

Joshua A. Zeichner
Editor

Acneiform Eruptions in Dermatology

A Differential Diagnosis



Editor

Joshua A. Zeichner, M.D.
Assistant Professor
Director of Cosmetic and Clinical Research
Dermatology Department
Mount Sinai Medical Center
New York, NY, USA

ISBN 978-1-4614-8343-4 ISBN 978-1-4614-8344-1 (eBook)
DOI 10.1007/978-1-4614-8344-1
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2013951661

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Chapter 3

Topical Therapies for Acne

Mary-Margaret Kober, Whitney P. Bowe, and Alan R. Shalita

3.1 Introduction

Topical treatment is a key component of acne therapy. Acne treatments target factors contributing to acne formation and act to normalize follicular keratinization and decrease sebaceous gland activity and follicular bacterial populations [1]. With early treatment, acne scarring, post-inflammatory hyperpigmentation, and psychological distress may be reduced or prevented [2]. Topical therapies for acne come in prescription and over-the-counter formulations. This chapter will focus on prescription products only.

3.2 Topical Retinoids

Biologically active molecules derived from vitamin A, topical retinoids have become a mainstay in acne therapy. Retinoids bind retinoic acid receptors (RARs) and retinoic X receptors (RXRs). Three subgroups of RARs exist: RAR- α (alpha), RAR- β (beta), and RAR- γ (gamma). RAR- α (alpha) is expressed throughout adult and embryonic tissue. RAR- β (beta) resides in dermal fibroblasts, and RAR- γ (gamma), present throughout the epidermis, is likely the receptor responsible for the positive effects retinoids exert on keratinocytes [3].

Once bound to their receptor, retinoids promote proliferation of basal keratinocytes, block the terminal stages of epithelial differentiation, and reduce filaggrin expression and proteolysis of keratins 1 and 14 [4]; these changes normalize keratinization and prevent the hyperproliferative state associated with comedo formation [5, 6]

M.-M. Kober, M.D. (✉) • W.P. Bowe, M.D. • A.R. Shalita, M.D.

Department of Dermatology, SUNY Downstate Medical Center,
450 Clarkson Road, Brooklyn, NY, USA

e-mail: mmkober@gmail.com; wpbowe@gmail.com; alan.shalita@downstate.edu

Currently, four topical retinoids are available: tretinoin, isotretinoin, tazarotene, and adapalene. However, only tretinoin, tazarotene, and adapalene are available in the United States.

3.2.1 Tretinoin (First-Generation Retinoids)

Tretinoin is the oldest of the retinoids and binds with equal affinity to all RAR receptors. Tretinoin demonstrates superiority to benzoyl peroxide (BP), sulfur-resorcinol, and vehicle in the reduction of inflammatory and noninflammatory acne lesions as well as the global severity of acne [7, 8].

Although there may be some improvement noted after 2–3 weeks, the most significant reduction in acne lesions is noted after 3–4 months of consistent use [9]. The histopathologic findings seen in skin receiving tretinoin include acanthosis, parakeratosis, and thinning of the stratum corneum [8], which correlates with the observation that the tretinoin-induced thinning of the stratum corneum allows for improved efficacy of topical antimicrobial products [10].

Ultraviolet light and oxidants such as benzoyl peroxide degrade tretinoin upon exposure [9]. Advances in formulation technology have allowed for the development of new tretinoin containing topicals that combat these limitations. One such example is the development of microsphere formations (Retin-A Micro®) that significantly decreases degradation [11]. Microsphere formulations also provide a gradual time release of tretinoin, increasing transdermal penetration and decreasing the irritation [12].

3.2.2 Tazarotene and Adapalene (Third-Generation Retinoids)

Tazarotene and adapalene only bind to RAR- β (beta) and RAR- γ (gamma) receptor subtypes, leading to reduced side effects compared to tretinoin.

Although similar in efficacy to tretinoin in the reduction of inflammatory lesions, tazarotene has proven to be superior to tretinoin in reducing the number of noninflammatory lesions [13]. Tazarotene also shows superiority compared to adapalene in clearing post-inflammatory hyperpigmentation caused by acne [13].

Adapalene shows similar efficacy to tretinoin in reducing inflammatory and non-inflammatory lesions and the global severity of acne [14]. However, when compared to tazarotene, adapalene is less effective in decreasing the number of inflammatory and noninflammatory lesions [15]. In general, adapalene demonstrates the best tolerability profile of the topical retinoids [16, 17].

Both tazarotene and adapalene have increased stability in the presence of ultraviolet light and BP as a result of replacing the labile, light sensitive double bonds of tretinoin with naphthoic acid rings [18]. This allows for the development of stable combination products containing third-generation retinoids with other active ingredients, such as BP.

Combination products are now available on the market, including adapalene/BP, tretinoin/clindamycin, and erythromycin/BP or clindamycin/BP. In addition to the comedolytic effects of retinoids, these products decrease *P. acnes* counts. Combination products often have faster results than monotherapy and improved patient compliance [19, 20].

The most common adverse reactions to topical retinoids include localized dry skin, erythema, and scaling. Compared to the newer formulations of retinoids, older forms of tretinoin caused more burning, erythema, and desquamation. Tolerance typically develops with continued exposure. Unlike systemic retinoids, studies have not demonstrated a teratogenic effect of topical retinoids; however, given the theoretical risk, many dermatologists advise patients to stop application during pregnancy [21].

Given the chronic nature of acne and its tendency to recur upon cessation of treatment, maintenance therapy is often required; first-line maintenance therapy is a topical retinoid. In one study of patients with moderate acne who had initial treatment with a topical retinoid and antimicrobial, those continued on topical retinoid therapy had significant less rebound and maintained few acne lesions compared to those who did not receive maintenance therapy [22].

3.3 Topical Antimicrobials

3.3.1 Antibiotics

Clindamycin and erythromycin represent the topical antibiotics most commonly used for acne treatment, although recent trends suggest that clindamycin is the most commonly prescribed [23]. Their mechanism of action is based on the reduction of *P. acnes* organisms present on the skin, leading to a reduction in inflammatory pathways and consequently a decrease in the number of inflammatory and noninflammatory acne lesions [24–26].

Several concerns have developed regarding the use of topical antibiotics, specifically surrounding the emergence of resistant strains of *P. acnes*. Rates of erythromycin and clindamycin resistant *P. acnes* have increased to 40 % globally, leading to a decrease in treatment efficacy of topical antibiotics [27–29]. Although resistance has emerged to both erythromycin and clindamycin, the clinical efficacy of clindamycin has been preserved relative to erythromycin [23].

Perhaps more concerning is the data suggesting pharyngeal colonization with *Streptococcus pyogenes* with chronic use of topical antibiotics [14]. Long-term antibiotic use has also shown the development of bacterial resistance in coagulase-negative staphylococci [30]. Although coagulase-negative staphylococci are rarely pathogenic, it may serve as a reservoir of bacterial resistant genes, spreading resistant genes to other organisms, such as *Staphylococcus aureus* [31].

Combining BP with a topical antibiotic reduces the emergence of resistant strains and improves efficacy [32]. Given the occurrence of antibiotic resistance with monotherapy of topical antibiotics, it is only recommended to use topical antibiotics

as part of combination therapy [33]. Several combination products are available that combine a topical antibiotic with BP into a single product. Combination gels have reduced antibiotic-resistant strains of *P. acnes* by 97 % [34] and have shown to improve patient adherence to treatment regimens [35].

Side effects of topical antibiotics are limited. The most common adverse effects include reactions at the site of application (erythema, scaling, stinging, or burning); these reactions have been shown to be at least in part dependent on the vehicle formulation [23, 24].

3.3.2 Azelaic Acid

The antimicrobial properties of azelaic acid make it another topical treatment option for acne [33]. Trials comparing azelaic acid to BP or topical clindamycin show similar reductions in the number of acne lesions [36]. Reduction in the number of lesions can be seen as early as 4–8 weeks; however, maximum benefit typically occurs after 16 weeks. Cutaneous side effects of stinging or burning may occur in 10–20 % of patients upon initial use; however, these side effects typically resolve with continued use and rarely necessitate the cessation of treatment [37, 38]. It should be noted, however, that one of the authors found little or no efficacy with the original formulation of azelaic acid and one laboratory found no antibacterial effect on *P. acnes*.

Topical clindamycin, erythromycin, and azelaic acid appear to be safe during pregnancy (Category B), with no reports of teratogenicity to date.

3.3.3 Dapsone

Topical dapsone has been approved for the treatment of acne vulgaris, although it may result in a more modest reduction in acne lesions compared to other therapies. It has an excellent tolerability profile, but may result in a temporary yellow discoloration of the skin when combined with BP [34]. Topical dapsone appears to work well as an adjuvant to topical retinoids, reducing the irritation and desquamation commonly associated with topical retinoids as well as significantly increasing their efficacy [34].

3.4 New Developments in Topical Acne Therapy

Novel topical acne therapies focus on targeting drug delivery to the follicle.

3.4.1 Liposomes

Liposomes are phospholipid bilayers that create a spherical vesicle with a central aqueous cavity and possess both hydrophobic and lipophilic properties. Clindamycin in liposomes has shown a statistically significant decrease in acne lesions compared to liposome-free clindamycin products [39]; similar efficacy has been seen with liposome-derived tea tree oil, salicylic acid, retinoids, and BP [40].

3.4.2 Micronization

Smaller particles permit deeper penetration into the pilosebaceous unit. Micronizing formulations create products of smaller particle sizes, with particles frequently less than 10 μm . A micronized formulation of tretinoin gel, Atralin[®], has demonstrated enhanced moisture capacity and tolerability with similar lesion reduction compared to generic tretinoin gel [41].

3.5 Treatment Guidelines

Mild acne responds to treatment with a topical retinoid with possible addition of BP and/or a topical antibiotic if inflammatory lesions are present. Mild-to-moderate acne typically requires combination therapy using one of the following regimens: a topical retinoid combined with BP and an oral antibiotic or a topical retinoid combined with a topical BP/antibiotic product [42]. Moderate-to-severe acne may be treated with topical retinoids in combination with BP, topical, and/or oral antibiotics; however, acne this severe may require systemic isotretinoin, discussed elsewhere.

3.6 Conclusion

Acne vulgaris is a chronic disease that requires a patient-centered approach. The most common topical treatments include retinoids and antibiotics with the addition of BP to reduce the development of antibiotic resistant strains of *P. acnes*. New products and novel formulation of existing drugs continue to expand the arsenal of available treatments and reduce adverse effects such as irritation and erythema. Maintenance therapy with topical retinoids is often recommended after initial treatment to prevent relapses.

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