Acne Agents, Topical Review

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FDA-approved Indications

All products are indicated for the topical treatment of acne vulgaris. Tazarotene (Tazorac) is additionally indicated for the treatment of plaque psoriasis.

Drug	Manufacturer
adapalene (Differin®)	Galderma
azelaic acid (Azelex®)	Allergen
benzoyl peroxide (Clinac™ BPO) (Inova™) (Lavoclen™) (Neobenz™ Micro) (Triaz®) (Zaclir™)	generic Ferndale JSJ Pharmaceuticals Prasco SkinMedica Medicis Hawthorn
benzoyl peroxide/ clindamycin (BenzaClin®) (Duac® CS)	 Sanofi-Aventis Stiefel
benzoyl peroxide/ erythromycin (Benzamycin® Pak)	generic Sanofi-Aventis
benzoyl peroxide/sodium hyaluronate (Zacare™ Kit)	Hawthorn
benzoyl peroxide/ salicylic acid (Inova™ 4/1, 8/2)	JSJ Pharmaceuticals
benzoyl peroxide/ sulfur (NuOx) (Sulfoxyl®)	 WraSer Stiefel
clindamycin (Clindagel®) (ClindaReach™) (Evoclin™)	generic Galderma DUSA Connetics Corp
erythromycin (Akne-Mycin®)	generic Coria Labs
sodium sulfacetamide (Klaron®)	generic Sanofi-Aventis
tazarotene (Tazorac®)	Allergen
Tretinoin (Atralin™) (Retin-A Micro®)	generic Coria Labs Ortho Derm
clindamycin/tretinoin (Ziana™)	Medicis

Overview

Acne vulgaris is the most common cutaneous condition in the United States. It is a disorder that affects primarily teenagers and young adults, but can sometimes persist beyond young adulthood. In adolescence, sebaceous glands increase sebum release after puberty. Small cysts called comedones form in hair follicles due to blockage of the pore due to retention of sebum and keratinous material. Bacterial activity, most often due to *Propionibacterium acnes*, within the comedones releases free fatty acids from sebum, causing inflammation within the cyst. This results in rupture of the cyst wall and subsequent inflammatory reaction due to extrusion of oily and keratinous debris from the cyst.

There are three categories of the severity of acne and includes either acne occurring on the face or the trunk of the body.[1] These categories are graded as mild, moderate, or severe depending on the presence and number of lesions, which consist of comedones, papules, pustules, and/or cysts. Mild acne is defined by the presence of fewer than 20 comedones, fewer than 15 inflamed papules, or fewer than 30 lesions consisting of the combination comedones and papules. Moderate acne is defined by the presence of 15-50 papules and pustules in addition to comedones and rare cysts, and the total number of lesions on the face can range from 30-125. Severe acne is defined by the presence of mostly inflamed nodules and cysts, and includes more than 125 lesions consisting of comedones, papules, and pustules.

The elimination of lesions is the goal of treatment. This is achieved by decreasing sebaceous gland activity, bacterial population, and inflammation. The available products work by different mechanisms to attack the causative events. Typically, retinoids such as tretinoin (Atralin, Retin-A Micro), adapalene (Differin), and tazarotene (Tazorac) are used to inhibit comedone formation and an antibiotic such as clindamycin or erythromycin suppresses *P. acnes*. Combination therapy is useful to limit growing resistance to antibacterial therapy, as well as enhance the efficacy of antibiotics by improving penetration into the lesions.[2,3,4] Since 1990, prescribing has trended more toward agents not reliant on antibacterial mechanisms.[5]

The American Academy of Dermatology (updated in 2007) and The Global Alliance to Improve Outcomes in Acne (updated in 2006) have created guidelines for the management of acne vulgaris.[6,7] Both guidelines recommend topical therapy as standard of care in mild to moderate acne treatment. A topical retinoid should be the cornerstone in treatment of most patients with acne as they target the microcomedone, which is the precursor to all acne lesions.[8] For inflammatory lesions, antibacterial agents are used in combination with other agents, but retinoids can be introduced even in mild cases of acne. Antibacterial monotherapy is avoided due to the concern for development of bacterial resistance.

Combination therapy is useful for mixed lesions as well as other cases with differing severity.[9,10,11,12,13] Combination of an antibacterial agent and an agent for decreasing comedones often results in increased efficacy and faster clearing, as opposed to antibacterial monotherapy, but combination therapy can also increase the incidence and severity of adverse effects. Often times this can be minimized by choosing the appropriate topical base for skin type, gel or solution for oily skin and creams or lotions for dry skin.[14] Other methods used to optimize therapy and prevent adverse effects include applying the agent to dry skin, and alternating the time of application of multiple treatment types. For example, an antibiotic may be applied in the morning, and a retinoid may be applied at bedtime).

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity and has been useful as a single agent and in monotherapy with antibiotics or retinoids in decreasing the number of lesions in mild to moderate acne.[15] Combining a topical antibiotic with benzoyl peroxide reduces the development of resistant strains of *P. acnes*.[16,17,18] This combination is more

effective and less irritating than benzoyl peroxide used alone. There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentration of drug.

Clindamycin has been associated with greater incidences of adverse effects when introduced into the systemic circulation compared to erythromycin, but the topical application of these products allows for minimal systemic absorption. There does not appear to be any significant differences in the efficacy of these topical antibiotics. Monotherapy with these topical antibiotics is not recommended due to the development of bacterial resistance.[19,20]

Azelaic acid (Azelex) exhibits comedolytic and antibacterial properties; it is not viewed as initial therapy.[21] Investigation of clinical efficacy for sodium sulfacetamide is lacking, as are the effects of combinations with sulfur. Sulfur is an older therapeutic agent exhibiting antimicrobial and keratolytic activity, and has demonstrated some usefulness in the treatment of acne.[22,23] The clinical evidence, however, demonstrating the efficacy of sulfur in acne treatment has not been consistently or reliably proven.

Adapalene and tazarotene have been shown to be at least as effective as tretinoin, often with a lower incidence of adverse effects.[24] However, tazarotene gel may be more irritating than tretinoin or adapalene. The tazarotene cream formulation may be better tolerated, but how it compares in effectiveness with adapalene or tretinoin remains to be determined.

Systemic treatment is generally required in cases of severe acne, and hormonal therapy is available for females. This review focuses on the available topical preparations for acne treatment.

Pharmacology

Clindamycin and erythromycin are antibiotics that inhibit bacterial protein synthesis at the ribosomal level by binding to the 50S ribosome and affecting the process of peptide chain initiation. They have been shown to have *in vitro* activity against *P. acnes*, an organism commonly associated with acne vulgaris. Antagonism has been reported between clindamycin and erythromycin. Sulfonamides such as sodium sulfacetamide (Klaron) probably work by acting as a competitive inhibitor of para-aminobenzoic acid utilization (PABA). PABA is an essential component for bacterial growth.

Benzoyl peroxide has a keratolytic and desquamative effect that may contribute to its efficacy. Benzoyl peroxide is bactericidal with activity against *P. acnes*, which is believed to be due to its oxidizing properties. It is available in combination with other agents such as antibiotics and sulfur, which contributes a mild keratolytic action. Salicylic acid causes desquamation of hyperkeratotic epithelium.

The exact mechanism of action of azelaic acid (Azelex) is not known. It has been shown to have antibacterial activity against *P. acnes* and *Staphylococcus epidermidis*, as well as a normalization of keratinization that leads to an anticomedonal effect.

Tazarotene (Tazorac) is a retinoid prodrug that, when activated, has antihyperproliferative, differentiation normalizing, and anti-inflammatory effects. The exact mechanism of action is unknown. Tretinoin (Atralin, Retin-A Micro), another retinoid, works by decreasing cohesiveness of follicular epithelial cells and decreasing microcomedone formation. It may also stimulate mitotic activity and increase turnover of follicular epithelial cells, causing extrusion of the comedones. Adapalene (Differin) is a modulator of cellular differentiation, keratinization, and inflammatory processes. Although the exact mechanism of action is unknown, adapalene

may normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation.

Pharmacokinetics[25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49]

Clindamycin is only one percent available systemically when administered topically. The low levels seen in the plasma are excreted unchanged in the urine.

Topically administered erythromycin is not detectable in the plasma.

Less than two percent of benzoyl peroxide is absorbed in the systemic circulation. Due to the lipophilic nature, benzoyl peroxide concentrates in the lipid-rich sebaceous follicles. The small amount that is systemically absorbed is converted to benzoic acid, which is further metabolized to benzoate. Benzoate is then excreted in the urine.

Tazarotene (Tazorac) is converted by ester hydrolysis to its active metabolite, tazarotenic acid. There is little parent compound absorbed in the plasma, and the small amount is highly plasma protein-bound. Tazarotenic acid is eliminated by the urinary and fecal routes. Its half-life is about 18 hours.

Tretinoin (Atralin, Retin-A Micro) has only been found in trace amounts in plasma when applied topically. It is a metabolite of Vitamin A.

Sulfacetamide (Klaron) is about four percent bioavailable and is excreted in the urine unchanged. The half-life of sulfacetamide varies between seven and 13 hours.

Pharmacokinetic studies with adapalene (Differin) have only found trace amounts in plasma when administered topically. Excretion is primarily by the biliary route.

Azelaic acid (Azelex) is about four percent bioavailable, and any absorbed drug is excreted unchanged in the urine. Its half-life is about 12 hours.

Contraindications/Warnings[50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74]

Products containing clindamycin or erythromycin (Benzaclin, Duac, Cleocin T, Clindagel, Clindareach, Evoclin, Ziana) are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Sulfacetamide (Klaron) is contraindicated in patients with hypersensitivity to sulfonamides. Tazarotene (Tazorac) is contraindicated in pregnant women or women who may become pregnant.

For patients using adapalene (Differin) or benzoyl peroxide-containing products, excessive or prolonged exposure to sunlight should be limited. Patients taking other photosensitizing medications should use additional caution. Weather extremes such as wind or cold may also be irritating. Patients should use caution to avoid contamination of hair, fabrics, and carpet with benzoyl peroxide products as bleaching and/or discoloration may result.

Pseudomembranous colitis has been reported with bacterial agents such as clindamycin and erythromycin, ranging in severity from mild to life-threatening, when administered orally or parenterally. Absorption of these antibiotics through the skin is minimal, however.

Concomitant topical acne treatment, as well as cosmetic products with drying effects, should be used with caution, as possible cumulative irritancy may occur.

During the early weeks of therapy, apparent exacerbations of acne may occur. This is caused by the product's action on previously unseen lesions and should not be viewed as a reason to discontinue therapy.

Fatalities have rarely occurred due to severe reactions to sulfonamides such as sulfacetamide. Sulfacetamide also contains sodium metabisulfite, which may cause allergic-type reactions in patients.

Azelaic acid (Azelex) can cause hypopigmentation.

Contact with eyes, eyelids, lips, and mucous membranes should be avoided. Breaks in the skin should also not come into contact with these products.

Avoid fire, flame, and smoking following use of any gel; they are flammable.

Drug Interactions

Concomitant use with cosmetics, medicated or abrasive soaps and cleansers, alcohol, astringents, spices, or lime grind or other agents that have a strong drying effect should be avoided. Benzoyl peroxide potentiates adverse effects seen with tretinoin during concurrent use.

Adverse Effects

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
adapalene (Differin)[75]	10-40	10-40	10-40	10-40	10-40	<1
azelaic acid (Azelex)[76]	<1	<1	<1	1-5	1-5	nr
benzoyl peroxide[77]	5	5	nr	nr	nr	nr
benzoyl peroxide (Clinac BPO)[78]	reported	reported	reported	nr	nr	nr
benzoyl peroxide (Inova)[79]	reported	nr	reported	reported	nr	nr
benzoyl peroxide (Lavoclen)[80]	reported	reported	reported	reported	nr	nr
benzoyl peroxide (Neobenz Micro)[81]	nr	nr	reported	nr	nr	nr
benzoyl peroxide (Triaz)[82]	nr	nr	reported	nr	nr	nr
benzoyl peroxide (Zaclir)[83]	5	5	nr	1-2.5	nr	nr
benzoyl peroxide/ clindamycin (BenzaClin)[84]	1	2	12	3	nr	1
benzoyl peroxide/ clindamycin (Duac)[85]	5-25	2-17	1-15	1-5	nr	nr
benzoyl peroxide/ erythromycin (Benzamycin Pak)[86]	2.5	0.5	7.6	2.5	nr	1.3
benzoyl peroxide/sodium hyaluronate (Zacare)[87,88]	5	5	nr	1-2.5	nr	nr
benzoyl peroxide/ salicylic acid (Inova 4/1)[89]	reported	nr	reported	reported	nr	nr
benzoyl peroxide/ sulfur (NuOx)[90]	5	5	nr	nr	nr	nr
benzoyl peroxide/ sulfur (Sulfoxyl)[91]	5	5	nr	nr	nr	nr
clindamycin (Cleocin T)[92]	7-16	7-11	18-23	10-11	7-11	nr
clindamycin (Clindagel)[93]	nr	0.6	nr	nr	0.6	nr
clindamycin (Clindareach)[94]	16	11	19	11	7	nr
clindamycin (Evoclin)[95]	nr	nr	1	6	1	nr
erythromycin (Akne-Mycin)[96]	reported	reported	nr	nr	nr	nr
sodium sulfacetamide (Klaron)[97]	<1	nr	nr	reported	<1	nr
tazarotene (Tazorac)[98]	10-30	10-30	10-30	10-30	1-5	nr
tretinoin (Retin-A)[99]	reported	nr	nr	nr	nr	reported
tretinoin (Retin-A Micro)[100]	reported	reported	reported	reported	reported	nr
tretinoin (Atralin)[101]	7	12	16	8	2	1
clindamycin/tretinoin (Ziana)[102]	26	17	1	2-4	4	reported

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product, and are reversible with discontinuation of use. nr = not reported

Special Populations[103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129]

Pediatrics

The safety and effectiveness of all these products in patients younger than 10 years of age have not been established; the exception is benzoyl peroxide (Nuox), which has been approved for patients as young as six years of age.

Pregnancy

Tazarotene (Tazorac) is a teratogenic substance; it is not known what level of exposure causes teratogenicity in humans. Tazarotene is classified as Pregnancy Category X. Other retinoids may cause fetal harm in pregnant women; tretinoin (Atralin, Retin-A Micro), adapalene (Differin), and clindamycin/tretinoin (Ziana) are Pregnancy Category C.

All other reviewed agents are Pregnancy Category C, with the exception of clindamycin and erythromycin products, which are Pregnancy Category B.

Dosages

Drug	Instructions	Availability
adapalene (Differin)	apply once daily at bedtime as directed	0.1% cream, gel 0.3% gel
azelaic acid (Azelex)	apply twice daily to affected areas	20% cream
benzoyl peroxide	apply to/wash affected areas one to four times daily	2.5, 2.75, 4, 4.5, 5, 5.25, 6.5, 8, 8.5, 10% gel 2.5, 5, 10% liquid 2.5, 4, 5, 5.25, 8, 10% wash 4.5, 5, 6.5, 8.5, 10% cream 3, 4.5, 6, 6.5, 8.5, 9% cleanser, pads 4% lotion
benzoyl peroxide (Clinac BPO)	apply once or twice daily as directed	7% gel
benzoyl peroxide (Inova)	apply once or twice daily as directed	4, 8% pad
benzoyl peroxide (Lavoclen)	apply once or twice daily as directed	4, 8% wash
benzoyl peroxide (Neobenz Micro)	apply once or twice daily as directed	3.5, 5.5, 8.5% cream 3.5, 5.5 % single-dose (SD) cream
benzoyl peroxide (Triaz)	apply once or twice daily as directed	3, 6, 9% cleanser 3, 6, 9% pads
benzoyl peroxide (Zaclir)	apply daily during the first week, then twice daily thereafter as directed	4, 8% lotion
benzoyl peroxide/clindamycin (BenzaClin)	apply twice daily or as directed	5%/1% gel
benzoyl peroxide/clindamycin (Duac)	apply once daily or as directed	5%/1% gel
benzoyl peroxide/ erythromycin (Benzamycin Pak)	apply twice daily to affected areas	5%/3% gel
benzoyl peroxide/sodium hyaluronate (Zacare Kit)	benzoyl peroxide lotion: apply daily for the first week, then apply twice a day as tolerated sodium hyaluronate: apply liberally and rub into affected area two to three times a day or as directed	4%/0.2%, 8%/0.2% gel
benzoyl peroxide/salicylic acid (Inova 4/1, 8/2)	apply once or twice daily as directed	4%/1%, 8%/2% benzoyl peroxide/salicylic acid pads
benzoyl peroxide/sulfur (NuOx)	ages 6-12: apply once daily as tolerated ages 12 and older: apply daily during the first week, then twice daily thereafter as tolerated	6%/3% gel
benzoyl peroxide/sulfur (Sulfoxyl)	apply daily during the first week, then twice daily thereafter as tolerated; initiate therapy with the 5%/2% strength	5%/2% (Regular strength), 10%/5% (Strong strength) lotion
clindamycin	apply twice daily to affected areas	1% gel, lotion, solution, pledgets
clindamycin (Clindagel)	apply once daily to affected areas	1% gel
clindamycin (Clindareach)	apply twice daily to affected areas	1% pads
clindamycin (Evoclin)	apply once daily to affected areas	1% foam
erythromycin	apply twice daily to affected areas	2% gel, pledgets, solution
erythromycin (Akne-Mycin)	apply twice daily to affected areas	2% ointment
sodium sulfacetamide (Klaron)	apply twice daily to affected areas	10% lotion
tazarotene (Tazorac)	apply once daily in the evening to affected areas	0.05, 0.1% cream, gel
tretinoin	apply once daily at bedtime as directed	0.025, 0.05, 0.1% cream 0.025, 0.01% gel
tretinoin (Retin-A Micro)	apply once daily in the evening to affected areas	0.04, 0.1% gel
tretinoin (Atralin)	apply once daily at bedtime to affected areas	0.05 % gel
clindamycin/tretinoin (Ziana)	apply once daily at bedtime to face	1.2%/0.025% gel

Before application of these products, the affected skin should be thoroughly washed, rinsed with warm water, and patted dry.

Benzamycin requires the addition of ethyl alcohol and must be refrigerated following reconstitution.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and acne vulgaris. Randomized controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There were many studies found using these criteria. Unacceptable data were determined to be those studies with any of the following characteristics: low number of patients enrolled, comparator drug not available in the U.S., manufacturer-sponsored, open-label, pooled data, unavailable strengths in U.S., use of different formulations of the same active ingredient, inadequate treatment duration, or split-face treatment. Many studies use the investigator-blinded design rather than using the double-blinded method.

adapalene (Differin) and benzoyl peroxide/clindamycin (Duac)

A multicenter, parallel-group, single-blind study of 109 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel, adapalene 0.1% gel, and the combination.[130] Primary endpoints were inflammatory, noninflammatory, and total lesion counts at weeks two, four, eight, and 12. Lesion count reduction and percentage change at week 12 were highest in the combination therapy group (p=NS) and lowest in the adapalene group (p=NS). Taken individually, the combination group had higher reductions in noninflammatory lesions and total lesions compared to the adapalene group (both $p<0.05$). At week 12, there were no significant differences among groups with regard to erythema, dryness, or peeling. A separate analysis of the adverse events showed that the combination therapy group had less erythema than patients in the adapalene group ($p<0.05$).

A randomized, assessor-blind study enrolled 130 patients with mild to moderate facial acne vulgaris to compare benzoyl peroxide 5%/clindamycin 1% gel and adapalene 0.1% gel for 12 weeks.[131] Lesion counts, acne grade, and global improvement were assessed at weeks one, two, four, eight, and 12. Both agents were effective, but benzoyl peroxide 5%/clindamycin 1% gel had a faster onset of action and a faster significant reduction in inflammatory and total lesion counts compared with adapalene gel. There was a statistically significant difference for both inflammatory lesions (p=0.001) and total lesions (p=0.004), between benzoyl peroxide 5%/clindamycin 1% gel versus adapalene gel, starting at week one and continuing onward. Inflammatory lesions remaining at week two in benzoyl peroxide 5%/clindamycin 1% gel versus adapalene gel were 55 percent versus 76 percent, respectively. At week two, benzoyl peroxide

5%/clindamycin 1% gel removed 38 percent more inflammatory lesions than adapalene gel. The trend in favor of benzoyl peroxide 5%/clindamycin 1% gel continued, but was less marked for the remainder of the study. Benzoyl peroxide 5%/clindamycin 1% gel was better tolerated than adapalene gel.

adapalene (Differin) and tazarotene (Tazorac)

A multicenter, double-blind, randomized, parallel-group study enrolled 164 patients with mild-to-moderate facial acne vulgaris to receive 15 weeks of treatment with alternate-day tazarotene 0.1% gel and vehicle gel on the intervening evenings or once daily adapalene 0.1% gel.[132] Both regimens were comparably effective with no significant between-group differences in efficacy measures. A total of 74 percent of tazarotene-treated subjects and 73 percent of adapalene-treated subjects achieved at least a 50 percent improvement in their acne. In addition, there were no clinically significant differences in tolerability. It appears that tazarotene treatment can be useful even in patients whose compliance may be suboptimal.

The efficacy and tolerability of tazarotene 0.1% gel and adapalene 0.1% gel were compared in a multicenter, double-blind, randomized, parallel-group study in 145 patients with mild-to-moderate facial acne vulgaris.[133] Both treatments were applied once daily in the evenings for up to 12 weeks. Treatment with tazarotene was associated with a significantly greater incidence of treatment success (=50 percent global improvement with 78 percent versus 52 percent; $p=0.002$) and significantly greater reductions in overall disease severity ($p<0.0001$), non-inflammatory lesion count ($p<0.0001$), and inflammatory lesion count ($p=0.0002$) compared with adapalene. In the early weeks of treatment, tazarotene was associated with greater levels of burning, pruritus, erythema, and peeling compared with adapalene ($p<0.01$); however, at the end of treatment, patients considered both treatments to be comparably well tolerated.

adapalene (Differin) and tretinoin

A dose range effect of two concentrations of adapalene gel as acne treatment was evaluated as well as a comparison of adapalene 0.1% gel with tretinoin 0.025% gel in the treatment of acne patients using two multicenter, investigator-masked, parallel group studies.[134] In the dose range study, 89 patients were enrolled, and 591 patients were in the concurrent controlled studies. Adapalene 0.1% gel was significantly more effective in treating acne lesions than adapalene gel 0.03%. Adapalene gel 0.1% was significantly more effective than tretinoin 0.025% gel in one study and of the same effectiveness in the other study. Adapalene gel was better tolerated than tretinoin gel.

The ten-week, multicenter, randomized, investigator-masked, active-controlled, parallel-group study compared adapalene 0.1% gel with tretinoin 0.05% cream in 409 patients with mild-to-moderate acne vulgaris.[135] Adapalene 0.1% gel demonstrated equivalent efficacy in reduction of acne lesion counts and global improvement of acne severity over ten weeks. Adapalene 0.1% gel was significantly better tolerated than tretinoin cream 0.05% in terms of erythema, dryness, desquamation, and stinging/burning.

The safety and efficacy of adapalene 0.1% gel compared with tretinoin 0.025% gel were evaluated in 150 Chinese patients with mild-to-moderate acne vulgaris in an eight-week, multicenter, randomized, controlled, investigator-masked, parallel-group study.[136] The results showed that adapalene 0.1% gel had efficacy equivalent to tretinoin 0.025% gel against acne lesions in Chinese patients, with a more acceptable tolerability profile.

To determine the tolerability and efficacy of adapalene 0.1% gel versus tretinoin 0.1% microsphere gel in 168 patients with acne vulgaris, a 12-week, multicenter, randomized,

controlled, investigator-masked, parallel-group study was conducted.[137] The efficacy of adapalene 0.1% gel was comparable to that of tretinoin 0.1% microsphere gel, and both treatments had similar onset of action. Cutaneous tolerability was noted in both groups, with scores significantly better with adapalene 0.1% gel than with tretinoin 0.1% microsphere gel. There were significantly fewer treatment-related adverse events reported with adapalene 0.1% gel.

A randomized, multicenter, investigator-masked study was conducted in 105 patients with mild to moderate acne vulgaris to compare the efficacy and safety of adapalene 0.1% gel with tretinoin 0.025% gel after three months of treatment.[138] In terms of efficacy, adapalene gel was found to be superior to tretinoin gel after one week of treatment, with respect to reduction in inflammatory lesion counts (32 percent versus 17 percent, respectively; p=0.001), total lesion counts (28 percent versus 22 percent; p=0.042) and global severity grade (28 percent versus 16 percent; p=0.001). No significant differences between the two treatments were found after 12 weeks of treatment for any of these variables. Evaluation of facial skin tolerance parameters showed significant differences between the two treatments in favor of adapalene for dryness, erythema, immediate and persistent burning, and pruritus for at least one time point. Quality of life scores improved more rapidly in the adapalene group than in the tretinoin group.

A study was designed to compare the efficacy and safety of adapalene 0.1% gel once daily and tretinoin 0.025% gel once daily in the treatment of grade II to II facial acne vulgaris.[139] Three hundred twenty-three patients were enrolled for 12 weeks in an investigator-masked, randomized, parallel-group, multicenter trial. Starting at weeks two and four, adapalene produced greater lesion reductions than did tretinoin for all lesion types. By week 12, the mean percent reduction in the different lesion counts was 49 percent versus 37 percent for total lesions (p<0.01); 46 percent versus 33 percent for non-inflammatory lesions (p=0.02); and 48 percent versus 38 percent for inflammatory lesions (p=0.06) in adapalene (Differin) and tretinoin treatment groups, respectively. Side effects were limited to a mild dermatitis occurring in both treatment groups.

benzoyl peroxide/clindamycin, benzoyl peroxide, and benzoyl peroxide/erythromycin

In the randomized, ten-week, multicenter, single-blind trial, 492 patients with moderate to moderately severe acne were treated twice daily with benzoyl peroxide 5%/clindamycin 1%, benzoyl peroxide 5%, or benzoyl peroxide 5%/erythromycin 3% and assessed every two weeks.[140] Compared with benzoyl peroxide, benzoyl peroxide/clindamycin demonstrated significantly greater reductions in inflammatory lesions (p=0.04) and significantly greater overall improvement as assessed by physicians (p=0.04) and patients (p<0.001). Benzoyl peroxide/clindamycin was not significantly more efficacious than benzoyl peroxide/erythromycin. Dry skin was the most frequent adverse event with all three therapies.

benzoyl peroxide/clindamycin, adapalene (Differin), and tretinoin microsphere (Retin-A Micro)

A multicenter, randomized, single-blind study of 353 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel in combination with either adapalene 0.1% gel or tretinoin microsphere 0.04% or 0.1% gel.[141] The primary endpoint was investigator global assessment, including variables of lesions counts, global disease severity, and disease signs and symptoms. A trend toward greater reduction in lesions at all time points was seen in the tretinoin 0.04% combination patients, but the difference did not reach statistical significance. The same trend was seen in global disease severity and disease signs and symptoms; none of the differences were statistically significant. Adverse events were minimal and mild in each group.

clindamycin and adapalene (Differin)/clindamycin

A total of 300 acne subjects entered a multicenter, randomized, investigator-blinded study comparing the efficacy and safety of adapalene 0.1% gel combined with clindamycin topical solution 1% versus clindamycin topical solution 1% alone.[142] A statistically significant greater reduction was observed from week four until week 12 in total lesion counts and from week eight on for inflammatory and non-inflammatory lesion counts during the initial treatment for combination therapy compared with monotherapy. In the second part of the study (weeks 12 to 24) completed by 241 subjects, the efficacy and safety of adapalene 0.1% gel alone as maintenance therapy were investigated. Results at week 24 for the reduction in all lesion counts during the maintenance phase were statistically significant in favor of adapalene (41.6 percent) compared with an increase for all lesion counts in the control group (92.1 percent). Adapalene alone or in combination with clindamycin topical solution was well tolerated.

A multicenter, randomized, investigator-blinded study investigated the efficacy and tolerability of adapalene 0.1% gel plus clindamycin 1% lotion compared with clindamycin plus vehicle for the treatment of mild to moderate acne vulgaris in 249 patients.[143] Clindamycin was applied twice daily and adapalene or vehicle gel once daily for 12 weeks. A significantly greater reduction of total lesions ($p<0.001$), inflammatory ($p=0.004$) and noninflammatory ($p<0.001$), were seen in the clindamycin/adapalene group than in the clindamycin/vehicle group. These significant treatment effects were observed as early as week four for both non-inflammatory and total lesion counts. The worst scores for scaling ($p<0.05$), dryness ($p<0.01$), and stinging/burning ($p<0.05$) were higher in the clindamycin/adapalene group than in the clindamycin/vehicle group.

clindamycin/benzoyl peroxide, benzoyl peroxide, and clindamycin

In a ten-week, multicenter, double-blind trial, 480 patients with moderate to moderately severe acne were randomized to receive twice daily treatment with benzoyl peroxide 5% plus clindamycin 1%, benzoyl peroxide 5%, clindamycin 1%, or vehicle.[144] Significantly greater reductions in the number of inflammatory and total lesions were demonstrated in patients using combination therapy compared with those using any of the individual components. Both physicians' and patients' global evaluations showed significantly greater improvements with the combination therapy than with individual components. Dry skin was the most frequent adverse event, occurring to a similar extent in the combination and benzoyl peroxide treatment groups.

A topical gel combining benzoyl peroxide 5% and clindamycin 1% was evaluated in a ten-week, randomized, double-blind trial involving 287 patients with moderate to moderately severe acne.[145] The combination demonstrated significantly greater reductions in inflammatory lesions than either of its components alone or vehicle. Significantly greater reductions in comedones and improvements in both physicians' and patients' global evaluations were obtained with the combination compared to clindamycin or vehicle. The reduction in comedones and the global improvements were similar between the combination and benzoyl peroxide. The combination's incidence of dry skin was similar to that found with benzoyl peroxide.

erythromycin and clindamycin

A 12-week, investigator-masked, randomized, parallel-group comparison of a gel formulation of erythromycin 2% with clindamycin 1% solution was performed in 102 patients with mild to moderate facial acne vulgaris.[146] Both agents were administered twice daily. Both medications significantly reduced the numbers of papules and open and closed comedones. No significant differences in lesion count reductions were detected between the treatment groups after eight and 12 weeks of treatment.

tazarotene (Tazorac), benzoyl peroxide, erythromycin/benzoyl peroxide, and clindamycin

A multicenter, investigator-masked, randomized, parallel-group study was performed in 440 patients with mild-to-moderate facial acne vulgaris to compare the efficacy and tolerability of tazarotene monotherapy with three combination regimens.[147] Patients received tazarotene plus benzoyl peroxide gel, tazarotene plus erythromycin/benzoyl peroxide gel, or tazarotene plus clindamycin phosphate lotion. The only combination therapy to achieve a significantly greater global improvement than tazarotene monotherapy was tazarotene plus clindamycin. For reducing noninflammatory lesions specifically, none of the combination regimens offered significant benefit over tazarotene monotherapy. For reducing inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide was significantly more efficacious than all the other regimens. Tazarotene plus clindamycin and tazarotene plus benzoyl peroxide reduced the incidence of adverse effects compared with tazarotene monotherapy; however, the difference was not statistically significant.

tazarotene (Tazorac) and tretinoin and clindamycin

A randomized, investigator-blinded, parallel group, multicenter study compared tazarotene 0.1% cream plus clindamycin 1% gel to tretinoin 0.025% gel plus clindamycin 1% gel, in 150 patients with facial acne vulgaris.[148] At 12 weeks, the reduction in lesion counts was greater for tazarotene/clindamycin versus tretinoin/clindamycin for both the non-inflammatory lesion count (71 percent versus 52 percent, p=0.01) and the inflammatory lesion count (77 percent versus 67 percent, p=0.053). More patients achieved =50 percent global improvement and =75 percent global improvement with tazarotene/clindamycin than with tretinoin/clindamycin (88 percent versus 75 percent, p=0.05 and 66 percent versus 52 percent p=0.10, respectively) at week 12. Both regimens were generally well tolerated. This study was supported through a grant from Allergan.

tazarotene (Tazorac) and tretinoin

The efficacy and tolerability of tazarotene 0.1% gel and tretinoin 0.1% microsphere gel were evaluated in a multicenter, double-blind, randomized, parallel-group study in 169 patients with mild-to-moderate inflammatory facial acne vulgaris for 12 weeks.[149] Both agents were associated with significant reductions from baseline in the non-inflammatory and inflammatory lesion counts. Tazarotene treatment was associated with a significantly greater incidence of treatment success (defined as $\geq$50 percent global improvement [67 percent versus 49 percent; p=0.03]) and significantly greater reductions in overall disease severity (36 percent versus 26 percent; p=0.02) and non-inflammatory lesion count (60 percent versus 38 percent at week 12; p=0.02) than tretinoin microsponge treatment. Both drugs were well tolerated.

A multicenter, double-blind, randomized, parallel-group study that compared the efficacy and tolerability of tazarotene and tretinoin was performed in 143 patients with mild-to-moderate facial acne vulgaris.[150] Patients were randomized to receive tazarotene 0.1% gel or tretinoin 0.025% gel once daily for 12 weeks. Tazarotene 0.1% gel was more effective than tretinoin 0.025% gel in reducing the open comedone count ($p \leq 0.05$) and the total non-inflammatory lesion count ($p \leq 0.05$). The total inflammatory lesion count was similar (p=NS). At some time points, tazarotene was associated with increased irritation, but peeling, erythema, dryness, burning, and itching never exceeded trace levels.

Summary

Acne vulgaris is a skin disease, which often begins during puberty in adolescents and can continue into adulthood, sometimes continuing into the thirties and beyond. It forms as a result of blockage of the hair follicle, but multiple factors are involved in the pathology of the disease.

The guidelines from the American Academy of Dermatology and from The Global Alliance to Improve Outcomes in Acne, topical retinoids are the initial drug of choice to treat mild to moderate acne, updated in 2007 and 2006, respectively. Topical retinoids are the initial topical drug of choice, because they are the only topical medications that affect terminal differentiation of the follicular epithelium. Combination therapy including a topical retinoid with a topical antibiotic is effective and considered the standard of care in patients exhibiting comedonal and inflammatory acne, which are caused by an inflammatory reaction to the fatty acid by-product released into the comedone by *P. acnes*. In addition, the combination of other topical therapies may be another treatment option after trying and not achieving desirable results with the use of topical retinoids and topical antibiotics in patients exhibiting this type of acne. Combination topical therapy with various agents can target the multiple pathophysiological factors involved in the development of acne. In other words, it can increase treatment efficacy, lead to faster lesion resolution, and minimize the potential for antibiotic resistance. For example, a topical antibiotic and benzoyl peroxide can be an effective combination, because benzoyl peroxide exhibits anti-inflammatory activity, and this combination minimizes development of *P. acnes* antibiotic resistance.

Other agents exist and are reserved for patients not responding to retinoids, benzoyl peroxide, or combination therapies with antibiotics. Azelaic acid is an agent that possesses comedolytic and antibacterial properties, but is not considered first-line by the guidelines. The combination of sulfur and sodium sulfacetamide is another available agent, but there is limited data regarding its efficacy.

In summary, topical retinoids are the first choice for treatment of acne, but when inflamed lesions are present, adding an antibiotic is a recommended standard of care. Benzoyl peroxide in combination with antibiotics may prove beneficial in the treatment of acne vulgaris, and is sometimes combined with a retinoid. Yet even though this combination maybe efficacious, the adverse effects of tretinoin, a retinoid, are magnified when combined with benzoyl peroxide. Finally, when choosing between single agent and combination therapies, patient tolerability and compliance factors should be taken into consideration in order to achieve the best results, and the patient should be informed that it may take at least two to four weeks before seeing a desirable response.

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