Therapeutic Class Overview
Topical Retinoids

Therapeutic Class

- **Overview/Summary:** Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules or nodules.[1-2] Four pathogenic factors interact in a complex manner to produce the various acne lesions, including sebum production by the sebaceous gland, *Propionibacterium acnes* follicular colonization, alteration in the keratinization process and the release of inflammatory mediators to the skin.[2] The effectiveness of the topical retinoids has been well documented and these agents are effective in both comedonal and inflammatory acne vulgaris.[1] The comedolytic and anti-comedogenic properties associated with topical retinoids result in a reduction in the formation of microcomedones and comedones.[2] Moreover, topical retinoids normalize desquamation, which facilitates the penetration of other topical agents.[2]

  There are currently three single-entity topical retinoid agents available, including adapalene (Differin®), tazarotene (Tazorac®) and tretinoin (Atralin®, Avita®, Retin-A®, Retin A-Micro® and Tretin-X®), that are all Food and Drug Administration (FDA)-approved for the treatment of acne vulgaris. Tazarotene is also FDA-approved for the management of plaque psoriasis.[3-11] Retin-A Micro® is a tretinoin microsphere gel and is the only topical retinoid product to use slow-release technology to help lessen the irritation caused by other acne vulgaris medications. In addition, a retinoid is formulated in combination with an antibiotic in two products. Adapalene/benzoyl peroxide (Epiduo®) and tretinoin/clindamycin phosphate (Ziana®) are both FDA-approved for the treatment of acne vulgaris in patients 12 years of age or older.[12,13] Adapalene 0.1% cream and gel and tretinoin (Retin-A®) are the only topical retinoids that are currently available generically.[14] As with systemic antibiotics, the use of topical antibiotics is associated with bacterial resistance. Antibiotics and benzoyl peroxide both target *P acnes*; however, benzoyl peroxide has not been associated with the development of bacterial resistance.[2]

Table 1. Current Medications Available in Therapeutic Class[3-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Adapalene (Differin®*)	Topical treatment of acne vulgaris	Cream: 0.1% Gel: 0.1% 0.3% Lotion: 0.1%	✔
Tazarotene (Tazorac®)	Topical treatment of acne vulgaris (0.1% only) and topical treatment of plaque psoriasis	Cream: 0.05% 0.1% Gel: 0.05% 0.1%	-
Tretinoin (Atralin®, Avita®, Retin-A®*, Retin-A Micro®, Tretin-X®)	Topical treatment of acne vulgaris	Cream: 0.025% 0.038% 0.05% 0.1%	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Gel: 0.01% 0.025% 0.04% 0.05% 0.1%	
Combination Products			
Adapalene/benzoyl peroxide (Epiduo®)	Treatment of acne vulgaris in patients ≥12 years of age	Gel: 0.1/2.5%	-
Tretinoin/clindamycin phosphate (Ziana®)	Treatment of acne vulgaris in patients ≥12 years of age	Gel: 1.2/0.025%	-

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- All of the topical retinoid products have consistently demonstrated a statistically significant improvement in acne lesions, physician assessment of acne severity or patient perceived acne severity compared to treatment with a vehicle alone.[15-30]
- The topical retinoid combination products have demonstrated significant improvements in acne symptoms and severity when compared to both their individual components and vehicle.[20,21,24,25]
- In a 12-week study by Lucky and colleagues, there was no significant difference in lesion count among patients receiving tretinoin 0.025% (Avita®) and those receiving tretinoin 0.025% (Retin-A®); however, both treatments were more effective compared to vehicle (*P* value not reported).[27]
- As monotherapy, adapalene may be less effective in improving the number of acne lesions compared to combination therapy with clindamycin/benzoyl peroxide over 12 weeks of treatment.[31,32]
- In a study by Tanghetti et al, there was no significant difference in the change in noninflammatory lesion counts, the primary endpoint, between patients receiving adapalene 0.3% gel and tazarotene 0.1% cream (59 vs 65%; *P*=0.074).[33]
- In two trials comparing adapalene and tretinoin, similar efficacy was seen between the two agents; however, there is conflicting evidence supporting improved tolerability with one agent over another.[34,35]
- Although tazarotene produced a more rapid improvement in papule count in one trial comparing tretinoin to tazarotene, by the end of the study period there was no statistical difference between the treatment groups with regard to closed comedones, investigator global assessment or papule count.[26,36]
- In a study by Zouboulis et al, the combination of adapalene/benzoyl peroxide was compared to clindamycin/benzoyl peroxide over 12 weeks. The primary endpoint, the percent reduction in inflammatory lesion count, was similar between the two treatment groups (76.8 vs 72.2%; *P*=0.76).[37] In another study, the combination of tretinoin/clindamycin significantly reduced the number of *Propionibacterium acnes* bacteria compared to clindamycin/benzoyl peroxide (*P*=0.003); however, there were similar reductions in inflammatory, noninflammatory and total lesion counts at 16 weeks between the treatment groups (*P* values not reported).[38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - For mild acne vulgaris (comedonal), a topical retinoid is considered initial treatment, while other patients with mild acne vulgaris (mixed and papular/pustular) should receive a topical retinoid and a topical antimicrobial as initial treatment.[2]
  - For moderate acne vulgaris (mixed and papular/pustular), treatment with oral antibiotic and a topical retinoid with or without benzoyl peroxide is considered first line, while patients with nodular acne vulgaris should receive an oral antibiotic and a topical retinoid and benzoyl peroxide is considered first-line treatment.[2]

  - Topical antibiotics (erythromycin and clindamycin) are effective in the treatment of acne vulgaris but are more effective when used in combination with benzoyl peroxide due to a synergy as well as the resulting elimination or reduction of bacterial resistance.[2,39]
  - Treatment of plaque psoriasis varies depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences.[40,41]
  - Topical corticosteroids are the cornerstone of psoriasis treatment for the majority of patients. Other topical agents include vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, nonmedicated topical moisturizers, salicylic acid, anthralin, coal tar and combination products.[40,41]
- Other Key Facts:
  - Adapalene (Differin®) 0.1% cream and gel and tretinoin (Retin-A®) formulations are available generically.[14]
  - Both combination products are only available as branded products.[14]

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Therapeutic Class Review
Topical Retinoids

Overview/Summary

Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules or nodules.[1-2] Four pathogenic factors interact in a complex manner to produce the various acne lesions, including sebum production by the sebaceous gland, *Propionibacterium acnes* follicular colonization, alteration in the keratinization process and the release of inflammatory mediators to the skin.[2] Several treatment options exist including topical agents, systemic antibiotics, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary/alternative therapies, and dietary restrictions.[1] The effectiveness of the topical retinoids has been well documented and these agents are effective in both comedonal and inflammatory acne vulgaris.[1] The comedolytic and anti-comedogenic properties associated with topical retinoids result in a reduction in the formation of microcomedones and comedones.[2] Moreover, topical retinoids normalize desquamation, which facilitates the penetration of other topical agents.[2]

There are currently three single-entity topical retinoid agents available, including adapalene (Differin®), tazarotene (Tazorac®), and tretinoin (Atralin®, Avita®, Retin-A®, Retin A-Micro® and Tretin-X®), that are all Food and Drug Administration (FDA)-approved for the treatment of acne vulgaris. Tazarotene is also FDA-approved for the management of plaque psoriasis.[3-11] Retin-A Micro® is a tretinoin microsphere gel and is the only topical retinoid product to use slow-release technology to help lessen the irritation caused by other acne vulgaris medications. In addition, a retinoid is formulated in combination with an antibiotic in two products. Adapalene/benzoyl peroxide (Epiduo®) and tretinoin/clindamycin phosphate (Ziana®) are both FDA-approved for the treatment of acne vulgaris in patients 12 years of age or older.[12,13] Adapalene 0.1% cream and gel and tretinoin (Retin-A®) are the only topical retinoids that are currently available generically.[14]

The combination of a topical retinoid plus an antimicrobial agent is becoming increasingly recognized as the first-line therapy for the treatment of acne vulgaris.[2-3] Traditionally, the treatment of acne vulgaris has been directed toward controlling *P acnes* and centered on the use of antibiotics. Combination retinoid and antimicrobial agents have the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions.[2,15] Data have demonstrated that these agents result in a faster and more complete clearing of acne vulgaris lesions compared to monotherapy.[2,15] As with systemic antibiotics, the use of topical antibiotics is associated with bacterial resistance. Antibiotics and benzoyl peroxide both target *P acnes*; however, benzoyl peroxide has not been associated with the development of bacterial resistance.

Current guidelines suggest adding benzoyl peroxide to retinoids when long-term antimicrobial use is necessary due to its bactericidal properties.[2,15] Generally, topical combination products are indicated in patients with mild to moderate acne vulgaris with an inflammatory component.[2,15] In addition to its use in acne vulgaris, guidelines recommend tazarotene for the treatment of psoriasis. Topical agents are useful in mild to moderate disease and adjunct treatment in extensive psoriasis.[16,17] The three ways in which tazarotene is thought to function when treating psoriasis are by normalizing abnormal keratinocyte differentiation, diminishing hyperproliferation and by decreasing expression of inflammatory markers.[16,17] Tazarotene is best used in combination with topical corticosteroids which are the cornerstone of treatment for plaque psoriasis.[16,17]

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Adapalene (Differin®*)	Topical retinoids	✔
Tazarotene (Tazorac®)	Topical retinoids	-
Tretinoin (Atralin®, Avita®, Retin-A®*, Retin-A Micro®, Tretin-X®)	Topical retinoids	✔

Generic Name (Trade name)	Medication Class	Generic Availability
Combination Products		
Adapalene/benzoyl peroxide (Epiduo®)	Topical retinoids/antibiotic	-
Tretinoin/clindamycin phosphate (Ziana®)	Topical retinoids/antibiotic	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[3-13]

Generic Name	Topical Treatment of Acne Vulgaris	Topical Treatment of Acne Vulgaris in Patients ≥12 Years of Age	Topical Treatment of Patients with Plaque Psoriasis
Single-Entity Agents			
Adapalene		✔	
Tazarotene	✔ (0.1% strengths only)*		✔
Tretinoin	✔		
Combination Products			
Adapalene/benzoyl peroxide		✔	
Tretinoin/clindamycin phosphate		✔	

*Tazorac® 0.1% gel is indicated for mild to moderate facial acne vulgaris.

In addition to its Food and Drug Administration-approved indication, tretinoin may also be used off-label in the treatment of acute promyelocytic leukemia, facial actinic keratosis, xerophthalmia and dysplasia of the cervix. Adapalene has been used off-label in the treatment of Rosacea.[17]

Pharmacokinetics

Table 3. Pharmacokinetics[3-13]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents					
Adapalene	Low	Poor	Minimal	None	17.2
Tazarotene	2 to 3	Poor	Minimal	Tazarotenic acid	18
Tretinoin	1 to 31 (topical)	Poor	63	13-cis-retinoic acid, 4-oxo-13-cis-retinoic acid, all-trans-4-oxo-retinoic acid	0.5 to 2.0
Combination-Products					
Adapalene/ benzoyl peroxide	Not reported	Not reported	Not reported	Benzoic acid	Not reported
Tretinoin/ clindamycin phosphate	Minimal	Not reported	Not reported	13-cis-retinoic acid, 4-oxo-13-cis-retinoic acid	Not reported

Clinical Trials

The clinical studies demonstrating the safety and efficacy of the topical retinoid products in their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[18-51]

All of the topical retinoid products have consistently demonstrated a statistically significant improvement in acne lesions, physician assessment of acne severity or patient perceived acne severity compared to

treatment with a vehicle alone. [20,21,28,29,31-35,38-40,43,45-47] In addition, the topical retinoid combination products have demonstrated significant improvements in acne symptoms and severity when compared to both their individual components and vehicle.[32-34,38,39]

The results of available studies have not shown a difference in tolerability profiles between the various adapalene formulations; however, adapalene 0.3% gel was significantly more effective compared to the 1% gel with regard to rates of successful treatment (*P*=0.020).[22,28] When tretinoin 0.4% gel microspheres was compared to tretinoin 0.1% gel microspheres over 12 weeks, the reduction from baseline in total lesion counts was not significantly different between the two groups; however, there was a greater reduction in inflammatory lesions with the lower strength (*P*<0.048). No difference in physician- or patient-assessed improvement was reported between the treatment groups.[42] In a 12-week study by Lucky and colleagues, there was no statistically significant difference in lesion count among patients receiving tretinoin 0.025% (Avita®) and those receiving tretinoin 0.025% (Retin-A®); however, both treatments were more effective compared to vehicle (*P* value not reported).[43]

As monotherapy, adapalene may be less effective in improving the number of acne lesions compared to combination therapy with clindamycin/benzoyl peroxide over 12 weeks of treatment.[23,24] In a study by Tanghetti et al, there was no significant difference in the change in noninflammatory lesion counts, the primary endpoint, between patients receiving adapalene 0.3% gel and tazarotene 0.1% cream (59 vs 65%; *P*=0.074).[25] In two trials comparing adapalene and tretinoin, similar efficacy was seen between the two agents.[26,27] Cunliffe et al reported greater tolerability with adapalene while Tu et al reported greater tolerability with tretinoin. [26,27] Although tazarotene produced a more rapid improvement in papule count in one trial comparing tretinoin to tazarotene, by the end of the study period there was no statistical difference between the treatment groups with regard to closed comedones, investigator global assessment or papule count.[40,41]

In a study by Zouboulis et al, adapalene/benzoyl peroxide was compared to clindamycin/benzoyl peroxide over 12 weeks. The primary endpoint, the percent reduction in inflammatory lesion count, was similar between the two treatment groups (76.8 vs 72.2%; *P*=0.76).[30] In a another study, the combination of tretinoin/clindamycin significantly reduced the number of *Propionibacterium acnes* bacteria compared to clindamycin/benzoyl peroxide (*P*=0.003); however, there were similar reductions in inflammatory, noninflammatory and total lesion counts at 16 weeks between the treatment groups (*P* values not reported).[36]

The only topical retinoid FDA-approved for the treatment of psoriasis is tazarotene. The results of two placebo-controlled studies demonstrate tazarotene significantly improves symptom and severity scores of psoriasis compared to vehicle alone.[45,46] When tazarotene was administered with a corticosteroid, the combination was more effective compared to the administration of calcipotriene.[48] Another study compared tazarotene in combination with calcipotriene to clobetasol alone and found similar improvements in scaling, plaque elevation and overall lesion severity between the treatment groups.[51]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acne Vulgaris				
Pariser et al[18] Adapalene/BPO 0.1%/2.5% gel QD	MC, OL Patients ≥12 years of age with acne vulgaris and 30 to 100 noninflammatory facial lesions, 20 to 50 inflammatory facial lesions and no active nodules or cysts	N=452 12 months	Primary: Percent lesion count reduction from baseline (total, inflammatory and noninflammatory), patient's assessment of acne vulgaris and safety Secondary: Not reported	Primary: The median percent reduction in total, inflammatory and noninflammatory lesion counts was 70.8, 76.0 and 70.0%, respectively (*P* value not reported). Reductions were observed starting as early as one week on therapy. By 12 months, 80.3% of patients reported a "moderate," "marked" or "complete" improvement. A minimal improvement was reported by 10.9% of patients and 8.8% reported no change or worsening. Treatment was safe and well tolerated. Local cutaneous tolerability of the study treatment was good throughout the study, with mean tolerability scores for erythema, dryness, scaling and burning/stinging all less than one (mild) at each study visit. The highest mean cutaneous tolerability scores were reported at week one and then decreased to levels similar to baseline scores throughout the treatment period. Secondary: Not reported
Troielli et al[19] Adapalene/BPO 0.1%/2.5% gel QD	MC, OL, PRO Patients ≥15 years of age with mild to moderate facial acne	N=105 12 weeks	Primary: Total, inflammatory and noninflammatory lesion counts, IGA score and safety Secondary: Not reported	Primary: Lesion counts were significantly reduced over 12 weeks of treatment with adapalene/BPO compared to baseline. There was a mean reduction in inflammatory lesions of 80.6 and 69.3% in noninflammatory lesions compared to baseline (*P*<0.001). Reductions in all types of lesions (inflammatory and noninflammatory) began soon after initiation of adapalene/BPO and continued throughout the duration of the evaluation period. The mean IGA score was significantly reduced from baseline following adapalene/BPO treatment (1.1 vs 2.9; *P*<0.001). Overall, effectiveness was evaluated as "good" or "very good" by 94% of patients while 4% of patients considered treatment to be negative (resulted in no change or worsening). A total of 87.5% of patients rated the tolerability as "good" or "very good," 10% of patients rated it as acceptable and the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				remaining 2.5% of patients rated it as poor. Burning at the application site was reported by 14.3% of patients. One case (1.1%) was considered to be of moderate severity and the remaining 13 cases were mild. Five patients (5.5%) discontinued treatment due to application site reactions. No other types of adverse reactions were reported during the study. Secondary: Not reported
Kawashima et al[20] Adapalene 0.1% gel QD vs vehicle gel QD	MC, PG, RCT, SB, VC Japanese patients 12 to 35 years of age with ≥30 total acne vulgaris lesions consisting ≥20 noninflammatory lesions, 10 to 100 inflammatory lesions and ≤2 nodulocystic lesions on the face	N=200 12 weeks	Primary: Reduction in total lesion counts Secondary: Reduction in noninflammatory and inflammatory lesion counts, safety, tolerability and patient satisfaction	Primary: The adapalene group consistently demonstrated greater reductions for all efficacy assessments compared to the vehicle group. The median percent reduction in total lesion counts was significantly greater in the adapalene group compared to the vehicle group (63.2 vs 36.9%; *P*<0.0001) with clinically meaningful differences being noted as early as one week. Secondary: The median percent reduction in noninflammatory and inflammatory lesion counts was significantly greater in the adapalene group (64.6 and 63.7%; *P*<0.0001) compared to the vehicle group (38.1 and 45.8%; *P*=0.0010). The proportion of patients with at least one adverse event in the adapalene group was 80.0 and 51.1% in the vehicle group. All related adverse events were dermatological with the most frequent being dry skin. Patient satisfaction was higher in the adapalene group relative to the vehicle group (60.0 vs 42.3%; *P* value not reported).
Eichenfield et al[21] Adapalene 0.1% lotion QD vs	2 DB, MC, PG, RCT, VC Patients ≥12 years of age with 20 to 50 papules and pustules and 30 to	N=1,075 12 weeks	Primary: Proportion of patients achieving ≥2 point reduction in IGA grade, absolute change in inflammatory,	Primary: In study I, significantly more patients receiving adapalene experienced a ≥2 point reduction in IGA grade compared to patients receiving placebo (26.3 vs 17.3%; *P*<0.001). A higher proportion of patients also achieved this improvement in study II compared to placebo (24.1 vs 16.4%; *P*<0.001). The absolute reductions in the number of total lesions, inflammatory lesions

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vehicle gel QD	100 noninflammatory lesions and IGA grade 3 or 4		noninflammatory and total lesion counts, safety and tolerability Secondary: Not reported	and noninflammatory lesions were significantly greater with adapalene compared to placebo in both studies (*P*<0.001 for all). Compared to placebo in study I, adapalene lotion significantly reduced the number of total lesions (39 vs 29%; *P*<0.001), inflammatory lesions (16.0 vs 12.5%; *P*<0.001) and noninflammatory lesions (23 vs 18%; *P*<0.001) at week 12. In study II, patients randomized to receive adapalene experienced significant reductions in total lesions (34 vs 26; *P*<0.001), inflammatory lesions (13 vs 12; *P*<0.001) and noninflammatory lesions (21 vs 15%; *P*<0.001) compared to the placebo group. In study I adverse events were reported by 75 patients receiving adapalene compared to 31 patients receiving placebo. In study II, 43 patients receiving adapalene experienced a treatment-related adverse event compared to 18 patients in the placebo group. The most commonly reported adverse event in both studies was dry skin, reported by 9.4 and 3.9% of patients receiving adapalene and placebo, respectively in study I and 5.4 and 2.1% in study II. Secondary: Not reported
Herndon et al[22] Adapalene 0.1% lotion QD vs adapalene 0.1% cream QD	2 AC, PRO, RCT, SB Patients ≥18 years of age with healthy skin	N=144 3 weeks	Primary: Tolerability parameters Secondary: Not reported	Primary: There were no statistically significant differences between the cream and lotion formulations with regard to worsening scores for erythema, scaling, dryness or stinging/burning (*P* value not reported). The cream was preferred over the lotion for most items of the Cosmetic Acceptability Questionnaire on product aesthetics. Participants favored lotion over the cream for residue left on the skin and having fewer odors. A large percentage of patients had no preference to one formulation over the other (*P* values not reported). Seven and nine patients receiving cream and lotion, respectively, reported treatment-related adverse events. The most common adverse event reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was dryness of the skin. Secondary; Not reported
Ko et al[23] Adapalene 0.1% gel QD vs clindamycin/BPO 1%/5% gel QD	AC, OL, PRO, RCT Patients ≥12 years of age with >12 inflammatory lesions but ≤3 nodules or cysts and >12 noninflammatory lesions with an acne grade 2 to 7 on Leeds revised acne grading	N=69 12 weeks	Primary: Change in total lesions, inflammatory lesions, noninflammatory lesions, acne severity, perception of global improvement Secondary: Not reported	Primary: Clindamycin/BPO was associated with statistically significant reductions in inflammatory lesions (*P*=0.0165) and total lesions compared to adapalene gel (*P*=0.0258) at 12 weeks. There was no statistically significant difference between the groups at week 12 with regard to the number of noninflammatory lesions (*P* value not reported). Acne grade improved for both groups according to Leeds revised acne grading; however, there was only a statistically significant difference at weeks two and four favoring clindamycin/BPO (*P*≤0.05 for both). Both treatments reduced KAGS scores from baseline; however, the difference between treatments was only statistically significant at week two (*P*≤0.05 favoring clindamycin/BPO gel over adapalene). Patient scores on the global improvement scale were rated “much improved” or “very much improved” by 68% of the clindamycin/BPO group and 61% of patients receiving adapalene (*P* value not reported). Both treatments were well tolerated with minimal adverse events, such as erythema, dry skin, desquamation, stinging/burning sensation and pruritus. Most adverse events occurred within one month of treatment and lasted less than one month. Combination treatment was better tolerated on point of local irritability but allergic reaction was suspected in four patients. Secondary: Not reported
Langner et al[24] Adapalene 0.1% gel QD	AC, MC, PG, RCT, SB Patients 12 to 39	N=130 12 weeks	Primary: Noninflammatory and inflammatory lesion counts,	Primary: Clindamycin/BPO was associated with a statistically significant reduction from baseline in total lesion count at week 12 compared to adapalene (*P*<0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs clindamycin/BPO 1%/5% gel QD	years of age with mild to moderate acne vulgaris and ≥15 inflammatory and/or noninflammatory lesions but ≤3 nodulocystic lesions and an acne grade 2 to 7 on Leeds revised acne grading		physician and patient reported acne severity and adverse events Secondary: Not reported	Combination treatment was associated with significantly fewer total lesions at all points evaluated throughout the study compared to adapalene treatment (*P*≤0.005 for all time points). Patients receiving treatment with combination therapy experienced statistically significant reductions in inflammatory lesions throughout the evaluation period compared to patients receiving adapalene (*P*≤0.001 for all time points). Clindamycin/BPO significantly improved the number of noninflammatory lesions compared to adapalene at week eight and week 12 (*P*≤0.05). Acne grade decreased in both treatment groups; however, this decrease was significant with clindamycin/BPO compared to adapalene as early as week one (*P*=0.013) and was maintained throughout the course of the study (*P*<0.038). Furthermore, there was a statistically significant improvement in physician-assessed severity with clindamycin/BPO as early as week one of treatment compared to adapalene (*P*≤0.007). The percentage of patients that rated themselves as "improved" increased over time to 90% by the end of the study for both groups. As in the physician's rating, the proportion improved was greater early in treatment (weeks one through eight) with combination therapy compared to adapalene therapy (*P*<0.005). The overall assessment of tolerance by the investigator showed that 77.0% of patients in the clindamycin/BPO group were rated as having "good" or "excellent" tolerance compared to 52.3% of patients in the adapalene group. The number of patients who reported at least one treatment-emergent adverse event was 32.3% in the combination treatment group compared to 30.8% of patients receiving adapalene (*P* value not reported). Secondary: Not reported
Tanghetti et al[25]	AC, MC, RCT, SB	N=180	Primary: Percent reduction	Primary: There was no statistically significant difference between adapalene and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Adapalene 0.3% gel QD vs tazarotene 0.1% cream QD	Patients ≥12 years of age with stable, moderate or severe acne vulgaris with 25 to 100 noninflammatory lesions (papules/ pustules), ≥50 noninflammatory lesions, ≤3 facial nodules and or cysts with a diameter ≥1 centimeter	16 weeks	in noninflammatory lesions at 12 weeks Secondary: Percent reduction in inflammatory lesions, IGA score, overall disease severity, adverse events and PIH severity	tazarotene with regard to the percent reduction in noninflammatory lesions at 12 weeks (59 vs 65%, respectively; *P*=0.074). When patients with >100 comedones at baseline were removed from the analysis (13/90 patients in the adapalene group and 2/90 patients in the tazarotene group), the difference remained nonsignificant (49 vs 52%; *P*=0.156). Secondary: There was no statistically significant difference between patients randomized to adapalene or tazarotene treatment with regard to the reduction in inflammatory lesions at week 12 (48 vs 63%, respectively; *P*=0.274) and week 16 (56 vs 68%, respectively; *P*=0.108). A significantly greater proportion of patients achieved a ≥50% reduction in total lesions at 16 weeks with tazarotene compared to adapalene (82 vs 64%; *P*=0.020) but not at 12 weeks (*P*=0.053). There was no statistically significant difference between the adapalene or tazarotene groups with regard to the proportion of patients experiencing a ≥50% reduction in inflammatory or noninflammatory lesions at week 12 (*P*=0.054 and *P*=0.288, respectively) and week 16 (*P*=0.055 and *P*=0.070, respectively). At week 12, the proportion of patients with a ≥2 grade improvement in IGA was 50.8% in the tazarotene group compared to 32.9% of patients receiving adapalene (*P*=0.036). There was no statistically significant difference in improvement between the groups at 16 weeks (*P*=0.0172). There was no statistically significant difference between the adapalene and tazarotene groups with regard to IGA at 12 *(P*=0.880) and 16 weeks (*P*=0.187). Tazarotene was associated with a statistically significant reduction in PIH index compared to adapalene at weeks 16 (*P*≤0.018). Tazarotene was associated with greater increases in erythema scores at week eight compared to adapalene (*P*=0.042). Tazarotene was also associated with statistically significant increases in scores for dry skin at week two compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to adapalene (*P*=0.021). Scores for skin burning were also increased from baseline in the tazarotene group compared to the adapalene group (*P*=0.10). No statistically significant difference in oiliness or pruritus was reported between the groups at any time point.
Cunliffe et al[26] Adapalene 0.1% gel, frequency not specified vs tretinoin 0.025% gel, frequency not specified	MA 5 RCTs of patients with mild to moderate acne vulgaris who received adapalene or tretinoin for 12 weeks in total	N=900 12 weeks	Primary: Total lesion counts, inflammatory lesion counts, noninflammatory lesion counts and tolerability Secondary: Not reported	Primary: There was a slight trend towards greater improvement in total and individual lesions with adapalene throughout the 12-week treatment period compared to tretinoin. No significant differences existed except at week one when adapalene demonstrated a significantly greater reduction in both inflammatory and total lesions (*P*<0.05). Analysis demonstrated that therapy with adapalene has a more rapid effect very early on in therapy, but the two therapies produce very similar changes in lesion counts at other time points. Greater local tolerability of adapalene compared to tretinoin was demonstrated at all evaluation periods (*P*<0.001). Adapalene demonstrated significantly fewer adverse events compared to tretinoin as evaluated by the mean objective score and the overall mean score (*P*<0.001). Secondary: Not reported
Tu et al[27] Adapalene 0.1% gel QD vs tretinoin 0.025% gel QD	R Asian patients with grade II to III acne vulgaris	N=150 8 weeks	Primary: Reduction in total number of noninflammatory and inflammatory acne vulgaris lesions, global assessment of improvement scale and safety Secondary: Not reported	Primary: Regarding the percent reductions in noninflammatory lesion counts, a measurable effect was evident for both agents by the end of treatment week two with adapalene (21.8%) and tretinoin (27.1%; *P* value not reported). By week eight, both groups experienced a 70% reduction in noninflammatory lesion counts (*P* values not reported). Similar results were reported with inflammatory lesion counts. Significant reductions were already apparent after two weeks of treatment with adapalene (29.8%) and tretinoin (33.1%; *P* values not reported). By week eight, the percent reduction in inflammatory lesion counts was 74.8% with adapalene and 72.2% with tretinoin (*P* value not reported). By week eight, adapalene led to complete clearance of lesions in 72.1% compared to 70.8% of patients receiving tretinoin (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				With regard to of overall global efficacy, therapy with adapalene or tretinoin was found to be essentially equivalent (*P* value not reported). The incidence and severity of erythema, scaling, burning and skin dryness were significantly higher in the adapalene group compared to the tretinoin group (*P* value not reported). The incidence and severity of pruritus was similar for both treatment groups. Secondary: Not reported
Thiboutot et al[28] Adapalene 0.3% gel QD vs adapalene 0.1% gel QD vs vehicle gel QD	AC, DB, MC, PG, RCT, VC Patients ≥12 years of age with 20 to 100 noninflammatory lesions, 20 to 50 inflammatory lesions and no nodules or cysts	N=653 12 weeks	Primary: Success rate (percentage of patients rated "clear" or "almost clear" on the IGA), percent lesion reduction from baseline (total, inflammatory and noninflammatory) Secondary: Response rate, percentage of patients who achieved ≥50% reduction in lesion counts (inflammatory, noninflammatory, and total), IGA, patients assessment of	Primary: Success rates for patients in the adapalene 0.3% group were significantly greater compared to those in the adapalene 0.1% group (*P*=0.020) and the vehicle group (*P*=0.005). In addition, a consistent dose-dependent response was observed at each time point. For patients completing 12 weeks of the study, success rates were 23.3, 16.9, and 10.0% in the adapalene 0.3%, 0.1% and vehicle gel groups, respectively (*P* value not reported). A post-hoc analysis of subgroups stratified by baseline IGA severity confirmed the dose-dependent trend for patients with moderate to severe IGA at baseline. Success rates at week 12 were 21.8, 15.4 and 4.2% for moderate to severe cases in the adapalene 0.3%, 0.1% and vehicle gel groups, respectively (*P* value not reported). Median percent changes from baseline for total, inflammatory and noninflammatory lesion counts at week 12, revealed a dose-dependent response in the adapalene groups. There was a statistically significant difference between the adapalene 0.3% and adapalene 0.1% groups in the percent reduction in total lesion counts (*P*=0.020) and inflammatory lesion counts (*P*=0.015). There was only marginal differences between the active groups in the percent reduction in noninflammatory lesion counts (*P*=0.061). Adapalene 0.3% was more effective compared to vehicle with regard to success rate (*P*=0.005) and in the percent lesion reduction in total,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			acne vulgaris, safety and tolerability	inflammatory and noninflammatory lesion counts (all *P*<0.001). Secondary: A dose-dependent difference between active treatment groups in response rates for total lesions (59.5 vs 48.7%; *P*=0.016), inflammatory lesions (66.1 vs 59.7%; *P*=0.107) and noninflammatory lesions (53.7 vs 43.7%; *P*=0.027) occurred for adapalene 0.3% and adapalene 0.1%, respectively at 12 weeks. The percentages of patients rating their skin as "clear" or showing a "marked improvement" were 29.8 and 24.2% for adapalene 0.3% and adapalene 0.1% groups, respectively (*P* value not reported). Adapalene 0.3% was statistically more effective compared to the vehicle at the end of the study for all secondary efficacy assessments (*P*<0.02 for all). Severe erythema occurred in 0.4 and 0.8% of patients following treatment with adapalene 0.3% and 0.1%, respectively. A similar incidence of scaling (1.2 vs 1.6%), dryness (0.8 vs 2.7%) or stinging/burning (3.6 vs 3.9%) was reported between groups (*P* values not reported). Treatment-related adverse events were experienced by 22.0, 12.0 and 4.5% of patients in the adapalene 0.3%, 0.1%, and vehicle gel groups. Most events occurred on the treated areas of skin and included dry skin and skin discomfort.
Poulin et al[29] Adapalene/BPO 0.1%/2.5% gel QD vs vehicle	DB, ES, MC, RCT, VC Patients with severe acne vulgaris who experienced a ≥50% global improvement after a previous 12-week treatment the	N=234 6 months	Primary: Percent change in inflammatory and noninflammatory lesion counts, lesion maintenance success rates, IGA success rate, IGA maintenance rate, relapse rates	Primary: After 24 weeks of treatment, patients receiving adapalene/BPO experienced statistically significant reductions in total lesions (26.0 vs 46.3%; *P*<0.01), inflammatory lesions (21.2 vs 28.6%; *P*<0.01) and noninflammatory lesions (31 vs 45%; *P*<0.01) compared to patients receiving the vehicle. Patients receiving adapalene/BPO experienced significantly greater lesion maintenance success rates (≥50% improvement in lesion count obtained with previous therapy) compared to subjects receiving vehicle for each lesion type (total lesions, 78.9 vs 45.8%; inflammatory lesions, 78.0 vs 48.3%; noninflammatory lesions, 78.0 vs 43.3%; *P*<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	current regimen		time to relapse and safety Secondary: Not reported	The IGA success rate (percentage of subjects rated "clear" or "almost clear") increased from 26.8 to 45.7% following six months of maintenance therapy with adapalene/BPO, whereas it decreased for the vehicle group from 37.5 to 25.6% during the same period (*P*<0.01). The IGA maintenance success rate was 70.7% in the group treated with adapalene/BPO compared to the vehicle group at six months (34.2%; *P*<0.001). Treatment with adapalene/BPO was associated with a statistically significant increase in the time until 25% of patients relapsed compared to treatment with placebo (175 vs 56 days; *P*<0.0001). Adverse events occurred in 4.1% of patients treated with adapalene/BPO compared to 0.8% of patients receiving placebo. The majority of subjects from both groups were "not bothered at all" by the treatment adverse events (74.3% with adapalene/BPO and 72.3% with vehicle; *P*=0.787). Secondary: Not reported
Zouboulis et al[30] Adapalene/BPO 0.1%/2.5% gel QHS vs clindamycin/BPO 1%/5% gel QHS	AC, MC, PG, RCT, SB Patients 12 to 45 years of age with facial acne and 25 to 80 inflammatory lesions and 12 to 100 noninflammatory lesions	N=382 12 weeks	Primary: Percent change in inflammatory lesion count Secondary: Proportion of patients achieving treatment success (improvement ≥2 grades from baseline on IGA scale), time to treatment	Primary: After 12 weeks of treatment, the mean reduction in inflammatory lesion count was 76.8% in the clindamycin/BPO group compared to 72.2% in the adapalene/BPO group (*P*=0.76). Secondary: Significantly more patients randomized to receive clindamycin/BPO achieved treatment success on the IGA scale compared to patients randomized to receive adapalene/BPO (30.5 vs 21.8%; *P*=0.046). The time to treatment success was significantly shorter in the clindamycin/ BPO group compared to those receiving adapalene/BPO (*P*=0.035). There was no statistically significant difference in the mean reduction in total

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			success, percent change in total lesion count, percent change in noninflammatory lesion count, absolute change in lesion counts and time to 50% reduction in lesion counts	lesion count at week 12 between the clindamycin/BPO group and adapalene/BPO group (69.1 vs 67.1%; *P*=0.420). Both treatments effectively reduced inflammatory and noninflammatory lesions over 12 weeks (*P* value not reported). There were no significant differences between the agents with regard to the absolute change in total, inflammatory and noninflammatory lesion counts at any time point. There were no significant differences with respect to the time to achieve a 50% reduction in total, inflammatory and noninflammatory lesion counts (*P* values not reported).
Gold et al[31] Adapalene/BPO 0.1%/2.5% gel QPM plus doxycycline 100 mg QAM vs vehicle QPM plus doxycycline 100 mg QAM	AC, DB, MC, PG, RCT, VC Patients 12 to 35 years of age with severe facial acne vulgaris (IGA score 4) and ≥20 inflammatory lesions, 30 to 120 noninflammatory lesions and ≤3 nodulocystic lesions	N=459 12 weeks	Primary: Percent change in total lesions Secondary: Percent change in inflammatory, noninflammatory lesions and IGA score	Primary: At 12 weeks, the reduction in total lesion count was significant greater with combination therapy with adapalene/BPO and doxycycline compared to doxycycline plus vehicle (64 vs 41%; *P*<0.001). Secondary: Similarly, adapalene/BPO with doxycycline significantly reduced inflammatory lesion counts compared to vehicle plus doxycycline at week 12 (72 vs 48%; *P*<0.001). Noninflammatory lesion counts were also significantly reduced by week 12 with adapalene/BPO plus doxycycline compared to vehicle plus doxycycline (61 vs 40%; *P*<0.001). The treatment success rate (percentage of participants with “clear” or “almost clear” ratings on IGA) was significantly higher with adapalene/BPO plus doxycycline compared to vehicle with doxycycline following 12 weeks of treatment (31.5 vs 8.4%; *P*<0.001).
Thiboutout et al[32] Adapalene/BPO 0.1%/2.5% gel, frequency not specified	DB, MC, PG, RCT, VC Patients ≥12 years of age with 30 to 100	N=517 12 weeks	Primary: Success rates (percent of patients rated “clear” or “almost clear” on the IGA)	Primary: For success rate, the adapalene/BPO combination (27.5%) was more effective compared to adapalene (15.5%; *P*=0.008), BPO (15.4%; *P*=0.003), and vehicle (9.9%; *P*=0.002) at week 12. Results among the treatment groups began to diverge early in favor of adapalene/BPO and continued to separate throughout the course of the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs adapalene 0.1% gel, frequency not specified vs BPO 2.5% gel, frequency not specified vs vehicle gel, frequency not specified	noninflammatory facial lesions, 20 to 50 inflammatory facial lesions and nodules or cysts		and percent lesion reduction (total, inflammatory, and noninflammatory) Secondary: Response rates (percentage of patients who achieved ≥50% reduction in lesion counts [total, inflammatory, and noninflammatory]), IGA, patients' assessment of acne vulgaris improvement, safety and tolerability	The lesion count analysis revealed a greater response for adapalene/BPO therapy relative to the other study groups. At week 12, the combination group was significantly more effective compared to adapalene, BPO and vehicle for changes from baseline in total, inflammatory and noninflammatory lesion counts (*P*<0.001 for all). Statistically significant differences in total lesion count reductions for combination therapy were observed as early as week one with adapalene/BPO (19.7%) compared to adapalene (13%; *P*=0.001) BPO (11.3%; *P*=0.01) and vehicle (7.8%; *P*=0.002). Secondary: The response rates for total, inflammatory and noninflammatory lesions were significantly greater with adapalene/BPO compared to monotherapy with adapalene, BPO and vehicle (*P*<0.05 for all). Differences between adapalene/BPO and all other treatments were statistically significant for full-scale IGA scales at week 12 (*P*<0.001). Patient assessment of acne vulgaris demonstrated a statistically significant improvement for adapalene/BPO compared to monotherapy with BPO (*P*=0.011) and vehicle (*P*<0.001). Differences in patient assessment of acne vulgaris with combination therapy compared to adapalene alone was not statistically significant (*P*=0.062). The safety and tolerability of adapalene/BPO and adapalene monotherapy were comparable (*P* values not reported). Local cutaneous tolerability was good for all treatments, with all mean tolerability scores at each visit and highest post-baseline scores for erythema, dryness, scaling and burning/stinging less than one (mild). A majority of subjects in all of the groups experienced mild or no irritation.
Gold et al[33] Adapalene/BPO 0.1%/2.5% gel QD	AC, DB, MC, PG, RCT, VC Patients ≥12 years of age with an acne	N=1,668 12 weeks	Primary: Success rate, median percentage change in	Primary; At 12 weeks, treatment with adapalene/BPO was associated with a significantly higher success rate compared to treatment with adapalene, BPO and vehicle monotherapy (30.1 vs 19.8, 22.2 and 11.3%, respectively; *P*≤0.006 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs adapalene 0.1% gel QD vs BPO 2.5% gel QD vs vehicle gel QD	vulgaris score of 3 on IGA scale, no cysts and ≤1 nodule		inflammatory, noninflammatory lesions and total lesions, patient severity assessment and safety Secondary: Not reported	From baseline to week 12, patients treated with adapalene/BPO experienced a median 62.1% reduction in inflammatory lesion counts compared to 50.0, 55.6 and 34.3% for patients receiving adapalene, BPO or vehicle monotherapy, respectively (*P*<0.05 for all). Adapalene/BPO significantly reduced the median number of noninflammatory lesions by 53.8% compared to 49.1, 44.1 and 29.5 with adapalene, BPO and vehicle monotherapy, respectively (*P*<0.05 for all). Combination treatment remained significantly more effective compared to monotherapy with regard to the reduction in total lesions at 12 weeks (*P*<0.05 for all). Participant assessment of acne improvement showed that adapalene/BPO was significantly more effective compared to adapalene, BPO and vehicle monotherapy (*P*≤0.008 for all). At week 12, complete, marked, and moderate improvement was reported for 73.5, 65.6, 66.7 and 55.0% of participants in the adapalene/BPO combination group compared to adapalene, BPO and vehicle monotherapy groups, respectively (*P* value not reported). The mean worst scores for tolerability signs and symptoms were all below grade one (mild). The overall safety of adapalene/BPO was comparable with adapalene and BPO monotherapy. The number of participants with at least one adverse event was similar across treatments. A low incidence of adverse events leading to discontinuation was observed: (2.7, 1.0, 1.2 and 0.5% of participants receiving adapalene/BPO, adapalene, BPO and vehicle, respectively. Most treatment-related adverse events were cutaneous and mild to moderate in severity. Dry skin was reported as the most common adverse event associated with adapalene/BPO. Secondary: Not reported
Gollnick et al[34]	AC, DB, MC, RCT, VC	N=1,670	Primary: Success rate,	Primary: The treatment success rate was significantly greater with adapalene/BPO

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Adapalene/BPO 0.1%/2.5% gel QD vs adapalene 0.1% gel QD vs BPO 2.5% gel QD vs vehicle gel QD	Patients ≥12 years of age with acne vulgaris on the face with 20 to 50 inflammatory lesions, 30 to 100 noninflammatory lesions and IGA score 3 (moderate acne)	12 weeks	percentage change in lesion counts, change in IGA, subject assessment of improvement and safety Secondary: Not reported	compared to adapalene, BPO and vehicle monotherapy (37.9 vs 21.8, 26.7 and 17.9%, respectively; *P*<0.001 for all). Patients randomized to receive adapalene/BPO experienced significantly greater reductions in total lesion counts compared to patients randomized to adapalene, BPO and vehicle monotherapy (65.4 vs 52.3, 48.2 and 37.1%, respectively; *P*<0.001 for all). Adapalene/BPO reduced inflammatory lesions by 70.3% compared to adapalene (57.1%), BPO (61.9%) and vehicle monotherapy (45.5%; *P*<0.001 for all). Adapalene/BPO significant reduced noninflammatory lesions by 62.2% compared to adapalene (50.4%), BPO (48.8%) and vehicle monotherapy (36.7%; *P*<0.001 for all). Significantly more patients had IGA assessments of “clear,” “almost clear” or “mild” with adapalene/BPO therapy compared to all three monotherapy treatment groups (*P*<0.001 for all). A significantly greater proportion of patients treated with adapalene/BPO assessed themselves as having “complete improvement” or “marked improvement” compared to those receiving adapalene (*P*=0.006), BPO (*P*<0.001) and vehicle (*P*<0.001). The majority of adverse events were dermatological nature, mild to moderate in severity, occurred early in the study and resolved without residual effects. The difference in related adverse events among the groups was mainly driven by an increase in dry skin: 21.2% for adapalene/BPO, 14.1% for adapalene, 8.4% for BPO and 5.3% for the vehicle. There were no cases of severe dry skin, yet two subjects (0.5%) in the adapalene/BPO group discontinued due to dry skin. No serious adverse were considered treatment-related. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chang et al[35] Tretinoin/clindamycin 0.025%/1.2% gel QD vs vehicle gel QD	AC, DB, MC, RCT, VC Patients ≥18 years of age with papulopustular facial rosacea and 4 to 50 facial inflammatory lesions	N=83 12 weeks	Primary: Change in absolute papule/pustule count on face at week 12, percent change in papule/pustule count at week 12 Secondary: Improvement in rosacea features (flushing, erythema, papules) at week 12, improvements in PGA, subject self assessments and tolerability	Primary: There were no statistically significant improvements from baseline in absolute papule/pustule count for combination treatment (14.4 vs 14.4; *P*=0.63) or placebo (18.7 vs 15.9; *P*=0.15). The percent change from baseline to 12 weeks in absolute papule/pustule count was not statistically significant between the groups (*P*=0.20). Secondary: Primary features of rosacea, assessed by PGA, were significantly improved with combination therapy compared to vehicle therapy for edema (*P*=0.03). No other features were statistically significant between the groups (*P*≥0.05 for all.
Jackson et al[36] Tretinoin/clindamycin 0.025%/1.2% gel QPM vs clindamycin/BPO 1%/5% gel QPM	MC, PG, RCT, SB Patients ≥12 years of age with moderate to severe facial acne vulgaris and 15 to 100 inflammatory lesions, 15 to 100 noninflammatory lesions and ≤2 facial nodules	N=54 16 weeks	Primary: Antimicrobial efficacy, lesion counts, IGA and overall disease severity Secondary: Not reported	Primary: At 16 weeks, there was a significantly greater reduction in *P acnes* count with clindamycin/BPO compared to tretinoin/clindamycin (-1.84 vs -0.78 $\log_{10}$ CFU/cm^2; *P*=0.003). There was a similar reduction from baseline in inflammatory lesions between patients receiving tretinoin/clindamycin compared to patients receiving clindamycin/BPO at 16 weeks (70.7 vs 74.1%; *P* value not reported). The reduction in noninflammatory lesions was similar between the tretinoin/clindamycin and clindamycin/BPO groups (52.8 vs 53.3%; *P* value not reported). The reduction in the total number of inflammatory lesions was similar between patients randomized to receive tretinoin/clindamycin compared to those

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				receiving clindamycin/BPO at 16 weeks (54.3 vs 52.4%; *P* value not reported). The IGA results were similar between tretinoin/clindamycin and clindamycin/BPO with regard to the proportion of patients experiencing improvement in at least one category (62.5 vs 60%; *P* value not reported). Overall disease severity was considered comparable between the two treatment groups with 80.0 and 87.5% of patients showing improvement, respectively (*P* value not reported). Secondary: Not reported
Babayeva et al[37] Tretinoin 0.5% cream plus clindamycin 1% lotion BID vs salicylic acid 3% plus clindamycin 1% lotion BID	AC, RCT, SB Patients 18 to 35 years of age with 10 to 50 inflammatory lesions and 10 to 100 noninflammatory lesions above the mandibular line	N=46 12 weeks	Primary: Percent reduction in total, noninflammatory and inflammatory lesions, time to 50% reduction in lesions, IGA, PGA, AQOL and status corneum hydration values Secondary: Not reported	Primary: There was no statistically significant difference in the noninflammatory lesion count between the two groups at any time throughout the study (*P*>0.05). There was a statistically significant reduction in inflammatory lesions with tretinoin plus clindamycin compared to salicylic acid plus clindamycin at week four (*P*=0.037); however, there were no differences at weeks eight and 12 (*P*>0.05 for both). Treatment with tretinoin plus clindamycin was associated with statistically significant reduction in total lesion counts compared to treatment with salicylic acid plus clindamycin at week four (*P*=0.005); yet, there were no significant differences at week eight and at week 12 (*P*>0.05). More patients treated with tretinoin plus clindamycin achieved a 50% reduction in total lesions compared to patients treated with salicylic acid plus clindamycin at week two (*P*≤0.05); however, there were no statistically significant differences at weeks four, eight or 12. There were no statistically significant differences between the treatment groups with regard to IGA over 12 weeks. With regard to PGA scores, the proportion of patients with ratings of

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				"excellent," "good" and "moderate" improvement were 0, 43.5 and 56.5%, respectively, in the salicylic acid plus clindamycin group and 8.7, 73.9 and 17.4% in the tretinoin plus clindamycin group (*P*=0.014). Both groups significant improved AQOL compared to their respective baseline values (*P*=0.017); however, there was no significant difference between the groups at the end of the study. There were no statistically significant differences between the two treatment groups in stratum corneum hydration at the end of the study. Furthermore, there were no changes compared to baseline for either of the treatment groups. Secondary: Not reported
Jarratt et al[38] Tretinoin/clindamycin 0.025%/1.2% gel QD vs clindamycin gel 1% QD vs tretinoin 0.025% gel QD vs vehicle gel QD	AC, DB, MC, PG, RCT, VC Patients ≥12 years of age with 17 to 40 inflammatory lesions, 20 to 150 noninflammatory lesions, no nodulocystic lesions and an ISGA score ≥2	N=1,649 12 weeks	Primary: Proportion of subjects with a ≥2 grade improvement on ISGA and absolute change in lesion counts (total, inflammatory and noninflammatory) Secondary: Proportion of subjects with SGA scores 0 or 1 at week 12 and the proportion of subjects with ISGA scores 0 or	Primary: A significantly higher proportion of patients treated with tretinoin/clindamycin improved by two grades on ISGA compared to monotherapy with clindamycin, tretinoin or placebo (36.3 vs 26.6, 26.1 and 20.2%, respectively; *P*<0.001 for all). The absolute change in total lesion count was significantly greater for the combination treatment compared to clindamycin (*P*=0.002), tretinoin (*P*=0.033) and vehicle (*P*<0.001) but not compared to clindamycin alone (*P*=0.167). Secondary: At 12 weeks, a greater proportion of patients achieved a SGA score 0 or 1 with combination treatment (67.2%) compared to placebo treatment (52.9%; *P*<0.001); however, there was no statistically significant differences compared to clindamycin treatment (63.6%; *P*=0.263) or tretinoin treatment (66.4%; *P*=0.835). A significantly higher proportion of patients receiving combination therapy achieved an ISGA score 0 or 1 (43.1%) compared to patients receiving clindamycin (36.6%; *P*=0.49), tretinoin (33.8%; *P*=0.001) and vehicle (22.7%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			1 at week 12	*P*<0.001), respectively.
Schlessinger et al[39] Studies I & II: Tretinoin/clindamycin 0.025%/1.2% gel QPM vs clindamycin 1.2% gel QPM vs tretinoin 0.025% gel QPM vs vehicle gel QPM Study III: Tretinoin/clindamycin 0.025%/1.2% gel QPM vs clindamycin phosphate 1.2% gel QPM	AC, DB, MC, PG, RCT, VC Patients ≥12 years of age with 20 to 50 inflammatory lesions, 20 to 100 noninflammatory lesions and two or less nodules	N=2,142 (Studies I & II) N=2,110 (Study III) 12 weeks (All studies)	Primary: Percent change from baseline in inflammatory, noninflammatory and total lesion counts, percentage of patients who were "clear" or "almost clear" or who had a ≥2 grade improvement or more at week 12 as assessed by the EGSS (all studies) Secondary: Safety (all studies)	Primary: Study I & II: The median percent reduction from baseline lesion counts was significantly greater for patients treated with tretinoin/clindamycin compared to clindamycin alone for inflammatory lesions (56.5 vs 48.6%; *P*=0.002), noninflammatory lesions (43.2 vs 28.7%; *P*<0.001) and total lesions (47.1 vs 37.4%; *P*<0.001). The median percent reduction from baseline lesion counts was significantly greater for patients receiving tretinoin/clindamycin compared to patients receiving tretinoin alone for inflammatory lesions (56.5 vs 46.4%; *P*<0.001), noninflammatory lesions (43.2 vs 37.3%; *P*=0.008) and total lesions (47.1 vs 39.6%; *P*<0.0001). Patients receiving treatment with tretinoin/clindamycin experienced a significantly greater reduction from baseline in inflammatory lesions (56.5 vs 32.3%; *P*<0.001), noninflammatory lesions (43.2 vs 23.9%; *P*<0.001) and total lesions (47.1 vs 22.8%; *P*<0.001). The combined results of the "clear" and "almost clear" EGSS demonstrated a significantly higher percentage in patients receiving tretinoin/clindamycin (21.0%) compared to patients treated with clindamycin, tretinoin and vehicle gel (16.0, 14.0 and 7.0%, respectively; *P*<0.001 for all). Study III: The median percent reduction from baseline lesion count for patients treated with tretinoin/clindamycin was significantly greater compared to patients treated with clindamycin alone with regard to inflammatory lesions (61 vs 45%; *P*<0.001), noninflammatory lesions (50 vs 41%; *P*<0.001) and total lesions (54 vs 47%; *P*<0.001). The combined results of the "clear" and "almost clear" EGSS demonstrated a significantly higher percentage in patients receiving tretinoin/clindamycin compared to patients treated with clindamycin alone (41 vs 34%; *P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary (all studies): The percentage of patients reporting at least one adverse event was similar in all groups (*P* values not reported).
Bershad et al[40] Tazarotene 0.1% gel BID vs tazarotene 0.1% gel QD plus vehicle gel QD vs vehicle gel BID	RCT, SB, VC Patients ≥12 years of age with mild to moderate facial acne vulgaris and 10 to 200 noninflammatory lesions, 10 to 60 inflammatory lesions, and ≤3 nodulocystic lesions	N=99 12 weeks	Primary: Reduction in acne vulgaris lesions, treatment success (50 to 100% improvement in global response to treatment) and improvement in overall disease severity Secondary: Adverse events	Primary: Reductions from baseline in noninflammatory lesions in the tazarotene QD and BID groups were significantly greater compared to the vehicle group from week four to week 12 (*P*=0.002 for both tazarotene groups compared to placebo). Reductions from baseline in noninflammatory and inflammatory lesions were significantly greater in the tazarotene QD and BID groups at week 12 compared to the group receiving vehicle BID. Reductions from baseline in noninflammatory lesions were 46.06, 41.13 and 2.48% in the tazarotene BID, QD and vehicle, respectively (*P* values not reported). Reductions from baseline in inflammatory lesions of 38.06, 33.58 and 8.76%, occurred for patients receiving tazarotene BID, QD and vehicle, respectively (*P*=0.01 for both tazarotene groups compared to placebo). Statistically significant differences between the two tazarotene groups and the vehicle group in overall disease severity scores were observed by week eight of treatment. By week 12, statistically significant reductions from baseline in overall disease severity scores were observed in patients receiving tazarotene BID or QD compared to the vehicle group (30.40 and 29.09 vs 2.78%; *P*<0.001). Secondary: The highest mean scores for peeling, erythema, dryness, burning and itching were observed in patients receiving tazarotene twice daily at week two and four. After week four, the occurrence and severity of peeling, erythema, dryness, burning and itching in the active treatment groups did not differ significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				from those in the vehicle group. Significantly more adverse events occurred in patients receiving tazarotene BID or QD compared to the vehicle group (*P*=0.002).
Kircik et al[41] Tretinoin microsphere 0.04% gel pump QPM vs tazarotene 0.05% cream QPM	PG, RCT, SB Patients ≥12 years of age with mild to moderate facial acne vulgaris and 15 to 60 inflammatory lesions, 10 to 100 noninflammatory lesions and ≤2 facial nodules	N=40 12 weeks	Primary: Investigator assessments of noninflammatory, inflammatory and total lesions Secondary: IGA of acne vulgaris severity, patient assessment of pruritus and burning and hyper-pigmentation and safety	Primary: Patients randomized to receive tretinoin experienced a more rapid improvement in papule counts from baseline to week four compared to those receiving tazarotene (-4.41 vs -3.95; *P* value not reported). Conversely, therapy with tazarotene produced a more rapid improvement in pustule counts from baseline to week four compared to the tretinoin group (-0.75 vs -0.47; *P* value not reported). At week 12, the papule count was lower in the tretinoin group compared to the tazarotene group with regard to papule counts (3.13 vs 3.45; *P* value not reported). At week 12, the mean decrease from baseline in pustule count was 1.20 in the tretinoin group and 1.40 in the tazarotene treatment group (*P* value not reported). There was a statistically significant reduction from baseline in noninflammatory lesions at week four in the tretinoin group (64.26%; *P*=0.0039), but not for patients in the tazarotene group (19.17%; *P* value not reported). At week 12, the mean percent change from baseline in noninflammatory lesions was 92.60% in the tretinoin group (*P*=0.0020) and 79.55% in the tazarotene group (*P*=0.0078). There were no intra- or inter-group significant differences observed in the percentage change from baseline in closed comedones (*P* values not reported). At week 12, the mean changes from baseline were -8.87 and -11.60, respectively for the two treatment groups. Secondary: There were no statistically significant differences between groups at any time point with regard to IGA. By week four, the mean IGA grade had decreased by -0.18 and -0.05 in the tretinoin and tazarotene groups, with 29.4 and 20.0% of the tretinoin and tazarotene groups achieving at least a one-point improvement in IGA grade. By week 12, change from baseline in IGA grade

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was -0.73 in the tretinoin group and -0.95 in the tazarotene group. At week four, mean dryness scores were significantly increased in tazarotene group (*P*=0.039). By week four, there was an increase from baseline in mean erythema scores for both groups; however, this was not statistically significant. Patients in both groups reported a one to two point decrease in mean erythema and dryness scores by week 12 (*P* values not reported). After four weeks, skin peeling was increased by two points from baseline in 25% of the tazarotene group and 0% in the tretinoin group (*P*=0.0498). By week 12, none of the tazarotene group had shown a decrease in peeling and 13.3% of the tretinoin group had experienced a one-point increase. At week 12, no pruritus was reported in the tretinoin group compared to 10% of the tazarotene group who reported a decrease of at least one point. In addition, 10% of the tazarotene group reported an increase of at least one point, and 5% reported an increase of at least two points. At week 12, no patients receiving tretinoin experienced a two-point or greater decrease in skin burning scores and 6.7% had a least a one-point decrease in burning scores. For the tazarotene group, 10% of patients had at least a one-point increase and 5% had at least a two-point increase in burning from baseline. The percentage of patients that experienced an adverse was 55.6% for the tretinoin group and 45% for the tazarotene group (*P* value not reported).
Berger et al[42] Tretinoin 0.04% gel microsphere QPM vs tretinoin 0.1% gel microsphere QPM	DB, MC, PG, RCT Patients 12 to 40 years of age with mild to moderate acne vulgaris with (20 to 150 total lesions consisting of 10 to 100 comedones and 10 to 50 inflammatory	N=156 12 weeks	Primary: Acne vulgaris lesion counts, IGA of treatment response and patient's self-assessment of the response to treatment relative to baseline	Primary: Both treatment groups were associated with reductions in total number of acne vulgaris lesions compared to baseline; however, they did not differ significantly from one another at any time point. At week 12, the least squares mean percent reduction in total lesion counts from baseline was 39.4% for tretinoin 0.04% and 34.4% for tretinoin 0.1% (*P*=NS). In addition, the absolute reduction from baseline in total lesion count was not significantly different between the two groups (18.1 and 16.4, respectively; *P* value not reported). Patients receiving tretinoin 0.1% experienced a greater reduction in inflammatory lesions at week two compared to the tretinoin 0.04% treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	lesions with ≤2 nodules)		Secondary: Tolerability	group (14.8 vs 6.0%; *P*<0.048). No statistically significant differences in the number of inflammatory or noninflammatory lesions existed between treatment groups at any other time point. No statistically significant difference was observed between the formulations with regard to the investigator's assessment of treatment (*P* value not reported). At week 12, a response of "excellent," "good" or "fair" was recorded for 79.5% of patients treated with tretinoin 0.04% and 73.1% of patients treated with tretinoin 0.1%. No statistically significant difference was observed between the two tretinoin formulations in terms of the patients' self-assessment of the treatment response (*P* value not reported). At week 12, 85.9% of patients in each group reported their acne "much improved" or "somewhat improved." Secondary: At least one adverse event was reported by 37.2 and 41.0% of patients receiving tretinoin 0.04% and 0.1% gel. The most common adverse events included erythema, peeling, dryness, burning/stinging, and itching. At week 12, the proportion of patients with worsening erythema was 25.6 and 12.9% for tretinoin 0.04% and 0.1% (*P*=0.035). Increases in dryness occurred most commonly at week two, with worsening observed in 23.1 and 42.3% of the tretinoin 0.04% and 0.1% groups. There were no significant differences in peeling, burning/stinging and itching between the two groups at any study week.
Lucky et al[43] Tretinoin 0.025% cream (Avita®) QPM vs tretinoin 0.025% cream (Retin-A®) QPM	DB, MC, PG, VC Patients with mild to moderate facial acne vulgaris and ≥ 30 noninflammatory lesions, a minimum of 10 inflammatory lesions, ≤4	N=271 12 weeks	Primary: Objective lesion counts and investigators' global evaluations of improvement Secondary: Skin irritation and adverse events	Primary: At days 56 and 84, the total lesion count in patients receiving either active treatment were significantly lower compared to patients in the vehicle group (*P*<0.05). The mean percent decrease in total lesion count was significantly greater for both treatment groups compared to the vehicle group at days 38, 56 and 84 (*P*<0.05). The two tretinoin treatment groups were not significantly different from one another with regard to improvements in total lesion count or mean percent reduction in total lesions at any time point. At days 56 and 84, the noninflammatory lesion counts in both of the active

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vs vehicle	nodulocystic lesions, and a total lesion count not surpassing 200			treatment groups were significantly lower compared to the vehicle group (*P*<0.05). The two active treatment groups were not statistically different from one another at any time for noninflammatory lesion counts or mean percent decrease in total noninflammatory lesions. At day 84, there was a statistically significant reduction in inflammatory lesions in patients applying Retin-A® cream compared to patients receiving the vehicle (*P*<0.05). Global evaluation scores for patients in the Ativa® group were significantly better compared to the vehicle group at all assessments on and after day 14 (*P*<0.05). Patients in the Retin-A® group experienced significantly improved global evaluation scores compared to the vehicle group at days 56 and 84 (*P*<0.05). The active treatment groups were not statistically significantly different from one another at any time. Secondary: The incidence of cutaneous adverse events generally peaked by day 14 of treatment. The most frequent events included eruption, dry skin, and exfoliation, with most rated as either "mild" or "moderate" in severity. Patients' subjective assessments of burning, itching, and tightness peaked at day 14 in patients receiving active treatment and then gradually cleared over the course of the study. Noncutaneous adverse events included flu-like syndrome, headaches and pain.
Draelos et al[44] Tretinoin 0.025% cream QHS plus BPO 5.5% BID vs Clindamycin/BPO 1%/5% gel BID plus tretinoin 0.025% cream QHS	AC, DB, MC, RCT Patients 18 to 50 years of age with mild to moderate acne	N=66 12 weeks	Primary: Lesion counts, tolerability, skin appearance and skin irritation Secondary: Not reported	Primary: Both treatment regimens were associated with a statistically significant reduction in noninflammatory and inflammatory lesion counts at weeks four, eight, 12 and week 16 compared to baseline (*P*<0.05 for all). The clindamycin/BPO plus tretinoin demonstrated a statistically significant reduction in open comedones at week two (*P*<0.05) that was not observed with tretinoin plus BPO. Treatment with tretinoin plus BPO demonstrated a statistically significant reduction in pustules at week two (*P*<0.05) that was not observed with clindamycin/BPO plus tretinoin treatment. Parity was established between treatments from week four onward. Treatment with tretinoin plus BPO significantly increased investigator-assessed erythema at week two compared to baseline (*P*=0.042); however,

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				this was not observed with clindamycin/BPO plus tretinoin treatment. Compared to baseline, a statistically significant increase in dryness and peeling was noted in both treatment groups (dryness week two; *P*=0.004 and *P*<0.001, respectively; peeling at week two; *P*=0.001 and *P*=0.002, respectively; and week four; *P*=0.039 and *P*=0.013, respectively). By week 12, dryness and peeling had resolved when assessed by the investigator. No increase in erythema was present by week 12. Both treatment groups demonstrated a statistically significant increase in stinging (*P*<0.001 for both), tingling (*P*≤0.007 for both), itching (*P*<0.05 for both), and burning (*P*<0.001 for both) at week two compared to baseline. Participant-assessed irritation had largely resolved by week eight in both groups. Secondary: Not reported
Plaque Psoriasis				
Weinstein et al[45] Tazarotene 0.1% gel QD vs tazarotene 0.05% gel QD vs vehicle gel QD	DB, MC, PG, RCT, VC Patients with stable plaque psoriasis on the trunk, legs, or arms that did not exceed 20% of total BSA with two target lesions of at least moderate severity for plaque elevation (2 on a scale of 0 to 4) with a minimum diameter of 2 cm on the elbow or knee and the trunk	N=324 12 weeks	Primary: Degree of plaque elevation, scaling and erythema, treatment success rates and time to initial treatment success Secondary: Cosmetic acceptability, amount of emollient used and adverse events	Primary: During most weeks, tazarotene 0.1% and 0.05% gel were significantly more effective compared to the vehicle gel in reducing the severity of signs and symptoms of target lesions (*P*<0.05 for both). Treatment with both strengths of tazarotene resulted in significantly greater decreases in plaque elevation at all treatment visits, improved scaling at all treatment visits beginning with week two, and improved erythema at most treatment visits during the second half of the treatment period (*P*<0.05 for all). Both treatment groups experienced significantly greater decreases in symptom scores for trunk or limb target lesions as compared to vehicle for all treatment visits beginning with week one (*P*<0.05) and for signs and symptoms for knee or elbow target lesions beginning with week two (*P*<0.05). Differences in treatment success rates were noted between the 0.1% and 0.05% gels. Tazarotene 0.1% resulted in significantly greater success rates compared to vehicle at weeks two through 12 for target lesions and all lesions

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or limbs			(*P*<0.05). Tazarotene 0.05% produced significantly higher success rates compared to vehicle beginning at week two for target lesions on the trunk or limbs and all lesions, and at week four for those on the knees and elbows (*P*<0.05 for all). Treatment success rates for patients treated with tazarotene 0.1% and 0.05% were 40 to 52%, respectively at week 12 for target lesions and 28 to 40%, respectively, for all lesions at week 24 (*P* values not reported). Initial treatment success occurred significantly faster in patients treated with tazarotene 0.1% (*P*<0.001) and 0.05% gel (*P*<0.05) compared to the vehicle treatment group. Secondary: The assigned treatment was rated cosmetically acceptable by approximately 85% of patients in each of the three treatment groups (*P* value not reported). There were no statistically significant differences among treatment groups with regard to the amount of emollient used (*P* value not reported). Emollient was used by 97 to 99% of patients, an average of one to two times daily. Treatment-related adverse events consisted predominantly of mild to moderate local irritation including pruritus, burning or erythema.
Weinstein et al[46] Tazarotene 0.05% cream QPM vs tazarotene 0.1% cream QPM vs vehicle cream QPM	2 DB, MC, PG, RCT, VC Patients ≥18 years of age with psoriasis involving at least 2% of the total BSA with baseline overall assessment of all lesions of at least 3 on a 6-point scale	N=1,303 (Study A=668, Study B=635) 12 weeks	Primary: Clinical success (based on an overall lesion assessment), plaque elevation, scaling, erythema, and global response to treatment Secondary: Safety	Primary: In Study A, the success rate with tazarotene 0.1% cream was significantly higher compared to the vehicle cream at weeks one, four, eight and 12 (*P*≤0.016), which was maintained throughout the 12-week post-treatment period (*P*≤0.029). Success rates with tazarotene 0.05% cream were significantly higher compared to the vehicle cream from weeks four to 24 (*P*≤0.034). Similar results were observed in Study B. Differences in clinical success rates between tazarotene 0.1% and 0.05% were not statistically significant. At the end of the treatment period (week 12), the success rates were 39.4% (Study A) and 50.7% (Study B) for tazarotene 0.1% and 41.7% (Study A) and 40.5% (Study B) for tazarotene 0.05%, and 24.5% (Study A) and 26.2% (Study B) for vehicle (*P* values not reported). In both studies, treatment with tazarotene 0.1% and 0.05% creams

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				significantly reduced plaque elevation and improved scaling of psoriatic lesions over the vehicle cream (*P*≤0.05). Erythema was less responsive to treatment with tazarotene. The treatment success rate, defined as the percentage of patients achieving a moderate or better global response to treatment (≥50% improvement) was significantly higher with tazarotene 0.1% compared to vehicle at all time points (except one) in both studies (*P*≤0.020). Differences in treatment success rates between tazarotene 0.1% and 0.05% creams were generally not statistically significant. By week 12, treatment success rates were 48.9% (Study A) and 58.8% (Study B) with tazarotene 0.1% cream and 42.7% (Study A) and 47.6% (Study B) with tazarotene 0.05% cream and 30.1% and 36.9% with vehicle (*P* values not reported). Secondary: Significantly more treatment-related adverse events were reported in the tazarotene groups compared to the vehicle group in both studies (*P* value not reported). The most frequently reported adverse events were skin-associated and included signs and symptoms of local skin irritation such as pruritus, erythema and burning sensation. Most adverse events were of mild to moderate severity.
Lebwohl et al[47] Tazarotene 0.1% gel plus fluocinolone acetonide 0.01% (low-potency) cream QD vs tazarotene 0.1% gel plus mometasone furoate 0.1% (mid-potency) cream QD	MC, RCT, SB Patients ≥21 years of age with stable, mild to moderate plaque psoriasis not exceeding 20% BSA involvement with overall baseline plaque elevation scores ≥4 on a 9-point scale	N=300 12 weeks	Primary: Plaque elevation, global response, and time to initial treatment success Secondary: Scaling, erythema, and overall lesional severity, and adverse events	Primary: Mean decreases from baseline in plaque elevation with all four treatment groups were statistically significant at all study visits (weeks two, four, eight and 12) as well as four weeks after treatment ended (*P* values not reported). In addition, tazarotene in combination with a mid- or high-potency corticosteroid demonstrated a trend toward greater improvement in plaque elevation compared to tazarotene plus placebo (*P* values not reported). Treatment success rates (percent of patients with a moderate response, a marked response, almost cleared, or completely cleared [about 50% improvement to completely cleared]) at week two were 42, 49, 73 and 58% in the tazarotene 0.1% plus placebo group, tazarotene 0.1% plus low-potency corticosteroid group, tazarotene 0.1% plus mid-potency corticosteroid group and the tazarotene 0.1% plus high-potency corticosteroid group. By week 12,

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vs tazarotene 0.1% gel plus fluocinonide 0.05% (high-potency) cream QD vs tazarotene 0.1% gel plus placebo cream QD The assigned corticosteroids or the placebo cream was applied QAM, and tazarotene 0.1% gel was applied QPM.				treatment success rates increased for all four groups (80, 79, 91 and 95%, respectively; *P* values not reported). Specifically, tazarotene 0.1% gel in combination with a mid- or high-potency corticosteroid produced significantly higher treatment success rates compared to tazarotene with placebo cream at weeks two, eight and 12 (all *P*<0.05). The median time to initial treatment success was two weeks for tazarotene plus mid-potency corticosteroid and three weeks for tazarotene plus high-potency corticosteroid. Both of these treatment regimens reached initial treatment success significantly faster than tazarotene plus placebo (*P* value not reported). The median time to initial treatment success for tazarotene plus placebo and a low-potency corticosteroid was four weeks. Secondary: All tazarotene combinations showed a statistically significant decreases in scaling and erythema and produced significant decreases in overall lesional severity from baseline at all study visits (*P*<0.05). Tazarotene 0.1% in combination with mid- to high-potency corticosteroids was significantly more effective at improving symptoms compared to tazarotene plus placebo at every study visit during the treatment period (weeks two to 12) (*P*<0.05). Tazarotene plus low-potency corticosteroid was significantly more effective than tazarotene plus placebo at week two (*P*<0.05). Tazarotene 0.1% in combination with a mid-potency corticosteroid significantly improved erythema at weeks two and four compared to tazarotene plus placebo (*P*<0.05). Tazarotene plus a high-potency corticosteroid was significantly more effective compared to tazarotene plus placebo at reducing erythema at week four (*P*<0.05). Tazarotene 0.1% in combination with a mid-potency corticosteroid was significantly more effective at reducing overall lesional severity at all visits compared to tazarotene plus placebo and tazarotene plus low-potency corticosteroid (*P*<0.05). Tazarotene 0.1% gel plus a high-potency

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				corticosteroid was significantly more effective than tazarotene plus placebo at week 12 ($P<0.05$). The incidence of treatment-related adverse events did not appear to increase substantially over the treatment period (weeks two to 12). Reported signs and symptoms of local irritation caused by tazarotene were consistent with what was expected of topical retinoids and included pruritus, erythema and burning.
Guenther et al[48] Tazarotene 0.1% gel QHS plus mometasone 0.1% cream QAM vs calcipotriene 0.005% BID	MC, PG, SB Adult patients with chronic, stable plaque psoriasis affecting 5 to 20% of total BSA	N=120 8 weeks of treatment with 12 week post-treatment follow-up phase	Primary: Physician-rated measures of efficacy including global improvement, plaque elevation, scaling, erythema, and percentage of BSA involvement; patient-rated assessments including efficacy of study treatment compared to previous therapies, comfort of treated skin, outlook for long-term control, and overall impression of treatment Secondary: Not reported	Primary: *Physician-rated assessments:* After two weeks of treatment, the proportion of patients achieving marked improvement (≥75% global improvement) was significantly higher in the tazarotene plus corticosteroid group compared to the calcipotriene group (45 vs 25% respectively; $P\leq0.05$). There was no statistically significant difference in the proportion of patients achieving complete or almost complete clearance between the two treatment groups at any time (*P* value not reported). For trunk lesions, the mean percentage reduction in plaque elevation was not significantly different between groups during the treatment phase, but was significantly higher in the tazarotene plus corticosteroid group at the end of treatment and week four of the post-treatment phase ($P\leq0.05$). For upper or lower limb lesions, no significant between-group differences in plaque elevations were observed at any point (*P* value not reported). For trunk lesions, the mean percent reduction in scaling was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at week four of the post-treatment phase ($P\leq0.05$). For upper or lower limb lesions, no significant between-group differences in scaling were observed at any point (*P* value not reported). For trunk lesions, the mean percent reduction in erythema was significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				greater in the tazarotene plus corticosteroid group compared to the calcipotriene group at week four of treatment and at the end of treatment ($P \leq 0.05$). For upper or lower limb lesions, no significant between-group differences in erythema were observed at any point (*P* value not reported). For trunk lesions, the mean percent reduction in BSA involvement was significantly greater in the tazarotene plus corticosteroid group compared to the calcipotriene group after two and four weeks of treatment ($P \leq 0.01$); however, no statistically significant differences were observed between groups in the post-treatment phase (*P* value not reported). For upper limb lesions, the tazarotene plus corticosteroid group experienced a significantly greater reduction in percentage of BSA involvement after two and four weeks of treatment compared to the calcipotriene group ($P \leq 0.05$ at two weeks and $P \leq 0.01$ at four weeks). No statistically significant differences were observed during the post-treatment phase between groups (*P* value not reported). For lower limb lesions, significance was only achieved for patients admitted to the post-treatment phase and only at the end-of-treatment visit ($P \leq 0.001$). *Patient-rated assessments:* A significantly greater proportion of patients rated treatment “more effective” or “much more effective” than previously-tried therapies in the tazarotene plus corticosteroid group compared to the calcipotriene group ($P \leq 0.05$). At the end of treatment, 16% of patients in the tazarotene plus corticosteroid group and 9% of patients in the calcipotriene group rated the comfort of their therapy as “somewhat comfortable,” 42 and 51% of patients rated it as “comfortable” and 27 and 25% of patients rated it as “very comfortable,” respectively (*P* value not reported). No significant between-group differences were observed in the proportion of patients who rated their outlook for long-term control as very promising or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				extremely promising at the end of the 12-week post-treatment phase (*P* values not reported). Overall impression of treatment favored the tazarotene plus corticosteroid regimen compared to the calcipotriene regimen (*P* value not reported); however, the percentages of patients who rated their impression of therapy as "favorable" or "highly favorable" did not differ between groups, with the exception of the 12-week post-treatment visit ($P \leq 0.05$). Secondary: Not reported
Tzung et al[49] Tazarotene 0.1% gel QHS plus petrolatum QAM vs calcipotriol 0.005% ointment BID Both treatments used in each patient on opposite sides of body.	CS, RCT, SB Patients 12 to 80 years of age with a diagnosis of psoriasis and a total of 50 target lesion pairs	N=19 12 weeks of treatment and 4 weeks of post-treatment evaluation	Primary: Severity scores for scaling, plaque elevation, erythema, overall lesion severity and patient self-reported efficacy Secondary: Not reported	Primary: At the end of the 12-week treatment period, tazarotene plus petrolatum was as effective as calcipotriol reducing scaling, plaque elevation, erythema and overall lesion severity (*P* values not reported). Erythema worsened with tazarotene plus petrolatum in week one and reduction of erythema was first observed in week two. The difference in erythema between treatments was not significant after eight weeks (*P* value not reported). Lesion severity scores worsened with both treatments during the post-treatment phase, though tazarotene plus petrolatum maintained the therapeutic effect significantly better in terms of scaling, plaque elevation, erythema and overall severity at week 16 ($P \leq 0.001$ for all). Patient-assessed success rates were 74% with tazarotene plus petrolatum and 85% with calcipotriol, though this difference was not statistically significant ($P \geq 0.46$). Secondary: Not reported
Schiener et al[50] Tazarotene 0.05% gel	CS, SB Patients with	N=10 Minimum	Primary: PASI	Primary: PASI scores decreased with both treatments and there was no statistically significant difference between treatment regimens (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD plus total body narrowband UVB irradiation QD four times per week vs calcipotriene 0.005% ointment QD plus total body narrowband UVB irradiation QD four times per week. Both treatments used in each patient on opposite sides of body.	widespread symmetrical psoriasis	duration of 4 weeks	Secondary: Not reported	Complete clearance of the skin was observed after a median of 19 treatment sessions for both treatment regimens. Secondary: Not reported
Bowman et al[51] Tazarotene 0.05% gel plus calcipotriene 0.005% ointment QAM and calcipotriene ointment QHS vs clobetasol 0.05% ointment BID Both treatments used in each patient on opposite sides of body.	CS, OL, PRO Patients ≥18 years of age with psoriasis that was chronically stable for at least one month prior to screening with at least one bilateral mirror image plaque on the trunk, arms or legs	N=15 (28 lesion pairs) 2 weeks of treatment, 4 weeks of post-treatment follow-up	Primary: Severity scores for erythema, scaling, and plaque elevation Secondary: Not reported	Primary: At the end of the two week treatment period, the tazarotene plus calcipotriene and clobetasol treatment groups demonstrated marked reductions in scaling, plaque elevation and overall lesional severity (P<0.0001 for all). There were no statistically significant differences between the tazarotene plus calcipotriene and clobetasol groups in the reduction in scaling (P=0.93), plaque elevation (P=0.76) and overall lesional severity scores (P=0.29). Erythema improved significantly more with clobetasol during the treatment period (P<0.01) but there was no significant difference between the treatments during the post-treatment period (P=0.20). Lesional severity scores worsened with both groups during the post-treatment phase. Plaque elevation returned more rapidly on the tazarotene plus calcipotriene treated area (P<0.01), but scaling, erythema and overall lesional severity were not significantly different between the two treatments (P>0.05). No treatment-related adverse events were reported on the clobetasol treated area. Adverse effects with tazarotene plus calcipotriene were mild and did not result in alteration of the treatment schedule for any patient.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, QAM=once daily in morning, QD=once daily, QHS=once daily at bedtime, QPM=once daily in evening
Study abbreviations: AC=active-controlled, CS=comparative study, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, SB=single-blind, VC=vehicle-controlled
Miscellaneous abbreviations: AQOL=acne quality of life, BPO=benzoyl peroxide, BSA=body surface area, CFU=colony-forming units, EGSS=evaluator global severity score, IGA=investigator global assessment, ISGA=investigator's static global assessment, KAGS=Korean acne grading system, OLA=overall lesion assessment, PASI=psoriasis area and severity index, PGA=physician global assessment, PIH=post inflammatory hyperpigmentation, UVB=ultraviolet B

Special Populations

Table 5. Special Populations[3-13]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Adapalene	Safety and efficacy in elderly patients have not been established. Approved for use in children ≥12 years of age.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use caution.
Tazarotene	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children ≥12 years of age.	No dosage adjustment required.	No dosage adjustment required.	X	Unknown; use caution.
Tretinoin	Safety and efficacy in elderly patients have not been established. Safety and efficacy of Atralin® in children <10 years of age have not been established. Safety and efficacy of Retin-A® and Retin-A Micro® in children <12 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use caution.
Combination Products					
Adapalene/ benzoyl peroxide	Safety and efficacy in elderly patients have not been established. Approved for use in children ≥12 years of age.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use caution.
Tretinoin/ clindamycin phosphate	Safety and efficacy in elderly patients have not been established. Approved for use in children ≥12 years of age.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use caution.

Adverse Drug Events

Table 6. Adverse Drug Events Reported (%) for the Treatment of Acne Vulgaris[3-13]

Adverse Event(s)	Single-Entity Agents				Combination Products	
	Adapalene (%)		Tazarotene Cream and Gel (%)	Tretinoin Cream and Gel (%)	Adapalene/ Benzoyl Peroxide (%)	Tretinoin/ Clindamycin Phosphate (%)
	Cream	Gel				
Dermatological						
Acne flares	<1	<1	-	1 to 10	-	-
Blistering	-	-	-	1 to 10	✔	-
Burning	<24	0.9 to 28.5	10 to 30	-	3 to 10	4
Dermatitis	<1	-	-	-	-	-
Contact dermatitis	<1	<1	-	-	3	-
Desquamation	-	1.6	10 to 30	-	-	-
Dryness	51	<44.7	-	>10	2 to 10	-
Dry skin	<42	7.7 to 14.0	10 to 30	-	7	1
Eczema	<1	<1	-	-	✔	-
Eyelid edema	<1	<1	-	-	✔	-
Erythema	<38	0.4 to 26.1	10 to 30	>10	1 to 8	26
Fissuring	-	-	1 to 10	-	-	-
Hyperpigmentation	-	-	1 to 10	-	-	-
Hypopigmentation	-	-	1 to 10	-	-	-
Irritation	-	1.0 to 1.5	1 to 10	-	1 to 2	-
Itching	-	-	-	-	-	4
Localized edema	-	-	1 to 10	1 to 10	-	-
Photosensitivity	-	-	1 to 10	-	-	-
Pruritus	<21	<1	10 to 30	>10	✔	-
Rash	<1	<1	-	-	✔	-
Scaling	<35	1.2 to 43.5	-	>10	1 to 9	17
Skin discoloration	<1	<1	1 to 10	-	✔	-
Skin discomfort	1	0.9 to 5.8	-	-	-	-
Skin pain	-	-	1 to 10	-	✔	-
Stinging	<24	3.6 to 28.5	10 to 30	1 to 10	2 to 7	2
Sun burn	2	0.6 to 1.2	-	-	✔	-
Other						
Cough	-	-	-	-	-	1
Conjunctivitis	<1	<1	-	-	✔	-
Facial swelling	-	-	-	-	✔	-
Nasopharyngitis	-	-	-	-	-	27
Pharyngolaryngeal pain	-	-	-	-	-	2
Sinusitis	-	-	-	-	-	1
Throat tightening	-	-	-	-	✔	-

Table 7. Adverse Drug Events Reported (%) for the Treatment of Psoriasis[6,7]

Adverse Event(s)	Tazarotene (%)
Bleeding	1 to 10
Burning/stinging	10 to 30
Desquamation	10 to 10
Dry skin	10 to 10
Erythema	10 to 30
Fissuring	1 to 10
Irritation	10 to 30
Irritation contact dermatitis	1 to 10
Pruritus	10 to 30
Rash	1 to 10
Skin inflammation	1 to 10
Skin pain	10 to 30
Worsening of psoriasis	10 to 30

Contraindications

Table 8. Contraindications[3-13]

Contraindication	Single-Entity Agents				Combination Products	
	Adapalene (%)		Tazarotene Cream and Gel (%)	Tretinoin Cream and Gel (%)	Adapalene/ Benzoyl Peroxide (%)	Tretinoin/ Clindamycin Phosphate (%)
	Cream	Gel				
Hypersensitivity to the active ingredient or any of the components in the vehicle	✔	✔	✔	✔	-	-
Hypersensitivity to erythromycin, clindamycin, benzoyl peroxide, sulfur or any components of the product	-	-	-	-	✔	-
Patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis	-	-	-	-	-	✔
Pregnant women; may cause fetal harm	-	-	✔	-	-	-
Women who may become pregnant	-	-	✔	-	-	-

Warnings/Precautions

Table 9. Warnings and Precautions[3-13]

Warning/Precaution	Single-Entity Agents				Combination Products	
	Adapalene (%)		Tazarotene Cream and Gel (%)	Tretinoin Cream and Gel (%)	Adapalene/ Benzoyl Peroxide (%)	Tretinoin/ Clindamycin Phosphate (%)
	Cream	Gel				
Avoid concomitant use of topical products that may be potentially irritating to	-	-	-	-	✔	-

Warning/Precaution	Single-Entity Agents				Combination Products	
	Adapalene (%)		Tazarotene Cream and Gel (%)	Tretinoin Cream and Gel (%)	Adapalene/ Benzoyl Peroxide (%)	Tretinoin/ Clindamycin Phosphate (%)
	Cream	Gel				
the skin						
Cutaneous signs and symptoms of treatment may occur (e.g., erythema, dryness)	✔	✔	-	-	✔	-
Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin	-	-	-	-	-	✔
External use only; avoid contact with eyes, lips and mucous membranes	✔	✔	✔	✔	-	✔
Photosensitizers; administer with caution if patient is concomitantly receiving drugs known to be photosensitizers	-	-	-	✔	-	-
Product should not be applied to cuts, abrasions, eczematous or sunburned skin	✔	✔	-	-	✔	-
Sunburn; use should be avoided until fully recovered	✔	-	-	✔	✔	-
Sunscreen; use of SPF (minimum of 15) and protective clothing should be utilized with this agent	-	-	✔	✔	✔	✔
Systemic absorption of clindamycin has been demonstrated following topical use of this product	-	-	-	-	-	✔
Ultraviolet light and environmental exposure should be avoided	✔	-	✔	✔	✔	✔
Use of waxing as a depilatory method should be avoided	✔	✔	-	-	✔	-
Use on eczematous skin may cause severe irritation	-	-	✔	-	-	-
Women of child-bearing age; warn of potential risk and use; obtain negative pregnancy test two weeks prior to initiating therapy	-	-	✔	-	-	-

Warning/Precaution	Single-Entity Agents				Combination Products	
	Adapalene (%)		Tazarotene Cream and Gel (%)	Tretinoin Cream and Gel (%)	Adapalene/ Benzoyl Peroxide (%)	Tretinoin/ Clindamycin Phosphate (%)
	Cream	Gel				
and encourage use of adequate birth-control measures						

Drug Interactions

Concomitant dermatologic medications and cosmetics that have strong drying effects should be avoided with topical retinoids.

Table 10. Drug Interactions[3-13]

Generic Name	Interacting Medication or Disease	Potential Result
Tretinoin	Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones)	Concurrent use of topical tretinoin and drugs known to be photosensitizers may augment the possibility of phototoxicity.
Tretinoin/ clindamycin phosphate	Erythromycin	Concurrent use of erythromycin and clindamycin may result in antagonistic effects and/or an increased risk of cardiotoxicity.
Tretinoin/ clindamycin phosphate	Neuromuscular-blocking agents	Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular-blocking agents.

Dosage and Administration

Table 11. Dosing and Administration[3-13]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Adapalene	Topical treatment of acne vulgaris in patients >12 years of age: Cream, gel: apply a thin film to affected area once nightly Lotion: apply a thin film to affected area once daily	Topical treatment of acne vulgaris in patients >12 years of age: Cream, gel: apply a thin film to affected area once nightly Lotion: apply a thin film to affected area once daily	Cream: 0.1% Gel: 0.1% 0.3% Lotion: 0.1%
Tazarotene	Topical treatment of acne vulgaris: Cream (0.1%), gel (0.1%): apply a thin film to affected area once nightly Topical treatment of plaque psoriasis: Cream, gel: initial, 0.05% cream or gel applied thinly to affected area once nightly; maintenance 0.05% or 0.1% applied thinly to affected area	Topical treatment of acne vulgaris in children ≥12 years of age: Cream (0.1%), gel (0.1%): apply a thin film to affected area once nightly Topical treatment of plaque psoriasis: in children ≥12 years of age: Cream, gel: initial, 0.05% cream or gel applied thinly to affected area once nightly; maintenance 0.05% or 0.1% applied thinly to affected area once nightly	Cream: 0.05% 0.1% Gel: 0.05% 0.1%

Generic Name	Adult Dose	Pediatric Dose	Availability
	once nightly		
Tretinoin	Topical treatment of acne vulgaris: Cream, gel: apply a thin film to affected area once nightly	Topical treatment of acne vulgaris in children ≥10 years of age (Atralin®) or ≥12 years of age (Retin-A Micro®): Cream, gel: apply a thin film to affected area once nightly	Cream: 0.025% 0.038% 0.05% 0.1% Gel: 0.01% 0.025% 0.04% 0.05% 0.1%
Combination Products			
Adapalene/ benzoyl peroxide	Topical treatment of acne vulgaris in patients >12 years of age: Gel: apply a thin film to affected area once daily	Topical treatment of acne vulgaris in patients >12 years of age: Gel: apply a thin film to affected area once nightly	Gel: 0.1/2.5%
Tretinoin/ clindamycin phosphate	Topical treatment of acne vulgaris in patients >12 years of age: Gel: apply a thin film to affected area once nightly	Topical treatment of acne vulgaris in patients >12 years of age: Gel: apply a thin film to affected area once nightly	Gel: 1.2/0.025%

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Dermatology: **New Insights into the Management of Acne: An Update from the Global Alliance to Improve Outcomes in Acne Group (2009)**[2]	• Acne vulgaris should be managed early and aggressively as a chronic disease to limit scarring; the disease is self-limiting in only 60% of cases. • Oral isotretinoin, the most effective acne vulgaris treatment developed to date, is administered during a 20-week period and sometimes must be given in repeated courses. • The combination of a topical retinoid and antimicrobial agent remains the preferred treatment approach for the majority of patients with acne vulgaris, especially in the presence of inflammatory lesions. • Due to the risk of bacterial resistance, antibiotics should be used for the shortest duration and should not be used as monotherapy but in combination with benzoyl peroxide. • Topical antibiotics combined with benzoyl peroxide and a topical retinoid may be used in mild to moderate acne vulgaris; oral antibiotics are recommended for moderate to moderately severe acne vulgaris. • Topical retinoids alone or in combination with benzoyl peroxide are recommended for the maintenance of acne vulgaris. • Long-term antibiotic use may be required in the rare cases in which the patient experiences acne vulgaris flares when oral antibiotics are discontinued. Global Alliance Acne Vulgaris Treatment Algorithm • For mild acne vulgaris (comedonal), treatment with a topical retinoid is considered first line; treatment with an alternative topical retinoid or azelaic

Clinical Guideline	Recommendations
	acid or salicylic acid are considered alternatives. • For mild acne vulgaris (mixed and papular/pustular), treatment with a topical retinoid and a topical antimicrobial is considered first line; treatment with alternative topical retinoid and alternative topical antimicrobial, or azelaic acid are considered alternatives. • For moderate acne vulgaris (mixed and papular/pustular), treatment with oral antibiotic and a topical retinoid with or without benzoyl peroxide is considered first line; treatment with an alternative oral antibiotic and alternative topical retinoid with or without benzoyl peroxide are considered alternatives. • For moderate acne vulgaris (nodular), treatment with an oral antibiotic and a topical retinoid and benzoyl peroxide is considered first line; treatment with oral isotretinoin or alternate oral antibiotic and an alternate topical retinoid (with or without) benzoyl peroxide/azelaic acid are considered alternatives. • For severe acne (nodular/conglobate), treatment with oral isotretinoin is considered first line; treatment with high dose oral antibiotic and a topical retinoid and benzoyl peroxide are considered alternative. • For maintenance therapy (mild to severe acne vulgaris), treatment with a topical retinoid with or without benzoyl peroxide is considered first line.
American Academy of Dermatology: **Guidelines of Care for Acne Vulgaris Management (2007)**[15]	<u>Standard of care</u> • Topical therapy is the standard of care in acne vulgaris treatment. • Systemic antibiotics are used in moderate to severe acne vulgaris and treatment-resistant forms of inflammatory acne vulgaris. • Intralesional corticosteroid injections are effective for large inflammatory lesions. <u>Topical therapy</u> • Topical retinoids reduce obstruction within the follicle and are useful in the management of both comedonal and inflammatory acne vulgaris. • The relative efficacy between topical retinoids (e.g., tretinoin, adapalene, tazarotene, isotretinoin [not available topically in the United States]) is unclear. • Benzoyl peroxide is a bactericidal agent and with the ability to prevent or eliminate the development of *P acnes* resistance, and is therefore used in combination with oral or topical antibiotics. • Topical antibiotics (erythromycin and clindamycin) are effective in the treatment of acne vulgaris but are more effective when used in combination with benzoyl peroxide due to a synergy as well as the resulting elimination or reduction of bacterial resistance. • Salicylic acid has moderately effective and less potent comedolytic properties than topical retinoids and is therefore used in patients intolerant to dermatological effects caused by topical retinoids. • The role of azelaic acid, sulfur, resorcinol, sodium sulfacetamide, aluminum chloride and zinc in the management of acne vulgaris is unclear due to limited clinical evidence and/or peer-reviewed literature. <u>Systemic antibiotics</u> • Doxycycline and minocycline are more effective than tetracycline. • Minocycline has been shown to be superior to doxycycline in reducing *P acnes*. • Erythromycin is effective but is associated with bacterial resistance and therefore its use should be limited to those who cannot tolerate tetracyclines (e.g., pregnant women and children <8 years of age due to the potential damage to the skeleton or teeth).

Clinical Guideline	Recommendations
	Hormonal agents • Oral contraceptives containing norgestimate with ethinyl estradiol and norethindrone acetate with ethinyl estradiol are Food and Drug Administration (FDA) approved for the management of acne vulgaris. Isotretinoin • Isotretinoin, a vitamin A derivative, is approved for the treatment of severe recalcitrant nodular acne vulgaris and possibly effective in treatment-resistant acne vulgaris or acne vulgaris producing physical or psychological scarring. • Since isotretinoin is a potent teratogenic, females of childbearing age must only be treated if they are participating in the approved pregnancy prevention and management program (iPLEDGE).
American Academy of Dermatology: **Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 3 and 4 (2009)**[16,17]	Topical therapies • Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, nonmedicated topical moisturizers, salicylic acid, anthralin, coal tar and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific FDA-approved indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid; however, the agent is typically used in combination with other topical therapies. Systemic therapies • Although biologics are often less toxic and not teratogenic, traditional systemic therapies (methotrexate, cyclosporine, acitretin) are still used more often due to oral route of administration and low cost. • Used more than 50 years ago, methotrexate is most commonly prescribed for severe, recalcitrant, disabling psoriasis when used in a weekly, single low-dose regimen for its effect on the immune system; concurrent folate supplementation may be warranted. • Though highly effective and known for its rapid effects, cyclosporine is associated with nephrotoxicity and hypertension; its use is restricted to one and two years in the United States and United Kingdom, respectively. • When used in conjunction with ultraviolet radiation B or psoralen and ultraviolet radiation A phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression; effects are dose-dependent and response is observed after three to six months. • Agents not FDA-indicated but used in psoriasis with limited supporting evidence include: azathioprine, fumarates (not approved in the United States), leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine.

Conclusions

Various options exist for the treatment of acne vulgaris including topical agents, systemic antibiotics, hormonal agents, isotretinoin, laser and light therapies, complementary/alternative therapies and dietary restrictions.[1] The topical retinoids, adapalene (Differin®), tazarotene (Tazorac®) and tretinoin (Atralin®, Avita®, Retin-A®, Retin A-Micro®, and Tretin-X®), are approved by the Food and Drug Administration (FDA) for the treatment of acne vulgaris, and tazarotene is also indicated for the management of plaque psoriasis.[3-11] In addition, there are two combination products available that combine a retinoid and an antibiotic. Adapalene/benzoyl peroxide (Epiduo®) and tretinoin/clindamycin phosphate/ (Ziana®) are both FDA-approved for the treatment of acne vulgaris in patients 12 years of age or older.[12,13] Currently, only adapalene 0.1% cream and gel and tretinoin (Retin-A®) are available generically.[14]

In general, the topical retinoid products have consistently demonstrated a statistically significant improvement in acne severity or patient-perceived acne severity compared to treatment with a vehicle alone. Similarly, the topical retinoid combination products have consistently demonstrated significant improvements in lesion counts and acne severity compared to their individual components.[21,21,28,29,31-35,38-40,43,45-47] In two trials comparing tretinoin and adapalene, similar efficacy was seen between the two agents.[26-27] No difference in efficacy was noted when tazarotene was compared to tretinoin in another study.[26,27,41] The results of studies comparing adapalene/benzoyl peroxide and tretinoin/clindamycin have not demonstrated a statistically significant difference in efficacy between the agents.[30,36]

Current treatment guidelines recommend using a combination of benzoyl peroxide and retinoids when long-term acne treatment is warranted.[2,15] In general, topical combination products are indicated in patients with mild to moderate acne vulgaris when an inflammatory component is present.[2,15] In addition to its use in acne vulgaris, guidelines recommend tazarotene for the treatment of psoriasis. Topical agents are useful in mild to moderate disease and adjunct treatment in extensive psoriasis.[16,17] When used, tazarotene may be most effective in combination with topical corticosteroids, often considered first-line treatment for plaque psoriasis.[16,17]

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