Treatment of Acne Vulgaris

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Context Management of acne vulgaris by nondermatologists is increasing. Current understanding of the different presentations of acne allows for individualized treatments and improved outcomes.

Objective To review the best evidence available for individualized treatment of acne.

Data Sources Search of MEDLINE, EMBASE, and the Cochrane database to search for all English-language articles on acne treatment from 1966 to 2004.

Study Selection Well-designed randomized controlled trials, meta-analyses, and other systematic reviews are the focus of this article.

Data Extraction Acne literature is characterized by a lack of standardization with respect to outcome measures and methods used to grade disease severity.

Data Synthesis Main outcome measures of 29 randomized double-blind trials that were evaluated included reductions in inflammatory, noninflammatory, and total acne lesion counts. Topical retinoids reduce the number of comedones and inflammatory lesions in the range of 40% to 70%. These agents are the mainstay of therapy in patients with comedones only. Other agents, including topical antimicrobials, oral antibiotics, hormonal therapy (in women), and isotretinoin all yield high response rates. Patients with mild to moderate severity inflammatory acne with papules and pustules should be treated with topical antibiotics combined with retinoids. Oral antibiotics are first-line therapy in patients with moderate to severe inflammatory acne while oral isotretinoin is indicated for severe nodular acne, treatment failures, scarring, frequent relapses, or in cases of severe psychological distress. Long-term topical or oral antibiotic therapy should be avoided when feasible to minimize occurrence of bacterial resistance. Isotretinoin is a powerful teratogen mandating strict precautions for use among women of childbearing age.

Conclusions Acne responses to treatment vary considerably. Frequently more than 1 treatment modality is used concomitantly. Best results are seen when treatments are individualized on the basis of clinical presentation.

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THE MANAGEMENT OF ACNE VULgaris by nondermatologists is increasing.[1] In this article we attempt to answer the question: what treatments in acne vulgaris have proven efficacy and how are these treatments best administered and individualized to optimize results and minimize complications? We considered the efficacy and safety of topical retinoids, topical antimicrobials, systemic antibiotics, hormonal treatments for women, and oral isotretinoin.

METHODS

A librarian-assisted literature search was performed for English-language randomized clinical trials. We used MEDLINE and EMBASE to identify all therapeutic clinical trials, meta-analyses, and systematic analyses concerning acne vulgaris from 1966 to 2004. We further cross-referenced bibliographies of identified articles. This search strategy identified 248 articles. We then evaluated titles and abstracts, and excluded studies that were not blinded, were not randomized, had sample sizes of fewer than 50, did not provide adequate information with respect to objective outcomes measures, contained no original data, pertained to treatments that are not available, did not involve humans, or were therapeutic failures. We used the following search words: *acne vulgaris*, *acne, tretinoin*, *tazarotene*, *adapalene*, *clindamycin*, *erythromycin*, *tetracycline*, *azelaic acid*, *benzoyl peroxide*, *minocycline*, *doxycycline*, *trimethoprim-sulfamethoxazole*, *flutamide*, *spironolactone*, *cyproterone-acetate*, *oral contraceptives*, *isotretinoin*, *clinical trials*, *review*, *therapy*, *treatment*, and *randomized controlled trials*.

We identified 29 randomized double-blind trials, which comprise the focus of this article. Where possible, data concerning responses to treatment were put in terms of percent reduction of inflammatory lesions, noninflammatory lesions (comedones), and total lesions.

A recent methodological literature review of acne therapy trials over the last 50 years found that methods of grading acne severity and methods of assessing outcome measures are highly incon-

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sistent.[2] There are more than 25 methods of assessing acne severity and more than 19 methods for counting lesions. Our literature review verifies the lack of standardized of methodology. Nevertheless, analysis of acne therapy data does allow conclusions to be drawn that can direct therapeutic decisions.

In addition to the randomized controlled trials (RCTs), we reviewed selected articles that included data collected or analyzed after the trial, including meta-analyses and other systematic reviews. We also mention selected non-RCTs when they represent best evidence concerning established therapies that have not yet been studied in well-designed RCTs.

Pathophysiology

The origin of acne vulgaris is complex and incompletely understood. At least 4 pathophysiologic events take place within acne-infected hair follicles: (1) androgen-mediated stimulation of sebaceous gland activity, (2) abnormal keratinization leading to follicular plugging (comedo formation), (3) proliferation of the bacterium *Propionibacterium acnes* within the follicle, and (4) inflammation. In addition to these 4 basic mechanisms, genetic factors,[3] stress,[4] and possibly diet may influence the development and severity of acne.[5]

TREATMENT OF ACNE VULGARIS

Topical Retinoids

Retinoids, first shown in the 1970s to be of value for treating acne, are derivatives of vitamin A that prevent comedone formation by normalizing desquamation of follicular epithelium. The 3 main topical retinoids are tretinoin, adapalene, and tazarotene.

Tretinoin has long been considered the gold standard with which new products are compared. A meta-analysis of 5 multicenter randomized investigator-blinded trials involving 900 patients[6] confirmed that total lesion counts reduced by 53% with tretinoin 0.05% gel and 57% with adapalene 0.1% gel (TABLE 1). Adapalene gel causes less irritation than tretinoin 0.05% gel, 0.1% microspere gel, or 0.05% cream.[6-9] Tazarotene 0.1% gel had proven efficacy in an RCT showing 52% total acne reduction of total lesions compared with 33% with vehicle.[10] Tretinoin was compared with tazarotene in a 12-week RCT with 169 patients.[11] Tazarotene 0.1% gel produced reductions in acne severity of 36% vs 26% with tretinoin 0.1% gel ($P=.02$). In another comparison trial, tazarotene 0.1% gel was more effective than tretinoin 0.025% gel in reducing noninflammatory lesion counts (55% vs 42%; $P=.042$) and equally effective in reducing inflammatory lesions.[12] In a multicenter RCT, adapalene 0.1% cream demonstrated a 38% reduction in total lesion counts vs 20% with vehicle.[13] In a 12-week RCT with 145 patients tazarotene 0.1% gel was significantly better than adapalene 0.1% gel in terms of mean reductions in overall disease severity (44% vs 24%; $P<.001$), noninflammatory lesion count (71% vs 48%; $P<.0001$), and inflammatory lesion count (70% vs 55%; $P=.0002$).[14] Alternate-day application of tazarotene 0.1% gel was equally effective to daily adapalene 0.1% gel in a 15-week RCT[15] (Table 1).

Tretinoin, is available as a gel (0.01% and 0.025%), cream (0.025%, 0.05%, and 0.1%), and liquid (0.05%). Cutaneous erythema, peeling, and edema with tretinoin are dose-related adverse effects. Adapalene 0.1% is available as a cream, gel, and solution, all with similar efficacy.[16] Tazarotene is available as 0.1% cream or gel formulations.

In summary, all topical retinoids effectively reduce the number of comedones and inflammatory lesions in the range of 40% to 70% (Table 1). Adapalene is less likely to cause skin irritation and is better tolerated than tretinoin or tazarotene, but tazarotene appears to be most efficacious.

Topical Antimicrobials

Currently available topical antimicrobials include clindamycin, erythromycin, tetracycline, and benzoyl peroxide. Azelaic acid may also be considered within this group because it has demonstrated antibacterial activity against intrafollicular *P acnes*.[17] Our discussion focuses on 5 well-designed, randomized, double-blind trials assessing the effectiveness of topical antibiotics in acne. Newer formulations have been studied most rigorously.

Original placebo-controlled RCTs with clindamycin and erythromycin showed a 46% to 70% reduction in inflammatory lesions[18-21] (Table 1). In another RCT, an erythromycin–4%-zinc combination reduced inflammatory lesions by 85% vs a 46% reduction using 2% erythromycin alone ($P<.001$).[22] Recent interest has centered around combinations of topical antimicrobials with benzoyl peroxide or retinoids. Support for combining erythromycin or clindamycin with benzoyl peroxide includes a randomized, 10-week, multicenter, single-blind trial that enrolled 492 patients in which treatment with the combination products used twice daily was more effective than benzoyl peroxide alone.[23] Additionally, a review of 3 clinical studies involving 1259 patients concluded that the combination of clindamycin 1% benzoyl–peroxide 5% was more effective than either drug used alone in reducing lesions and suppressing *P acnes*.[24] In 2 RCTs 334 patients were treated once nightly with either a combination clindamycin–benzoyl peroxide gel, benzoyl peroxide alone, clindamycin alone, or vehicle[25] (Table 1). After 11 weeks, 66% of patients in the clindamycin and benzoyl peroxide group experienced a good or excellent response compared with 41% in the benzoyl peroxide group, 36% in the clindamycin group, and 10% in the vehicle group. A similar 16-week trial showed a 53% lesion reduction with clindamycin 1% benzoyl–peroxide 5% vs 28% with clindamycin alone ($P=.013$).[26]

Combining topical antibiotics with topical retinoids is also effective. Adapalene gel 0.1% plus clindamycin 1% was studied in a 12-week RCT involving 249 patients with mild to moderate acne. A significantly greater reduction in total ($P<.001$), inflammatory ($P=.004$), and noninflammatory lesions ($P<.001$) was seen in the clindamycin-plus-adapalene group than in the

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Table 1. Clinical Trials in Topical Acne Therapy

Source	No. of Patients	Study Type	Length of Treatment, wk	Type of Acne*	Treatment	Reduction in Lesions, %		
						Inflammatory	Noninflammatory	Total
Topical Retinoids								
Cunliffe et al,[6] 1998	900	Meta-analysis	12	Mild to moderate facial acne	Adapalene 0.1% gel Tretinoin 0.025% gel	52 51	58 52	57 53
Shalita et al,[10] 1999	446	Randomized, double-blind, placebo-controlled, multicenter	12	Mild to moderate facial acne	Tazarotene 0.1% gel Tazarotene 0.05% gel Vehicle	42 39 30	55 45 35	52 44 33
Leyden et al,[11] 2002	169	Randomized, double-blind, multicenter	12	Mild to moderate facial acne	Tazarotene 0.1% gel Tretinoin 0.1% gel	56 46	60 38	. . .
Webster et al,[12] 2001	143	Randomized, double-blind, multicenter	12	Mild to moderate facial acne	Tazarotene 0.1% gel Tretinoin 0.025% gel	54 44	55 42	. . .
Lucky et al,[13] 2001	237	Randomized, double-blind, multicenter	12	Mild to moderate facial acne	Adapalene 0.1% cream Vehicle	36 19	38 20	38 20
Webster et al,[14] 2002	145	Randomized, double-blind, multicenter	12	Mild to moderate facial acne	Tazarotene 0.1% gel Adapalene 0.1% gel	70 55	71 48	. . .
Leyden et al,[15] 2001	164	Randomized, double-blind, multicenter	15	Mild to moderate facial acne	Adapalene 0.1% gel Tazarotene 0.1% gel†	54 57	58 55	. . .
Topical Antimicrobials								
Becker et al,[18] 1981	358	Randomized, double-blind, placebo-controlled, multicenter	8	Mild to moderate acne	Clindamycin phosphate Clindamycin hydrochloride Vehicle	66 63 42	. . .	. . .
Dobson and Belknap,[19] 1980	253	Randomized, double-blind, multicenter, placebo-controlled	12	Mild to moderate acne	Erythromycin 1.5% solution Vehicle	70 5	26 55	40 30
Lesher et al,[20] 1985	225	Randomized, double-blind, multicenter, placebo-controlled	12	Mild to moderate acne	Erythromycin 2% Vehicle	46 19	. . .	. . .
Jones and Crumley,[21] 1981	156	Randomized, double-blind	12	Moderate to severe facial acne	Erythromycin 2% Vehicle	51 33	. . .	. . .
Habbema et al,[22] 1989	122	Randomized, double-blind, multicenter	12	Moderate to severe facial acne	Erythromycin–4%-zinc solution Erythromycin 2% lotion	85 46	68 49	. . .
Lookingbill et al,[25] 1997	334	Randomized, double-blind, placebo-controlled, multicenter	11	Mild to moderate facial acne	Clindamycin–1%/BP 5% gel Clindamycin–1% gel BP 5% gel Vehicle	61 35 39 5	36 9 30 0	. . .
Cunliffe et al,[26] 2002	79	Randomized, double-blind	16	Mild to moderate facial acne	Clindamycin–1% plus/BP 5% gel Clindamycin–1%	. . .	. . .	53 28
Oral and Topical Treatments								
Katsambas et al,[33] 1989	92	Randomized, double-blind, placebo-controlled	12	Moderate acne	Azelaic acid 20% Placebo	72 47	56 0	. . .
Hjorth and Graupe,[34] 1999	333 261	Randomized, double-blind, multicenter	20 24	Moderate to severe acne; Moderate to severe acne	Azelaic acid 20% Oral tetracycline Azelaic acid 20% Oral tetracycline	83 86 79 79	. . .	. . .

Abbreviation: BP, benzoyl peroxide; ellipses, data were not reported in the trial.
*For an example of acne severity, see the Figure.
†Therapy is taken on alternate days.

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clindamycin-plus-vehicle group.[27] Other trials with clindamycin-tretinoin and erythromycin-tretinoin have shown similar results.[28-32]

Azelaic acid 20%, in an RCT that enrolled patients with moderate acne resulted in a 72% reduction of inflammatory lesions vs 47% with placebo.[33] Two RCTs compared oral tetracycline with topical azelaic acid 20%.[34] Reductions in inflammatory lesion counts were 83% for azelaic acid and 86% for oral tetracycline in one study and 79% for both drugs in another (Table 1). The efficacy of azelaic acid in mild to moderate acne matches that of tretinoin 0.05%, benzoyl peroxide 5%, or topical erythromycin 2%.[17]

Adverse effects of topical antibiotics include erythema, peeling, dryness, and burning.[35] Benzoyl peroxide can also cause an irritant dermatitis and bleach hair, clothes, and bed linens. A recent consensus has recommended that topical antibiotics should not be used alone due to the potential for bacterial resistance and relatively slow onset of action.[35] Antimicrobial resistance with benzoyl peroxide or azelaic acid has not been reported. Combining antibiotics with benzoyl peroxide is the most common practice. A minimum of 6 to 8 weeks of treatment is recommended.[35]

Oral Antibiotics

Systemic antibiotics used in acne vulgaris have both antimicrobial and anti-inflammatory properties. They reduce *P acnes* within follicles, thereby inhibiting production of bacterial-induced inflammatory cytokines.[36] Tetracycline and erythromycin suppress leukocyte chemotaxis[37] and bacterial lipase activity[38] while minocycline and doxycycline inhibit cytokines and matrix metalloproteinases thought to contribute to inflammation and tissue breakdown.[39] The main systemic antibiotics used in acne vulgaris are tetracycline, doxycycline, minocycline, and erythromycin.

Relatively few RCTs have studied the use of oral antibiotics in treating acne. A 12-week RCT involving 200 patients[40] showed a reduction in inflammatory lesions by 64% with tetracycline vs 67% with erythromycin and a reduction in noninflammatory lesion counts by 34% with tetracycline vs 22% with erythromycin (TABLE 2). In another comparison trial topical clindamycin 1% showed a 72% reduction vs a 57% reduction using oral tetracycline and a 12% reduction with placebo.[41]

Doxycycline was recently studied in a RCT in which 51 patients received either a submicrobicidal dose (20 mg twice daily) for 6 months or placebo. Mean reduction in total lesions was 52% with doxycycline vs 18% with placebo ($P<.01$; Table 2).[42] Even low doses of doxycycline may be effective by inhibition of collagenases including matrix metalloproteinases.[39] Doxycycline is frequently dosed at 100 mg/d for acne treatment although best evidence for those doses comes from small studies.[43]

The efficacy of minocycline was assessed in a Cochrane review,[43] which concluded that minocycline is an effective therapy for moderate acne, but its efficacy compared with other acne therapies could not be reliably determined due to methodological flaws in the comparative trials. In a 3-month double-blind RCT, minocycline was somewhat more effective in reducing inflammatory lesion counts compared with zinc gluconate (67% vs 50%; $P<.001$).[44] Antimicrobial effects against *P acnes* are greater with minocycline than with doxycycline or tetracycline,[45] and higher lipid solubility favors its bioavailability in pilosebaceous units.

Oral tetracycline is usually prescribed at a dosage of 500 mg twice a day. The absorption of tetracycline is reduced by food and dairy products; therefore, it must be taken on an empty stomach. Adverse effects include gastrointestinal tract dyspepsia, vaginal candidiasis in women, and a small risk of photosensitivity. In children younger than 10 years, tetracycline can cause enamel hypoplasia and a yellowish discoloration of the forming teeth.[46] Doxycycline has traditionally been used at a dose of 50 to 100 mg twice daily. Success with 20 mg/d may change clinical practice over time.[42] Doxycycline causes gastrointestinal tract upset and is more likely than tetracycline to cause photosensitivity.[46] Doxycycline can be taken with food. Tetracyclines should not be taken immediately before sleep because the pills may lodge in the esophagus and cause ulceration.

Minocycline is prescribed in a dosage range of 50 to 100 mg twice daily. Adverse effects include vertigo, dizziness, ataxia, and rarely a bluish discoloration of the skin.[46] Minocycline has also been reported to be associated with drug induced lupus, autoimmune hepatitis, and a hypersensitivity syndrome.[47] The relative risk of developing a lupuslike syndrome with minocycline is 8.5 (95% confidence interval [CI], 2.1-35.0) compared with 1.7 (95% CI, 0.4-8.1) for other tetracyclines.[48]

Antibiotic-resistant strains of *P acnes* have increased steadily since the 1970s and are now found in more than 50% of cases in Europe and the United Kingdom.[49] Resistance of *P acnes* to oral antibiotics is associated with treatment failures.[50] The effect of resistance to *P acnes* with topical antimicrobial use is unclear.[51] Resistance to tetracyclines is less common than to erythromycin[49] and is least with minocycline.[52]

Recommendations for reducing antibiotic resistance in acne have been published recently and include using combined topical therapy—such as retinoids, benzoyl peroxide, or both when using topical antibiotics—and avoiding long-term use of topical or oral antibiotics when feasible.[35]

Hormonal Therapy

Hormonal treatments for acne are tolerated in women only. These treatments, which decrease androgen expression, are based on the requirement for androgens in the pathophysiologic development of acne.[53-54] A direct relationship between levels of circulating androgens and acne severity has not been established although prior studies suggest some degree of hyperandrogenemia in women with acne.[55-57]

Antiandrogenic compounds include oral contraceptives (OCs) and androgen-receptor blockers such as flutamide, spironolactone, and cyproter-

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one acetate. Several OCs are now approved for use in acne. All contain 35 µg of estrogen or less. None of the androgen-receptor blockers are approved by the US Food and Drug Administration for use in the treatment of acne.

Oral contraceptives suppress ovarian androgens and reduce bioavailable testosterone by an estrogen-mediated increase in steroid hormone binding globulin. After 6 months, 2 multicenter RCTs involving 507 women with moderate acne found that triphasic norgestimate and ethinyl estradiol (EE, Orthotri-cyclin [Ortho-McNeil Pharmaceutical Inc, Raritan, NJ]) had decreased inflammatory lesions by approximately 50% compared with a 30% reduction with placebo.[58,59] Two RCTs studying the efficacy of 20 µg of EE plus 100 µg of levonorgestrel (Alesse [Wyeth, Madison, NJ]) showed total acne improvement of 23% to 40% compared with 9% to 23% with placebo (Table 2).[60,61] A recent RCT involving 128 women showed an acne-lesion count reduction of 63% using the combination

Table 2. Clinical Trials in Oral Acne Therapy

Source	No. of Patients	Study Type	Length of Treatment, wk	Type of Acne	Treatment	Reduction in Lesions, %		
						Inflammatory	Noninflammatory	Total
					Antibiotics			
Gammon et al,[40] 1986	200	Randomized, double-blind, multicenter	8	Moderate to severe acne	Oral erythromycin	67	22	. . .
					Oral tetracycline*	64	34	
Braathen,[41] 1984	87	Randomized, double-blind	8	Moderate to severe acne	Oral tetracycline, 500 mg twice per d	57	. . .	. . .
					Clindamycin 1%	72		
					Placebo	12		
Skidmore et al,[42] 2003	51	Randomized, double-blind placebo-controlled, MC	24	Moderate facial acne	Oral doxycycline, 20 mg twice per day	50	54	52
							11	18
					Placebo	30		
Dreno et al,[44] 2001	332	Randomized, double-blind multicenter	12	Moderate acne	Oral minocycline, 100 mg/d	67	. . .	. . .
					Zinc gluconate, 30 mg/d	50		
					Oral Contraceptives			
Lucky et al,[58] 1997	257	Randomized, double-blind placebo-controlled, multicenter	24	Moderate acne in women	Ethinyl estradiol, 35 µg plus norgestimate, 180 µg, 215 µg, or 250 µg of	62	. . .	53
					Placebo	39		27
Redmond et al,[59] 1997	250	Randomized, double-blind placebo-controlled, multicenter	24	Moderate acne in women	Ethinyl estradiol, 35 µg plus norgestimate, 180 µg, 215 µg, or 250 µg of	51	. . .	46
					Placebo	35		34
Thiboutot et al,[60] 2001	350	Randomized, double-blind placebo-controlled, multicenter	24	Moderate acne in women	Ethinyl estradiol, 20 µg plus levonorgestrel 100 µg	47	25	40
					Placebo	33	14	23
Leyden et al,[61] 2002	371	Randomized, double-blind, placebo-controlled	24	Moderate acne in women	Ethinyl estradiol, 20 µg pluslevonorgestrel, 100 µg	32	13	23
					Placebo	22	4	9
Van Vloten et al,[62] 2002	128	Randomized, double-blind, multicenter	36	Mild to moderate acne in women	Ethinyl estradiol, 30 µg plus drospirenone, 3 mg	74	50	63
					Ethinyl estradiol, 35 µg plus cyproterone acetate, 2 mg	75	60	59
					Isotretinoin			
Jones et al,[81] 1983	76	Randomized, double-blind	16	Moderate to severe acne	Isotretinoin, 0.1 mg/kg per d	80	. . .	. . .
					Isotretinoin, 0.5 mg/kg per d	80		
					Isotretinoin, 1.0 mg/kg per d	89		
Strauss et al,[82] 1984	150	Randomized, double-blind multicenter	20	Severe acne	Isotretinoin, 0.1 mg/kg per d	79	. . .	. . .
					Isotretinoin, 0.5 mg/kg per d	79		
					Isotretinoin, 1.0 mg/kg per d	89		
Strauss et al,[83] 2001	600	Randomized, double-blind multicenter	20	Severe nodular acne	Isotretinoin, 1.0 mg/kg per d	90	. . .	. . .
					Micronized isotretinoin, 0.4 mg/kg per d	87		

Ellipses indicate that data were not reported in the trial.
*Variable doses used.

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drugs of 35 µg of EE plus 3 mg of drospirenone (Yasmin [Berlex, Montreal, Quebec]) and a 59% reduction using 35 µg of EE plus 2 mg of cyproterone acetate (Diane-35 [Berlex]).[62] Neither Alesse nor Yasmin is marketed for acne although both are used extensively for that indication.

Outside of the United States, the OC containing 35 µg of EE plus 2 mg of cyproterone acetate is the combination to which newer OCs have usually been compared for acne treatment. The progestin, cyproterone is an effective androgen-receptor blocker when used at higher doses in men with prostate cancer[63] and in women with acne, hirsutism, and polycystic ovary syndrome.[64] Best evidence for the use of this combination for acne comes from open studies or comparison trials with newer OCs containing levonorgestrel, drospirenone, and desogestrel. At least 60% improvement was demonstrated with all the above OCs.[62,65,66] In Europe, the antiandrogen–progestin chlormadinone has been combined with EE in an oral contraceptive (Belara [Grunenthal, Aachen, Germany]) and has been shown to be superior to an OC containing levonorgestrel in treating acne.[67]

Safety profiles are reasonable for OCs containing 35 µg of EE or less. Cardiovascular risks are not significantly increased in nonsmokers,[68] and breast cancer risks have not been shown to be increased overall.[69] The risk of deep-vein thrombosis increases from 1 per 10 000 woman-years to 3.4 per 10 000 woman-years during the first year and decreases therafter.[70] Contraindications to using OCs in an otherwise healthy woman include smoking, migraine headaches with aura, and hypertension.[71]

Androgen-receptor blockers used in acne include spironolactone, flutamide, and cyproterone acetate. Spironolactone is well established as an aldosterone-blocking agent at doses of 25 mg/d in patients with heart failure.[72] Higher doses (50-100 mg/d) are required for androgen-receptor blockade. Cyproterone acetate, in addition to being used as the progestin in the OC Diane-35, is used in doses of 50 to 100 mg/d in women with hirsutism (not available in the United States). Flutamide, a nonsteroidal androgen-receptor blocker commonly used in prostate cancer is used in women with hirsutism and acne at doses of 250 to 500 mg/d.

Best evidence for the use of spironolactone in acne comes from 4 studies in which spironolactone alone or as an adjunct in doses of 50 to 200 mg/d showed 50% to 70% improvement of acne.[73-76] A randomized comparison study of 53 participants showed a 50% improvement in acne and seborrhea among those who received a combination of 100 mg/d of spironolactone with an OC vs an 80% improvement among those who received 250 mg of flutamide with an OC.[77] Together with OCs, cyproterone acetate 50 to 100 mg/d is also effective in treating acne.[78,79] Cyproterone acetate is, however, most commonly used in the low-dose formulation (2 mg) as part of an oral contraceptive.

Isotretinoin

Isotretinoin, a naturally occurring metabolite of vitamin A, inhibits sebaceous gland differentiation and proliferation, reduces sebaceous gland size, suppresses sebum production, and normalizes follicular epithelial desquamation. Isotretinoin is indicated in severe nodular acne and acne unresponsive to other therapies. It is used at a dosage of 0.5 to 1 mg/kg per day with a cumulative dosage of 120 to 150 mg/kg over a 4- to 6-month treatment period.

Isotretinoin was first shown to be effective in a nonrandomized clinical trial at an average dose of 2 mg/kg per day for 4 months in 14 patients with severe acne.[80] Complete clearing occurred in 13 of 14 patients and all 14 had prolonged remissions. A dose-response RCT involving 76 patients showed that at 4 months, total acne lesions were reduced by 80% with a treatment of 0.1 mg/kg per day or 0.5 mg/kg per day and by 89% with 1.0 mg/kg per day.[81] A significantly greater treatment failure rate (45%) was observed with the lowest dose (0.1 mg/kg per day dosage). A related dose-comparison trial in 150 patients found that retreatment was required in 42% of patients receiving 0.1 mg/kg per day and only 10% of patients receiving 1 mg/kg per day (Table 2).[82] A new micronized formulation of isotretinoin (0.4 mg/kg per day) was equivalent in efficacy and safety to standard isotretinoin (1 mg/kg per day).[83,84]

A 10-year follow-up of 88 patients who received isotretinoin in an initial dose of 0.5 or 1 mg/kg per day showed that 23% required a second course of isotretinoin,[85] usually within 3 years of stopping therapy. The daily and cumulative dosage was an important factor in determining relapse rate. Patients receiving 0.5 mg/kg per day had a relapse rate of 39% vs 22% in those taking 1 mg/kg per day ($P<.05$). A cumulative dosage of less than 120 mg/kg had a significantly higher relapse rate than those given a larger dose (82% vs 30%, respectively; $P<.01$). A recent chart review of 179 patients who had received 1 course of isotretinoin revealed that at the 3-year follow up, 35% had no recurrence; 16% required topical therapy; 27% required the use of oral antibiotics, and 23% required more isotretinoin.[86]

Adverse effects of isotretinoin include dry lips, dry skin, dry eyes, decreased night vision, headache, epistaxis, and backache. Less common adverse effects include benign intracranial hypertension, so therapy must be stopped if a patient experiences persistent headaches. Isotretinoin can also be associated with a mild to moderate elevation in liver enzymes and in serum lipid indices, especially triglycerides.[87] It is generally well accepted that baseline cholesterol, fasting triglycerides, and liver function tests be done. Follow-up tests are recommended at weeks 4 and 8. If these test results are normal, further testing at week 12 may not be necessary.

Isotretinoin is a proven teratogen, and its use necessitates adequate contraception during and 6 weeks after therapy, as well as baseline and monthly pregnancy tests. Major malformations occur in 40% of infants exposed to isotretinoin in the first trimester.[88] It is strongly recommended that patients have 2 negative pregnancy tests be-

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Figure. Severity and Type of Acne

fore starting isotretinoin and regular monthly pregnancy tests thereafter. Current prescribing regulations in the United States require physicians to identify on each prescription that patients have met the above qualifications and have signed a consent form. Further measures are being discussed to mandate a single, centralized registration and tracking system for all health care professionals involved with isotretinoin. A recent evidence-based review examined the issue of an increasing number of reported cases of depression and suicide associated with isotretinoin.[89] Epidemiological evidence for an association between isotretinoin and depression is currently lacking.[89] Furthermore, there is a 24.7% and 13.3% prevalence of anxiety and depression, respectively, in patients with acne.[90] Until well-designed studies are conducted, patients and their relatives must be informed about depressive symptoms, and screening for depression should be an essential part of each visit.

CASE-BASED CLINICAL APPLICATIONS

Diagnosis

The diagnosis of acne vulgaris is usually uncomplicated. Differential diagnoses mainly include rosacea, perioral dermatitis, bacterial folliculitis, and drug-induced acneiform eruptions. The presence of comedones confirms the diagnosis of acne vulgaris.

Evidence-based literature in acne treatment is growing, and there is sufficient evidence to justify specific treatments for most clinical presentations. Successful outcomes frequently require nuance in management and a thorough understanding of all treatment modalities. Good outcomes are based on what is perceived by the patient as well as what can be measured. Since morbidity in acne is primarily emotional (psychological), different degrees of success may satisfy different individuals. Acne severity fluctuates over time and treatments often need to change accordingly.

Comedones Only

For this treatment, topical retinoids are the mainstay of treatment. Choices include tretinoin, adapalene, and tazarotene (FIGURE, A). Treatment response expectations are in the range of a 40% to 70% reduction in number of comedones within 12 weeks.[6,11,14] Creams and lower concentrations of retinoids are less irritating but may take longer for a response than higher concentrations and gels. Short-contact therapy, starting with 30 seconds and building up to 1 hour or more followed by washing, was demonstrated effective and safe in a study with tazarotene gel[91] and could be considered with all topical retinoids. Application should be to the entire area of involvement. Maintenance treatment is usually required.

Inflammatory Acne (Papules and Pustules), Mild to Moderate Severity

Topical antibiotics are the treatment of choice for these patients (Figure, B). Choices include benzoyl peroxide, azelaic acid, clindamycin, erythromycin, and dual agents combining benzoyl peroxide with either erythromycin or clindamycin. Current recommendations favor combining topical antimicrobial products with topical retinoids if they can be tolerated by patients.[27,35,92] Benzoyl peroxide, 2% to 10%, is an inexpensive and effective antimicrobial that is not associated with antimicrobial resistance.[93] The dual-agent products combining topical antibiotics (clindamycin, erythromycin) with benzoyl peroxide are more effective than antibiotics alone.[23-25,93] Best results require 8 to 12 weeks and maintenance therapy is usually required. Reasonable response expectations are in the range of 30% to 80%.[17-20,25,26]

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Moderate to Severe Inflammatory Acne

Oral antibiotics including the tetracyclines (minocycline, doxycycline, tetracycline) are the first-line choices (Figure, C). Erythromycin is recommended less often because of its association with resistant *P acnes*.[94] Trimethoprim-sulfamethoxizole has been reported to be successful, but there is an unacceptably high risk of severe adverse events. Response expectations with oral antibiotics are in the range of 64% to 86%.[34,40]

All oral antibiotics require a minimum of 6 to 8 weeks of treatment. There are no strict regulations on duration of use, but the recent increase in the prevalence of resistant organisms has resulted in current recommendations to encourage using antibiotics for shorter periods and to avoid the long-term use of antibiotics for maintenance therapy.[35]

Severe Papulonodular Acne

Oral isotretinoin is indicated for severe papulonodular acne (Figure, D), treatment failures, scarring, or frequently relapsing acne or in cases where psychological distress is severe. Isotretinoin is used as a single-drug therapy except for women for whom concomitant OCs are strongly recommended. Best responses are seen with daily doses of 1 mg/kg per day for a period of 20 weeks or a total accumulative dose of 120 mg/kg.[85]

A rare adverse effect of isotretinoin is called acne fulminans, characterized by extensive erosive lesions, fever, arthralgias, and leukocytosis. Treatment requires systemic corticosteroids. In a recent report of 25 cases of acne fulminans, best responses were seen with 0.5 to 1.0 mg/kg of prednisone daily for 4 to 6 weeks, with isotretinoin resumed on week 4, starting with 0.5 mg/kg per day and increasing gradually.[95]

Women With Acne

Hormonal treatments with OCs or androgen-receptor blockers have been shown to be helpful and are reviewed elsewhere.[96] For a woman with acne who desires birth control, OCs are an excellent initial choice. Oral contraceptives do not preclude using standard therapies if indicated. Approved OCs for use for acne include Orthotricyclin (in the United States and Canada), Estrostep (in the United States [Pfizer, New York, NY), and Diane-35 (Canada). The results of RCTs and other best evidence, expected improvement with OCs alone is from 40% to greater than 70% (TABLE 3).

For those who do not respond to OCs, androgen-receptor blockers, alone or as adjuncts to OCs, have response expectation in the range of 50% to 80%. A treatment dosage of 50 to 100 mg/d of Spironolactone is well tolerated, with adverse effects including diuretic effect, breast tenderness, and menstrual irregularities if OCs are not used concomitantly.[97] Another well-tolerated treatment is 250 mg/d flutamide . Its potential adverse effects include gastrointestinal tract upset and, at higher doses, hepatotoxicity. Periodic liver function tests are recommended with any dose of flutamide. Similar to spironolactone is 50 to 100 mg/d of cyproterone acetate. Hepatotoxicity has been reported rarely in men receiving cyproterone acetate for prostate cancer[98] and in women receiving OCs containing cyproterone acetate.[99] Hormonal treatments for acne treatment are usually prolonged, depending on response and tolerance.

Laboratory Studies

For women with regular menstrual cycles, serum-androgen measurements

Table 3. Most Common Adverse Effects of Systemic Acne Medications

Drug	Approximate Frequency
Oral Antibiotics	
Dyspepsia, %	30
Photosensitivity	Rare (highest: doxycycline)
Benign intracranial hypertension	Rare
Hypersensitivity reaction	Rare
Lupuslike syndrome*	
Tetracyclines as a group	14.2 Cases per 100 000 prescriptions
Minocycline	52.8 Cases per 100 000 prescriptions
Isotretinoin, %	
Mucocutaneous (cheilitis)	95
Tetratogenicity	25-40 of exposed fetuses
Hypertriglyceridemia	25
Elevation of liver transaminases	15
Hypercholesterolemia	7
Oral contraceptives, %	
Dysmenorrhea	10
Nausea	2-10
Breast tenderness	6
Headache	5
Depressed mood	3-30
Venous thromboembolism†[70]	3.4 per 10 000 woman-years† Highest during first year of use
Spironolactone, %‡	
Diuretic effect	30
Dysmenorrhea	20
Dysphoria	20
Breast tenderness	18
Flutamide§	
Hepatotoxicity, %	1 (doses >500 mg)
Cyproterone acetate‖	
Hepatotoxicity	Rare (doses of 50-100 mg)

*Sturkenboom et al.[48]
†Lidegaard et al.[70]
‡Shaw et al.[97]
§Lin et al.[98]
‖Rudiger et al[99] and Legro.[100]

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are not necessary. For those with rapid onset of hyperandrogenism and virilization, an androgen-secreting ovarian or adrenal tumor can be excluded with a normal total testosterone and dehydroepiandosterone sulfate levels, respectively. Irregular menses, hirsutism, obesity, or a family history of type 2 diabetes suggest a possible endocrinopathy, such as polycystic ovary syndrome. Further studies may be indicated, which could include measurement of gonadotropins, free testosterone, 17-hydroxy progesterone, prolactin, and androstenedione.[57,100] Unfortunately, there is no widely accepted best laboratory test in this setting.[101]

Conclusion

Current treatments in acne target one or more of the known mechanisms involved in the disease. Combining more than 1 treatment frequently yields optimal responses. Patients may require adjustment of therapies depending on their degree of improvement and level of tolerance to the treatments.

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Study concept and design: Shaw, Haider.
Acquisition of data: Shaw, Haider.
Drafting of the manuscript: Shaw, Haider.
Critical revision of the manuscript for important intellectual content: Shaw, Haider.
Study supervision: Shaw.

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