as second-line treatment after clindamycin, oral minocycline, and topical BPO [25]. Since topical retinoids inhibit microcomedones that are the precursor lesions of acne, they are recommended in most forms of acne. In acne patients, microcomedones are observed histopathologically even in normal-appearing skin. This underlines the fact that topical acne drugs can also be applied to normal-appearing skin [26].

Mild, noninflammatory acne can be treated by topical retinoids alone. If the comedonal lesions present together with inflammatory lesions topical retinoids should be combined with antimicrobial agents. As the combination treatment targets multiple pathophysiological factors, it is possible to get faster and permanent results. In the first-line treatment of moderate inflammatory acne, topical retinoids are recommended in combination with antimicrobial agents. Topical retinoids are the essential part of the maintenance treatment of acne [1–4, 13, 14].

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