LEADING ARTICLE

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Newer Approaches to the Treatment of Acne Vulgaris

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Abstract

The multifactorial etiology of acne vulgaris makes it challenging to treat. Current treatments include topical retinoids, benzoyl peroxide, topical and systemic antibiotics, azelaic acid, and systemic isotretinoin. Adjunctive and/or emerging approaches include topical dapsone, taurine bromamine, resveratrol, chemical peels, optical treatments, as well as complementary and alternative medications. The purpose of this paper is to discuss the therapies available for acne and their latest developments, including new treatment strategies (i.e. re-evaluation of the use of oral antibiotics and avoidance of topical antibiotic monotherapy, use of subantimicrobial antibiotic dosing, use of low-dose isotretinoin, optical treatments), new formulations (microsponges, liposomes, nanoemulsions, aerosol foams), new combinations (fixed-combination products of topical retinoids and topical antibiotics [essentially clindamycin] or benzoyl peroxide), new agents (topical dapsone, taurine bromamine, resveratrol) and their rationale and likely place in treatment. Acne vaccines, topical natural antimicrobial peptides, and lauric acid represent other promising therapies.

1. Introduction

Acne vulgaris is one of the most common disorders encountered in dermatology practice.[1,2] Epidemiologic studies in Western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%, depending on the method of lesion counting.[3-5] Although acne is a disease primarily of adolescence, it may, to some degree, persist into adulthood in a significant proportion of individuals, particularly women.[4,6] The disease burden of acne has the ability to elicit in some sufferers significant mental health concerns due to a heightened sense of shame relating to appearance.[7,8]

Current understanding of acne pathogenesis continues to evolve. Acne is an androgen-dependent disorder of pilosebaceous follicles. There are four primary pathogenic factors that interact to produce acne lesions: (i) increased and altered androgen-dependent sebum production; (ii) altered keratinization leading to comedones; (iii) *Propionibacterium acnes* follicular colonization; and (iv) release of inflammatory mediators into the skin.[1,2] Although family history and environment factors have an important role in the disease, the exact sequence of events and how they interact remains unclear. Management, therefore, is a multifactorial approach with several treatment options targeted toward the multiple factors contributing to

are compounded by the profusion of available treatments and by the relative paucity of trials with active comparators. Concerns about antibiotic resistance and isotretinoin safety as well as the rise of novel adjunctive treatments bring new perspectives to the treatment of acne. Alternatives to refractory acne, aversion to prescription medications, adverse effects to conventional therapy, and poor adherence to conventional therapy drive interest in novel approaches. This review summarizes the latest developments in the treatment of acne and their rationale and likely place in treatment.

1.1 Literature Search Parameters

An extensive search was performed at the beginning of the project. A systematic electronic search strategy was used to retrieve all the recently published (January 2007–December 2011) clinical trials investigating therapies for acne. This review focused on the therapy of acne and not on other forms of acne. We obtained data from MEDLINE (National Library of Medicine), PubMed, Current Contents, HomInform (Glasgow) [database of references to journal articles and books on homeopathy], reference lists, and textbooks. There was no restriction on language. The selected keywords were 'acne,' 'comedones,' 'vulgaris,' 'treatment,' 'therapy,' 'retinoids,' 'isotretinoin,' 'benzoyl peroxide,' 'azelaic acid,' 'antibiotics,' 'dapsone,' 'laser,'

2. Acne Therapy

The large number of products and product combinations, and the scarcity of comparative studies, has led to disparate guidelines. Because of the paucity of evidence, these guidelines rely on the opinions of experts, many of whom declare significant potential conflicts of interest.[2,9-12] Conventional treatments include topical retinoids, benzoyl peroxide, azelaic acid, topical and systemic antibiotics, systemic isotretinoin, and combined oral contraceptives for women.[2,9-12] Novel approaches encompass recent developments in conventional treatments as well as emerging therapies. These different therapies are summarized in table I.

Table I. Conventional, emerging, and experimental anti-acne therapies for acne vulgaris

Therapies	Main concerns
Conventional	
Topical therapies	
Topical retinoids	Local irritation
Fixed-combination products of topical retinoids and topical antibiotics or BPO	Local irritation
BPO	Local irritation
Azelaic acid	Local irritation
Topical antibiotics	Antibiotic resistance
Systemic therapies	
Isotretinoin	Safety concerns
Systemic antibiotics	Antibiotic resistance
Oral contraceptives	Lack of comparisons with other standard therapies
Emerging	
Topical dapsone	Lack of comparisons with other standard therapies
Taurine bromamine	Lack of comparisons with other standard therapies
Chemical peels	Lack of comparisons with other standard therapies, local adverse effects
Optical treatments	Lack of comparisons with other standard therapies, local adverse effects, high cost
Complementary and alternative medications	Inconclusive results
Sodium sulfacetaminde	Clinical data limited to case series
Resveratrol	Clinical data limited to one open-label pilot study
Experimental	
Vaccination, natural antimicrobial peptides	Absence of published clinical data

BPO = benzoyl peroxide.

2.1 Retinoids

2.1.1 Topical Retinoid Therapy

Topical retinoids represent a mainstay of acne treatment because they expel mature comedones, reduce microcomedone formation, and exert anti-inflammatory effects through a number of pathways, including downregulating toll-like receptors, cytokines, and nitric oxide.[13] Topical retinoids have a favorable safety profile distinct from the toxicity of their systemic counterparts. They are contraindicated in pregnancy, and women of childbearing age must use effective contraception. 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 environment factors such as sun exposure or temperature.[13] They do not seem to cause temporary worsening of acne lesions.[14]

The broad anti-acne activity and safety profile of topical retinoids justifies their use as first-line treatment in mild to moderate forms of acne, more particularly in comedonal forms of acne, as well as for maintenance therapy;[9-13] these agents can also minimize the potential for relapse, which is part of the natural history of acne.[15]

A meta-analysis of five multicenter, randomized, investigator-blind trials involving 900 patients showed adapalene 0.1% gel to be as effective as, but less irritating than tretinoin 0.025% gel,[16] so that adapalene should be selected in preference to tretinoin and isotretinoin.

Fixed-combination products of topical retinoids and topical antibiotics (essentially clindamycin) or benzoyl peroxide are significantly more efficacious in reducing the number of inflammatory and non-inflammatory lesions compared with retinoid monotherapy.[17-19] Furthermore, patients taking combination therapy show faster signs of improvement.[20] The quicker onset of action is believed to lead to greater patient adherence and to reduce the amount of antibiotic exposure and risk of *P. acnes* resistance.

Lately, formulation technology has focused on providing more efficient penetration of the retinoids into the skin layers or greater stability to the retinoid molecules so that lower concentrations of retinoids might afford better tolerability, but maintain good efficacy. These potential novel systems for agent delivery include microsponges, liposomes, nanoemulsions, and aerosol foams. A micronized formulation of tretinoin (0.05%)

gel has been developed that provides a more efficient delivery of tretinoin, because of its optimal particle size, no degradation by benzoyl peroxide, and better cutaneous tolerability than tretinoin microsphere (0.1%) gel without compromising efficacy.[21,22] Retinoic acid-loaded, solid, lipid nanoparticles represent another interesting alternative to reduce retinoic acid-induced skin irritation without reducing efficacy.[23] Retinol has a lower biologic activity but a better tolerability. Combination products using retinol with substances with anti-inflammatory and antibacterial activity might increase this biologic activity.[24]

2.1.2 Isotretinoin Therapy

Oral isotretinoin was approved for use in acne in 1982. Targeting the four primary pathogenic factors of acne, it remains arguably the most effective acne medication available. Although comparative trials are missing, clinical experience confirms that the relapse rates after treatment with isotretinoin are the lowest among all the available therapies. Originally, it was reserved for severe, recalcitrant, nodular acne that was unresponsive to topical therapy. Although many authorities believe that isotretinoin should be reserved for severe acne not responding to appropriate antibiotics and topical therapy, the published data and opinion of some experts support systemic isotretinoin being considered as the first-line treatment for severe papulopustular, moderate nodular, and severe nodular/conglobate acne.[1,2,9-12,25,26] Reasons supporting oral isotretinoin as a first-line treatment for severe acne include clinical effectiveness, prevention of scarring, and quick improvement of a patient's quality of life.

The evidence on the best dosage, including cumulative dosage, is rare and partly conflicting. In most trials, higher dosages have lead to better response rates whilst having less favorable safety/tolerability profiles. However, there is cumulative evidence that low-dose isotretinoin might be a useful treatment option for moderate acne.[26-28] Attempts to determine the cumulative dose necessary to obtain an optimal treatment response and low relapse rate have not yet yielded sufficient evidence for a strong recommendation. Research is also needed to investigate whether isotretinoin could be beneficial if used sooner for moderate cases. Although effective against severe acne, isotretinoin is associated with significant adverse effects, including cheilitis, dry skin and mucous membranes, epistaxis, increased risk of cutaneous *Staphylococcus aureus* infections, temporary worsening of lesions, photosensitivity, increased serum lipids, myalgias, hyperlipidemia, pseudotumor cerebri, and teratogenicity.[2] Associations with inflammatory bowel disease are controversial.[29,30] There are plausible biologic mechanisms by which retinoids might induce psychopathology.[2] A systematic review of isotretinoin use and depression and suicidal behavior published in 2007 did not find any evidence to support the notion that depressive symptoms or diagnosis increased after treatment, and some in fact, demonstrated a trend toward fewer or less severe depressive symptoms after isotretinoin therapy.[31] The picture is a complex one as depression and suicidal ideation occur with severe acne in the absence of isotretinoin treatment.[32,33] The current recommendation is that patients with severe acne with a history of attempted suicide should not automatically be refused isotretinoin but should be monitored for suicidal behavior after treatment has ended.[34] Claims of injury have fueled hysteria among laypersons about the use of this drug. Overwhelmed with worries of its potential adverse effects, the public forgets that withholding isotretinoin therapy is not without its own risks. Isotretinoin therapy can prevent lifelong and permanent physical and psychological scarring that comes as a matter of course with severe acne.[2,25,26,35] Over 20 million people worldwide have taken the drug, with several studies demonstrating its safety and few long-term adverse effects.[35]

2.2 Antibiotics

2.2.1 Topical Antibiotics

How topical antibiotics improve acne has not been clearly defined, but they seem to act directly on *P. acnes* colonization and its subsequent proinflammatory effects on comedogenesis. The most commonly used topical antibiotics are clindamycin and erythromycin. However, studies on *P. acnes* resistance have highlighted the need for treatment guidelines to restrict the use of antibiotics in order to limit the emergence of resistant strains. It has been argued that the most likely effect of resistance is to reduce the clinical efficacy of antibiotic-based treatment regimens to a level below that which would occur in patients with fully susceptible flora.[36] Some trials have suggested a clear association between *P. acnes* resistance to the appropriate antibiotic and poor therapeutic response.[36] There is a gradual decrease in the efficacy of topical erythromycin in clinical trials of therapeutic intervention for acne, which is probably related to the development of antibiotic-resistant propionibacteria.[37] Decreased clinical efficacy of antibiotics for dermatologic conditions other than acne or for non-dermatologic infectious diseases appears as another major threat. Monotherapy with topical antibiotics is thus no longer recommended.[2,9-12,36-38]

2.2.2 Systemic Antibiotics

Although antibiotics have shown effectiveness in terms of reducing the number of acne lesions, most antibiotic courses are

not curative. The use of antibiotics for acne has been questioned owing to resistance concerns, especially since they are repeatedly used for long periods at low doses. Furthermore, there is a low evidence level that oral antibiotics are more effective than topical preparations for mild-to-moderate facial acne.[39] Tetracyclines are the first-line oral antibiotic therapy in acne. Overall, there is insufficient evidence to support one tetracycline over another in terms of efficacy.[40] There could be no justification in continuing to use minocycline as a first-line therapy in acne because of an uncertainty safety profile and a lack of advantages over other tetracyclines (i.e. first-generation cyclines, doxycycline and lymecycline).[40,41]

In the range of dosages investigated in the clinical studies, the tetracycline dosage seems to have no impact on efficacy.[40] Although two trials of subantimicrobial dosing (i.e. the prescription of low doses that are anti-inflammatory but not antimicrobial) have shown a reduction in the number of inflammatory and non-inflammatory lesions,[42,43] the studies are too small to make reliable estimates of bacterial resistance that could be promoted by the lower doses used.

As a consequence of resistance concerns, the use of oral antibiotics should be limited (indication, duration) and topical antibiotic monotherapy should be avoided.[2,9-12,36-38] Other recommendations are that we should use stricter cross-infection control measures when assessing acne in the clinic and combine any topical/systemic antibiotic therapy with broad-spectrum antibacterial agents, such as benzoyl peroxide.[11,36,43]

Although oral macrolides like erythromycin may represent an alternative in patients who are intolerant or allergic to tetracyclines and may be used in pregnancy, there is little evidence to support the use of other oral antibiotics (i.e. clindamycin, cotrimoxazole, quinolones).

2.3 Benzoyl Peroxide

Benzoyl peroxide is a safe and effective over-the-counter preparation that reduces the number of *P. acnes* by suppressing growth without the risk of resistance selection. Low concentration (2.5% or 5%) benzoyl peroxide is recommended, since it is less irritating and there is no clear evidence that stronger preparations are more effective.[44] Single-agent benzoyl peroxide works as well as oral antibiotics. It has greater activity than topical tretinoin against inflammatory lesions.[45] The anti-acne activity and safety profile of benzoyl peroxide justifies its use as first-line treatment in mild to moderate forms of acne, more particularly in papular/pustular forms of acne.[12,46] Several studies suggest that the efficacy of benzoyl peroxide can be enhanced when used in combination with topical retinoids, antibiotics (essentially clindamycin[19,46] and, more recently, nadifloxacin[47]), and tertiary amines, such as an allylamine. However, a recent systematic review showed that combination products containing benzoyl peroxide were only incrementally better than benzoyl peroxide alone.[48]

2.4 Azelaic Acid

Azelaic acid has both antimicrobial and anticomedonal properties. The data on azelaic acid (15% or 20%) show an inferior efficacy compared with benzoyl peroxide[49,50] in reducing non-inflammatory lesions but a similar efficacy in reducing inflammatory lesions.[49,50] There are very little data comparing the efficacy of adapalene, topical isotretinoin, or topical antibiotics with azelaic acid. Azelaic acid shows a trend towards a better tolerability/safety profile compared with benzoyl peroxide (5%),[49] topical adapalene,[50] and tretinoin.[51]

2.5 Topical Dapsone

Topical dapsone 5% gel offers documented efficacy for the reduction of both inflammatory and non-inflammatory acne lesions. Topical dapsone is superior to placebo but has yet to be compared with standard topical treatments. It has been proven safe, presenting none of the hematologic risks associated with oral dapsone. With regard to safety, the studies demonstrated that the concentrations of dapsone and N-acetyl dapsone remain low and do not accumulate over time once steady state is reached. Topical dapsone 5% gel also appears to be safe to use in patients with glucose-6-phosphate dehydrogenase deficiency.[52] Data suggest the vehicle formulation enhances healing and contributes to tolerability, making topical dapsone 5% gel a worthwhile anti-inflammatory treatment for patients with mild-to-moderate acne.[53,54]

2.6 Taurine Bromamine

Taurine bromamine, the product of taurine and hypobromous acid, exerts anti-inflammatory and antibacterial properties against *P. acnes* and *Staphylococcus epidermidis*. In a double-blind investigation, the efficacy and safety of 3.5 mM taurine bromamine cream versus clindamycin gel were comparable.[55] These data suggest that taurine bromamine can be used as a topical agent in the treatment of acne, especially in patients who have already developed antibiotic resistance, but needs to be confirmed by further studies.

2.7 Chemical Peels

The most common chemicals used include α-hydroxy acids such as glycolic acid and β-hydroxy acids such as salicylic acids.[1,56] *In vitro* data demonstrate that glycolic acid has moderate growth inhibitory and bactericidal effects on *P. acnes*.[57] Search of the literature revealed very few clinical trials of peels in acne;[56] a majority of these trials included small numbers of patients, were not controlled, and were open label. The evidence that is available does support the use of chemical peels in acne as all trials had generally favorable results despite differences in assessments, treatment regimens, and patient populations. Notably, no studies of chemical peels have used an acne medication as a comparator.[56]

2.8 Other Topical Therapies

Salicylic acid is an exfoliant and is a component of many over-the-counter preparations. No studies support routine use of salicylic acid in preference to other topical therapies. Some data suggest that the addition of salicylic acid to other topical therapies (i.e. clindamycin plus benzoyl peroxide) may improve the clinical outcome.[58]

An over-the-counter emollient foam, containing sodium sulfacetaminde 10% and sulfur 5% exhibiting moisturization properties as well as antibacterial activities against *P. acnes in vitro* has been shown to be effective in a limited series of patients with acne.[59] Further studies are obviously required to assess its usefulness.

Recently, a single-blind, vehicle-controlled, pilot study showed positive results for resveratrol on acneic skin. Resveratrol is a natural phytoalexin exhibiting activity against *P. acnes* as well as anti-inflammatory properties and is produced by some spermatophytes, such as grapes and other plants.[60]

2.9 Oral Contraceptives

All types of combined oral contraceptives seem to be effective in reducing inflammatory and non-inflammatory acne lesions, but there is no clear evidence that those containing additional cyproterone offered any further benefit.[61] Although there are few studies comparing combined oral contraceptives with other acne treatments, hormonal therapy is regarded as an excellent choice for women who need oral contraception.[9,61,62] However, dermatologists have historically been reluctant to prescribe oral contraceptives for acne because of long-standing recommendations requiring a preliminary pelvic examination and Papanicolaou smear before initiation of therapy. In recent guideline shifts, expert panels and major health organizations have reached a consensus that oral contraceptive provision no longer necessitates the performance of a pelvic examination and Papanicolaou smear.[63] Another Cochrane review failed to show any benefit of spironolactone for acne, based on limited studies.[64]

2.10 Optical Treatments (Laser Therapy, Light Sources, and Photodynamic Therapy)

Optical therapies that have been used to treat acne include broad-spectrum continuous-wave visible light (blue and red), intense pulsed light, pulsed dye lasers, potassium titanyl phosphate lasers, photodynamic therapy (PDT), and pulsed diode laser.

Light therapy is based on the observation that *P. acnes* is capable of synthesizing chromophores such as porphyrins.[65] Whereas blue light has been shown to photoinactivate *P. acnes*, it does not penetrate skin very far. On the other hand, red light, which is less effective at porphyrin activation, can reach deeper sebaceous glands.[66] Compared with light therapy, lasers have the ability to concentrate coherent light on a smaller area of tissue. Although there are some studies of the treatment of non-inflammatory lesions with laser and light sources, the published evidence is still very scarce. There is conflicting evidence regarding the efficacy of red light against inflammatory lesions compared with placebo. Blue light has superior efficacy against inflammatory lesions/total lesions compared with placebo.[67,68] The combination of blue-red light therapy may act synergistically and be more effective at reducing the number of inflammatory lesions.[67] There is insufficient evidence regarding the efficacy of all other light and laser interventions compared with placebo.[69]

PDT refers to the use of aminolevulinic acid, methyl-aminolevulinic acid, or other photosensitizing agents to enhance the effect of subsequent light or laser therapy. Topical application of these molecules results in significant build-up of porphyrins in sebaceous glands and the efficacy of PDT in acne is believed to be related in part to a decrease in sebaceous gland activity following light activation of the photosensitizer. Most trials of PDT showed some benefit, which was greater with multiple treatments, and better for non-inflammatory acne lesions. However, the improvements in inflammatory acne lesions were not better than with topical adapalene 1% gel.[70]

There are also some studies showing that treatment with the infrared 1450 nm diode laser reduces inflammatory acne lesions and may provide a long-term remission in acne. The presumed mechanism of acne improvement is through heating of the sebaceous gland and reduced sebaceous gland activity.[71]

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