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SYSTEMATIC REVIEW

Topical Retinoids in Acne Vulgaris: A Systematic Review

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Abstract

Background Topical retinoids are a first-line treatment for acne vulgaris.

Objective This systematic review aims to evaluate the efficacy, safety, and tolerability of topical retinoids approved in the United States for the treatment of acne vulgaris.

Methods A PubMed and Embase search was conducted using the search terms 'adapalene,' 'tretinoin,' 'tazarotene,' and 'acne vulgaris.' Selection of articles fit the following inclusion criteria: clinical trials evaluating both efficacy and safety/tolerability of topical retinoids approved in the United States for the treatment of acne vulgaris and published between January 1, 2008 and September 1, 2018. Exclusion criteria included clinical trials involving 20 subjects or fewer, subjects under 12 years of age, and topical retinoid combination therapies with moisturizers or aloe vera. Of 424 search results found, a total of 54 clinical trials were chosen based on selection criteria.

Results Topical retinoids are superior to vehicle in improving Investigator Global Assessment and Investigator's Static Global Assessment (24.1–28.8% and 13.3–17.3%, respectively; $p < 0.001$). A topical retinoid combined with benzoyl peroxide led to IGA improvement compared with vehicle (26.1–34.9% vs 7–11.8%; $p < 0.001$) at Week 12. Topical retinoid plus an oral antibiotic was superior to vehicle in reducing lesion counts (64–78.9% vs 41–56.8%, $p < 0.001$). There was no significant difference in efficacy between tretinoin and tazarotene. Tretinoin 0.05% resulted in 62% of patients experiencing AEs compared with adapalene 0.1% (19%) and adapalene 0.3% (40%). More patients receiving adapalene were tolerant of the AEs compared with tazarotene (55.4% vs 24.4%; $p < 0.0012$).

Conclusions Topical retinoids are safe and efficacious for the treatment of acne vulgaris. They should be used in combination with benzoyl peroxide to optimize results in patients. The differences in efficacy of topical retinoids appears minor; therefore, the type of topical retinoid is not as important as choosing a particular strength of topical retinoid and combining it with an antimicrobial agent. Adapalene has a superior tolerability profile amongst topical retinoids.

Key Points

Topical retinoids are safe and efficacious for the treatment of acne vulgaris.

Combination of a topical retinoid with an antimicrobial agent is more efficacious than topical retinoid monotherapy.

Adapalene has a superior tolerability profile amongst topical retinoids

1 Introduction

Topical retinoids are used in the treatment of both noninflammatory and inflammatory acne. Currently, the Food and Drug Administration (FDA) has approved three topical retinoids: adapalene, tazarotene, and tretinoin. These

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agents help normalize follicular keratinization and decrease keratinocyte cohesiveness, thereby reducing follicular occlusion and comedone formation [1]. Topical retinoids also compete with factors involved in the acne inflammation response, enhance penetration of other topical acne medications, and accelerate resolution of acne-induced post-inflammatory hyperpigmentation.

Updates from Global Alliance on Improving Outcomes in Acne consider topical retinoids as first-line therapy individually or in combination with benzoyl peroxide [2]. For patients with inflammatory acne, combination therapy with a topical retinoid and antimicrobial agent is recommended [2]. Patients who respond to initial treatment can further use topical retinoids as maintenance therapy, which can diminish prolonged use of antibiotics [2]. However, the common side effects of skin irritation and discomfort may impede adherence to long-term therapy with topical retinoids [3].

Updates from consensus guidelines and recent clinical trials prompted a systematic review of the efficacy, safety, and tolerability profile of topical retinoids. We analyzed both monotherapy and combination therapy of each topical retinoid and compared topical retinoids to elucidate their role in acne treatment and provide possible recommendations for their use.

2 Methods

A PubMed and Embase search was conducted using the search terms 'adapalene,' 'tretinoin,' 'tazarotene,' and 'acne vulgaris.' Selection of articles fit the following inclusion criteria: clinical trials evaluating both efficacy and safety/tolerability of topical retinoids approved in the United States for the treatment of acne vulgaris and published between January 1, 2008 and September 1, 2018. Exclusion criteria included clinical trials of 20 subjects or fewer, trials involving subjects under 12 years of age, and trials involving topical retinoid combination therapies with moisturizers or aloe vera. Of 424 search results found, a total of 54 clinical trials were chosen based on selection criteria (Fig. 1). Publications were divided by monotherapy, combination therapy, and comparison trials. Quality of literature was assessed using Jadad criteria (Table 1) [4].

3 Results

3.1 Adapalene Monotherapy

3.1.1 Efficacy

Two multicenter, randomized, double-blind, parallel, vehicle-controlled studies assessed the safety and efficacy of

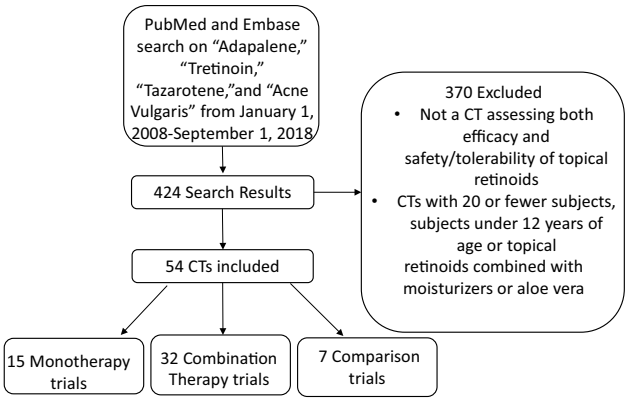

Fig. 1 Flowchart of literature search. *CT* clinical trial

adapalene 0.1% lotion versus vehicle applied daily in 2148 subjects for 12 weeks (Table 2). The primary endpoints were a 2-point reduction in Investigator Global Assessment (IGA) and absolute change in inflammatory (IN), noninflammatory (NIN), and total lesion count (TLC) from baseline to Week 12. In the first and second study, more adapalene-treated patients had a 2-point reduction in IGA compared with control (26.3% vs 17.3% and 24.1% vs 16.4%, respectively; $p < 0.001$). At Week 12 of the first study, adapalene-treated patients had greater median absolute reductions from baseline compared with control in TLC (39 vs 29), as well as IN (16 vs 12.5) and NIN (23 vs 18) lesion counts ($p < 0.001$). In the second study, adapalene-treated patients also had greater median absolute reductions from baseline compared with control in TLC (34 vs 26), IN (13 vs 12), and NIN (21 vs 15) lesion counts ($p < 0.001$) [5].

Thielitz et al. randomized 55 subjects to azelaic acid (AzA) 15% gel twice daily for 9 months, AzA 15% gel twice daily for 3 months followed by a 6-month observation, or adapalene 0.1% gel once daily for 9 months. The primary endpoints were change in IN lesion counts, Investigator's Static Global Assessment (ISGA), and Leeds Revised Acne Grading Scale (LRAGS) at Week 36. There was no difference between treatment groups [6].

A multi-center, investigator-blinded study randomized 175 subjects to microsphere adapalene 0.1% gel or conventional adapalene 0.1% gel daily for 12 weeks. The primary endpoints were percent reduction in TLC, IN, and NIN lesions at Week 12. There was no difference between treatment groups [7].

Ko et al. randomized 69 subjects to clindamycin phosphate/benzoyl peroxide (CLNP/BPO) 1%/5% or adapalene 0.1% gel once daily for 12 weeks. The primary endpoints were absolute change in TLC, IN, and NIN lesions and acne severity. CLNP/BPO was superior to adapalene in reducing TLC (44.2 vs 34; $p = 0.0258$) and IN (28.6 vs 18.6; $p = 0.0165$) lesions at Week 12. There was no difference in NIN lesions and acne severity between treatment groups at Week 12 [8].

Table 1 Jadad criteria

	Points	Criteria
Randomization	2	The method to generate randomization sequence was described and appropriate (computer generated, table of random numbers, etc.)
	1	The method to generate randomization sequence was not described
	0	The method to generate randomization sequence was described but inappropriate
Double blinding	2	The method of double blinding was described and appropriate
	1	The method was described as double-blind, but no description of blinding procedure was provided
	0	The method was described as double-blind, but the description of the procedure was inappropriate
Withdrawal or dropouts	1	The number and reason for withdrawal was described
	0	No description of number and reason for withdrawal provided

A single-center, double-blind study randomized 60 patients to adapalene 0.1% gel or BPO 2.5% gel once daily for 12 weeks. The primary endpoints were change in TLC, IN, and NIN lesions. Adapalene was superior to BPO in reducing TLC (20 vs 15.8; $p<0.001$) and NIN (9.07 vs 7.27; $p=0.02$) lesions at Week 12. There was no significant difference in IN lesions between groups at Week 12 [9].

An open clinical trial randomized 220 patients to adapalene 0.1% or BPO 4% once daily for 20 weeks. The primary endpoint was percent clearance of lesions. There was no significant difference between groups [10].

Weiss et al. assessed the long-term safety and efficacy of adapalene 0.3% gel applied once daily in 551 subjects for 52 weeks. At Week 52, there was a > 75% reduction in TLC, IN, and NIN lesions [11].

A multicenter, investigator-blinded study randomized 200 Japanese subjects to adapalene 0.1% gel or vehicle once daily for 12 weeks. The primary endpoint was percent reduction in TLC. Adapalene-treated subjects had a greater reduction in TLC than vehicle-treated subjects (63.2% vs 36.9%; $p<0.0001$) [12].

A multi-center, investigator-blinded study randomized 130 subjects to CLNP/BPO gel or adapalene 0.1% gel once daily for 12 weeks. The primary endpoint was reduction in IN lesion counts. CLNP/BPO-treated subjects had a greater median percent reduction in IN lesions than adapalene-treated subjects (82% vs 55%; $p<0.001$) [13].

3.1.2 Safety and Tolerability

About 10.3% of adapalene-treated subjects experienced treatment-related adverse events (AEs) compared with 4.7% in the vehicle group [5]. Common AEs include dry skin, peeling, and erythema [5, 9, 11–13]. Most events were mild in severity [10]. Two subjects in the adapalene 0.1% lotion group reported serious AEs of skin burning sensation and skin discomfort [5]. The adapalene-treated group had more irritation compared with AzA during the first 12 weeks but improved over time [6].

3.2 Adapalene Combination Therapies

3.2.1 Efficacy

A multicenter, randomized, parallel, double-blind, control study assessed adapalene/benzoyl peroxide (A/BPO) 0.3%/2.5% gel versus vehicle gel applied once daily in 286 subjects with moderate-to-severe acne (Table 3). The primary endpoints included success rate of clear or almost clear IGA and a change in IN and NIN lesion count from baseline to Week 12. At Week 12, A/BPO 0.3%/2.5% gel treatment had a higher IGA success rate compared with vehicle in both males (26.9% vs 9.1%, respectively; $p=0.039$) and females (33.6% vs 11.1%, respectively; $p=0.009$). From baseline to Week 12, A/BPO 0.3%/2.5% gel treatment reduced more IN lesions than vehicle in both males (27.1 vs 12.6) and females (24.3 vs 11.4), and NIN lesions in both males (48.1 vs 17.4) and females (35.9 vs 18.1; $p<0.001$). A/BPO 0.3%/2.5% gel had a higher IGA success rate compared with vehicle for both subjects over age 18 years (34.9% vs 11.5%; $p=0.021$) and subjects aged 12–17 years (26.1% vs 9.3%; $p=0.020$). A/BPO 0.3%/2.5% gel treatment reduced IN lesions more than vehicle in patients over age 18 years (24.2 vs 14) and ages 12–17 years (27.1 vs 8.7), and reduced NIN lesions more than vehicle in patients over 18 years (33.3 vs 19.6) and ages 12–17 years (40.4 vs 14.7; $p<0.001$) [14].

Alexis et al. randomized 503 subjects with moderate-to-severe acne to A/BPO 0.3%/2.5%, A/BPO 0.1%/2.5%, or vehicle gel once daily for 12 weeks. A/BPO 0.1%/2.5% acted as a control for tolerability; efficacy data were not reported for this group. Subjects were categorized into Fitzpatrick Skin Type (FST) I to III and FST IV to VI. The primary endpoints were IGA success rate of clear or almost clear and change in IN and NIN lesion counts. In subjects with FST I to III, more subjects receiving A/BPO 0.3%/2.5% gel achieved IGA success compared with vehicle (32% vs 7%; $p=0.001$). There was no difference in IGA success between A/BPO 0.3%/2.5% and vehicle in subjects with FST IV to VI. For subjects with FST I to III, A/BPO 0.3%/2.5% gel was

Table 2 Adapalene monotherapy

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Eichenfield et al. [5]	Randomized, double-blind	Adapalene 0.1% or vehicle daily	1075	12	% Patients with 2-point reduction in IGA	Adapalene: 26.3% Vehicle: 17.3%; $p < 0.001$	5
					Reduction in inflammatory count	Adapalene: 16 Vehicle: 12.5; $p < 0.001$	
					Reduction in noninflammatory count	Adapalene: 23 Vehicle: 18; $p < 0.001$	
					Reduction in TLC	Adapalene: 39 Vehicle: 29; $p < 0.001$	
Thielitz et al. [6]	Randomized, single-blind	Azelaic acid 15% for 9 mo, Azelaic acid 15% for 3 mo, followed by 6-mo observation, Adapalene 0.1% for 9 mo	55	36	Reduction in inflammatory lesion count, ISGA and LRAGS	No significant difference	3
Iftikhar et al. [10]	Randomized	Adapalene 0.1% vs BPO 4%	220	24	Percent clearance of lesions	No significant difference	3
Weiss et al. [11]	Open-label, multicenter	Adapalene 0.3%	551	52	Reduction in TLC, inflammatory and noninflammatory lesions	>75% reduction in all types of lesions	1
Kawashima et al. [12]	Randomized, investigator-blinded	Adapalene 0.1% gel or vehicle	200	12	% Reduction in TLC	Adapalene: 63.2% Vehicle: 36.9% $p < 0.0001$	2
Langner et al. [13]	Randomized, investigator-blinded	CLNP/BPO gel or adapalene 0.1% gel	130	12	Median % reduction in inflammatory lesions	CLNP/BPO: 82% Adapalene:55% $p < 0.001$	3
Eichenfield et al. [5]	Randomized, double-blind	Adapalene 0.1% or vehicle daily	1066	12	% Patients with 2-point reduction in IGA	Adapalene: 24.1% Vehicle: 16.4%; $p < 0.001$	5
					Reduction in inflammatory count	Adapalene: 13 Vehicle: 12; $p < 0.001$	
					Reduction in noninflammatory count	Adapalene: 21 Vehicle: 15; $p < 0.001$	
					Reduction in TLC	Adapalene: 34 Vehicle: 26; $p < 0.001$	
Rao et al. [7]	Randomized, single-blind	Microsphere adapalene 0.1% gel or conventional adapalene 0.1% gel	175	12	% Reduction in TLC, inflammatory and noninflammatory lesion count	No significant difference	3
Babaeinejad et al. [9]	Randomized, double-blind	Adapalene 0.1% gel or BPO 2.5% gel	60	12	Reduction in TLC	Adapalene: 20 BPO: 15.8; $p < 0.001$	5
					Reduction in noninflammatory count	Adapalene: 9.07 BPO: 7.27; $p = 0.02$	
					Reduction in inflammatory count	No significant difference	

Table 2 (continued)

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Ko et al. [8]	Randomized, open-label	CLNP/BPO 1%/5% gel or adapalene 0.1% gel	69	12	Reduction in TLC	CLNP/BPO 1%/5% gel: 44.2 Adapalene 0.1% gel: 34; $p = 0.0258$	2
					Reduction in inflammatory count	CLNP/BPO 1%/5% gel: 28.6 Adapalene 0.1% gel: 18.6; $p = 0.0165$	
					Reduction in noninflammatory count	No significant difference	
					Reduction in acne severity	No significant difference	

BPO benzoyl peroxide, *CLNP* clindamycin phosphate, *IGA* Investigator Global Assessment, *ISGA* Investigator's Static Global Assessment, *LRAGS* Leeds Revised Acne Grading Scale, *TLC* total lesion count

more effective than vehicle in reducing IN (62.1% vs 28.7%) and NIN (63.6% vs 32.9%; $p < 0.001$) lesions. For FST IV to VI, A/BPO 0.3%/2.5% gel was more effective than vehicle in reducing IN (63.7% vs 45%) and NIN (61.1% vs 34%; $p < 0.05$) lesions [15].

A double-blind, parallel-group study randomized 503 subjects to A/BPO 0.3%/2.5% gel or vehicle once daily for 12 weeks. The co-primary endpoints were IGA success rate of clear or almost clear and a change in IN and NIN lesion count from baseline to Week 12. More patients treated with A/BPO 0.3%/2.5% achieved IGA success compared with vehicle (33.7% vs 11.0%; $p < 0.001$). At Week 12, A/BPO 0.3%/2.5% was superior to vehicle in reducing IN lesion (27.0 vs 14.4) and NIN lesion (40.2 vs 18.5) counts ($p < 0.001$) [16].

Another randomized, double-blind, parallel study of 252 subjects with severe inflammatory acne received either A/BPO 0.3%/2.5%, A/BPO 0.1%/2.5%, or vehicle gel once daily for 12 weeks. The primary endpoints were IGA success rate of clear or almost clear and change in IN and NIN lesion counts from baseline to Week 12. More subjects receiving A/BPO 0.3%/2.5% achieved an IGA success rate compared with vehicle (31.9% vs 11.8%; $p = 0.029$). There was no difference in primary endpoints between A/BPO 0.1%/2.5% and vehicle. At Week 12, A/BPO 0.3%/2.5% gel was more effective than vehicle in reducing IN (35.2% vs 15.5%; $p < 0.001$) and NIN lesions (45.6% vs 17.3%; $p < 0.001$) [17].

A double-blind parallel study randomized 459 subjects to oral doxycycline 100 mg once daily and either A/BPO 0.1%/2.5% gel or vehicle gel once daily for 12 weeks. The primary endpoint was a percentage change from baseline in TLC. A/BPO 0.1%/2.5% gel with doxycycline was superior to vehicle at all study visits. Clinical benefit was seen as early as Week 2, at which time a third of the final effect was already obtained. By Week 12, subjects treated with A/BPO 0.1%/2.5% reduced TLC more than vehicle (64% vs 41%; $p < 0.001$). A/BPO 0.1%/2.5% was superior to vehicle for IGA success rate at Week 8 (9.9% vs 2.6%; $p = 0.001$) and Week 12 (31.5% vs 8.4%; $p < 0.001$). A/BPO 0.1%/2.5% was more effective than vehicle in reducing both IN (72% vs 48%) and NIN lesion counts (61% vs 40%; $p < 0.001$) [18].

Fleischer et al. randomized 301 subjects to dapsone gel in combination with adapalene 0.1% gel, benzoyl peroxide 4% gel, or moisturizer. The primary efficacy endpoint was a change in IN lesion counts from baseline to Week 12. There was no difference in mean reduction of IN lesions between the three treatment arms. However, dapsone plus adapalene 0.1% gel reduced more NIN lesions (47% vs 30%) and TLC (51% vs 39%; $p < 0.004$) than dapsone plus moisturizer [19].

A double-blind parallel study randomized 1668 subjects to A/BPO 0.1%/2.5% gel combination, adapalene 0.1% gel monotherapy, BPO 2.5% gel monotherapy, or vehicle gel applied once daily for 12 weeks. The primary endpoints

Table 3 Adapalene combination therapy

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Stein Gold et al. [14]	Randomized, double-blind, parallel	A/BPO 0.3%/2.5% or vehicle daily	286	12	% Patients with IGA of clear or almost clear	A/BPO: 26.1–34.9% Vehicle: 9.1–11.5%; $p<0.05$ A/BPO: 26.1–34.9% Vehicle: 9.1–11.5%; $p<0.05$	5
					Reduction in inflammatory count	A/BPO: 24.2–27.1 Vehicle: 8.7–14; $p<0.001$	
					Reduction in noninflammatory count	A/BPO: 33.3–48.1 Vehicle: 14.7–19.6; $p<0.001$	
Alexis et al. [15]	Phase III, randomized, double-blind, parallel	A/BPO 0.3%/2.5%, A/BPO 0.1%/2.5%, or vehicle daily	503	12	% Patients with IGA of clear or almost clear	A/BPO: 32% Vehicle: 7%; $p=0.001$	5
					% Reduction in inflammatory count	A/BPO: 62.1–63.7% Vehicle: 28.7–45%; $p<0.001$	
					% Reduction in noninflammatory count	A/BPO: 61.1–63.6% Vehicle: 32.9–34%; $p<0.05$	
Stein Gold et al. [16]	Randomized, double-blind, parallel	A/BPO 0.3%/2.5%, A/BPO 0.1%/2.5%, or vehicle daily	503	12	% Patients with IGA of clear or almost clear	A/BPO: 33.7% Vehicle: 11%; $p<0.001$	5
					Reduction in inflammatory count	A/BPO: 27 Vehicle: 14.4; $p<0.001$	
					Reduction in noninflammatory count	A/BPO: 40.2 Vehicle: 18.5; $p<0.001$	
Weiss et al. [17]	Randomized, double-blind, parallel	A/BPO 0.3%/2.5%, A/BPO 0.1%/2.5%, or vehicle daily	252	12	% Patients with IGA of clear or almost clear	A/BPO: 31.9% Vehicle: 11.8%; $p=0.029$	5
					% Reduction in inflammatory count	A/BPO: 35.2% Vehicle: 15.5%; $p<0.001$	
					% Reduction in noninflammatory count	A/BPO: 45.6% Vehicle: 17.3%; $p<0.001$	
Gold et al. [18]	Randomized, double-blind, parallel	Doxycycline + either A/BPO 0.1%/2.5% or vehicle daily	459	12	% Reduction in TLC	A/BPO: 64% Vehicle: 41%; $p<0.001$	4
Fleischer et al. [19]	Randomized, double-blind	Dapsone gel + either A/BPO 0.1%/4% or moisturizer daily	301	12	% Reduction in inflammatory count	No statistical difference between three treatment arms	5

Table 3 (continued)

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Gold et al. [20]	Randomized, double-blind, parallel	A/BPO 0.1%/2.5%, Adapalene 0.1%, BPO 2.5%, or vehicle daily	1668	12	% Patients with IGA of clear or almost clear	A/BPO: 30.1% Adapalene: 19.8% BPO: 22.2% Vehicle 11.3%; $p < 0.05$	3
					% Reduction in inflammatory count	A/BPO: 61.2% Adapalene: 50% BPO: 55.6% Vehicle: 34.3%; $p < 0.05$	
					% Reduction in noninflammatory count	A/BPO: 63.8% Adapalene: 49.1% BPO: 44.1% Vehicle: 29.5%; $p < 0.05$	
Tan et al. [21]	Randomized, investigator-blinded	Doxycycline + A/BPO 0.1%/2.5% or oral isotretinoin	266	20	% Reduction in facial nodules	Doxycycline +A/BPO: 88.7% Isotretinoin: 95.6%; $p < 0.01$	3
					% Reduction in papules/pustules	Doxycycline +A/BPO: 79.6% Isotretinoin: 95.2%; $p < 0.01$	
					% Reduction in comedones	Doxycycline +A/BPO: 75.9% Isotretinoin: 92.3%; $p < 0.01$	
					% Reduction in TLC	Doxycycline +A/BPO: 78.2% Isotretinoin: 92.9%; $p < 0.01$	
					% Patients with 2-grade IGA improvement	Doxycycline +A/BPO: 73.7% Isotretinoin: 90.2%; $p < 0.01$	
Takigawa et al. [22]	Randomized, parallel	Adapalene 0.1% + nadifloxacin 1% or adapalene 0.1%	184	12	% Reduction in inflammatory lesions	Adapalene + nadifloxacin: 66% Adapalene: 51%; $p = 0.0056$	3
Hayashi and Kawashima [23]	Randomized, open-label, parallel	Adapalene 0.1%, faropenem switched to adapalene 0.1%, or adapalene 0.1% + faropenem	160	4	% Reduction in inflammatory count	Adapalene: 44.5% Switch therapy: 46.7% Combination: 63.3%; $p < 0.05$	3

Table 3 (continued)

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Tan et al. [24]	Randomized, double-blind	(Doxycycline + A/BPO 0.1%) + A/BPO 0.1%/2.5% or (doxycycline + vehicle) + vehicle	243	36	% Patients with IGA of clear or almost clear	(Doxycycline + A/BPO) + A/BPO: 50% (Doxycycline + vehicle) + vehicle: 25%; $p < 0.05$	4
Kobayashi et al. [25]	Randomized	Adapalene 0.1% + nadifloxacin 1% or adapalene 0.1%	50	8	% Reduction in inflammatory count	Adapalene + nadifloxacin: 53% Adapalene: 30%; $p = 0.011$	3
Dreno et al. [26]	Randomized, double-blind	Lymecycline + A/BPO 0.1%/2.5% or lymecycline + vehicle	378	12	% Reduction in TLC	Lymecycline + A/BPO: 74.1% Lymecycline + vehicle: 56.8%; $p < 0.001$	5
Zouboulis et al. [29]	Randomized, investigator-blind	C/BPO 1%/5% with hydrating excipients or A/BPO 0.1%/2.5%	382	12	% Reduction in inflammatory count	No significant difference	2
Nicklas et al. [31]	Randomized, single-blind	Photodynamic therapy vs doxycycline 100 mg plus adapalene 0.1% gel	46	12	Reduction in acne lesions	No significant difference	3
Ghosh and Das [32]	Randomized, open-label	Nadifloxacin/BPO 1%/2.5% or A/BPO 0.1%/2.5%	38	12	Reduction in TLC	A/BPO: 94.9% Nadifloxacin/BPO: 83.2%; $p < 0.05$	3
Jawade et al. [33]	Randomized, investigator-blinded	A/BPO 0.1%/2.5%, adapalene 0.1% or BPO 2.5%	132	12	IGA success of clear or almost clear	A/BPO: 37.2% Adapalene: 23.3% BPO: 19.4%; $p < 0.05$	3
					Reduction in TLC	A/BPO: 75.4% Adapalene: 60.5% BPO: 59.2%; $p = 0.0002$	
					Reduction in inflammatory lesions	A/BPO: 75.9% Adapalene: 58.6% BPO: 53.4%; $p = 0.008$	
					Reduction in noninflammatory lesions	A/BPO: 74.8% Adapalene: 61.0% BPO: 57.6%; $p = 0.001$	

Table 3 (continued)

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Shwetha et al. [34]	Randomized	Clindamycin/adapalene 1%/0.1% vs clindamycin/BPO 1%/2.5%	120	12	Reduction in TLC	Clindamycin/adapalene: 0.7 Clindamycin/BPO: 0.51; $p < 0.001$	3
					Reduction in noninflammatory lesions	Clindamycin/adapalene: 0.68 Clindamycin/BPO: 0.49; $p < 0.001$	
					Reduction in inflammatory lesions	Clindamycin/adapalene: 0.77 Clindamycin/BPO: 0.57; $p < 0.001$	
Prasad et al. [30]	Randomized, open-label	Nano-emulsion adapalene/CLNP 0.1%/1% or conventional formulation adapalene/CLNP 0.1%/1%	209	12	% Reduction in TLC	Nano-emulsion adapalene/CLNP: 79.7% Conventional formulation adapalene/CLNP: 62.7%; $p < 0.001$	3
					% Reduction in inflammatory count	Nano-emulsion adapalene/CLNP: 88.7% Conventional formulation adapalene/CLNP: 71.4%; $p < 0.001$	
					% Reduction in noninflammatory count	Nano-emulsion adapalene/CLNP: 74.9% Conventional formulation adapalene/CLNP: 58.4%; $p < 0.001$	
Poulin et al. [27]	Randomized, double-blind	Doxycycline + A/BPO 0.1%/2.5% or doxycycline + vehicle	243	24	% Reduction in inflammatory count	Doxycycline + A/BPO: 78.9% Vehicle: 45.8%; $p < 0.001$	4
					% Reduction in noninflammatory count	Doxycycline + A/BPO:78.0% Vehicle: 43.4%; $p < 0.001$	
					% Patients with IGA of clear or almost clear	Doxycycline + A/BPO: 70.7% Vehicle: 34.2%; $p < 0.001$	

Table 3 (continued)

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Gollnick et al. [28]	Randomized, double-blind	A/BPO 0.1%/2.5%, adapalene 0.1%, BPO 2.5%, or vehicle	1670	12	% Patients with 2-point reduction in IGA	A/BPO: 75% Adapalene: 62.5% BPO: 58.5% Vehicle: 52.6%; $p < 0.001$	4
					% Reduction in inflammatory count	A/BPO: 70.3% Adapalene: 57.1% BPO: 61.9% Vehicle: 45.5%; $p < 0.001$	
					% Reduction in noninflammatory count	A/BPO: 62.2% Adapalene: 50.4% BPO: 48.8% Vehicle: 36.7%; $p < 0.001$	
					% Reduction in TLC	A/BPO: 65.4% Adapalene: 52.3% BPO: 48.2% Vehicle: 37.1%; $p < 0.001$	

A/BPO adapalene/benzoyl peroxide, *C/BPO* clindamycin/benzoyl peroxide, *CLNP* clindamycin phosphate, *IGA* Investigator Global Assessment, *TLC* total lesion count

included IGA success rate of clear or almost clear and median percent change in IN, NIN, and TLC. About 30.1% of patients treated with A/BPO 0.1%/2.5% achieved an IGA success rate compared with 19.8% of patients treated with adapalene monotherapy, 22.2% treated with BPO monotherapy, and 11.3% with vehicle ($p < 0.05$). IGA success was seen as early as Week 4 for A/BPO 0.1%/2.5% combination therapy compared with adapalene 0.1% monotherapy and vehicle ($p = 0.008$ and $p = 0.004$, respectively). Patients receiving A/BPO 0.1%/2.5% had a median 61.2% reduction in IN lesion counts compared with a 50% reduction with adapalene monotherapy, 55.6% with BPO monotherapy, and 34.3% with vehicle ($p < 0.05$). Patients receiving A/BPO 0.1%/2.5% therapy had a median reduction of 63.8% in NIN lesion counts compared with 49.1% with adapalene monotherapy, 44.1% with BPO monotherapy, and 29.5% with vehicle ($p < 0.05$) [20].

Tan et al. randomized 266 subjects with severe nodular acne to doxycycline 200 mg plus A/BPO 0.1%/2.5% or oral isotretinoin (ISO) over 20 weeks. The primary endpoint was an IGA success rate of 2-grade improvement and percentage change from baseline in facial nodules, papules/pustules and TLC. ISO had a higher IGA success rate compared with doxycycline plus A/BPO (90.2 vs 73.7%; $p < 0.01$). ISO was superior to doxycycline plus A/BPO in reducing nodules (95.6% vs 88.7%), papules/pustules (95.2% vs 79.6%), comedones (92.3% vs 75.9%) and TLC (92.9% vs 78.2%; $p < 0.01$) at Week 20 [21].

A multicenter study randomized 184 subjects to adapalene 0.1% gel plus nadifloxacin 1% cream or adapalene 0.1% gel applied daily for 12 weeks. The primary endpoint was reduction in IN lesions. Adapalene plus nadifloxacin therapy was superior to adapalene monotherapy in reducing IN lesions (66% vs 51%; $p = 0.0056$) at Week 12 [22].

A multicenter, open-label, parallel-group study randomized 160 subjects with moderate-to-severe acne to 4 weeks of adapalene gel 0.1% monotherapy, 2 weeks of oral faropenem 600 mg followed by 2 weeks of adapalene 0.1% gel, or 4 weeks of combination therapy consisting of adapalene 0.1% gel and oral faropenem 600 mg. The primary endpoint was a percent reduction in IN lesion counts. The oral faropenem/adapalene combination therapy was superior to monotherapy and switch therapy in reducing IN lesion count (63.3% vs 44.5% vs 46.7%; $p < 0.05$) [23].

Two consecutive, double-blind studies randomized 243 subjects to oral doxycycline 100 mg and either A/BPO 0.1%/2.5% or vehicle gel for the first 12 weeks. Those who achieved 50% global improvement from baseline were re-randomized to receive either A/BPO 0.1%/2.5% or vehicle gel daily for an additional 24 weeks. The primary endpoint was IGA success rate of clear or almost clear. The combination therapy of doxycycline and A/BPO was superior to doxycycline and vehicle in IGA success rate (44.5% vs 16%;

$p < 0.05$) at Week 12. The combination of (doxycycline and A/BPO) plus A/BPO was superior to (doxycycline and vehicle) plus vehicle in IGA success rate (50% vs 25%; $p < 0.05$) at Week 36 [24].

A multicenter trial randomized 50 subjects with moderate-to-severe acne to adapalene 0.1% gel and nadifloxacin 1% cream or adapalene 0.1% gel monotherapy for 8 weeks. The primary endpoint was percent reduction in IN lesions. The adapalene/nadifloxacin treatment was superior to adapalene monotherapy in reducing IN lesions (53% vs 30%; $p = 0.011$) [25].

Dreno et al. randomized 378 subjects to oral lymecycline 300 mg with either A/BPO 0.1%/2.5% or vehicle gel for 12 weeks. The primary endpoint was median percentage change of TLC from baseline to Week 12. Oral lymecycline with A/BPO was superior to lymecycline with vehicle in reducing TLC (74.1% vs 56.8%; $p < 0.001$) [26].

A multicenter, double-blind study randomized 243 subjects with severe acne vulgaris to oral doxycycline 100 mg daily and either A/BPO 0.1%/2.5% or vehicle gel daily for 24 weeks. The primary endpoints were percent change in IN and NIN lesion counts and IGA success rate of clear or almost clear. A/BPO plus doxycycline was superior to vehicle group in reducing IN (78.9% vs 45.8%) and NIN lesions (78.0% vs 43.4%; $p < 0.001$). The A/BPO group was superior to vehicle in IGA success rate (70.7% vs 34.2%; $p < 0.001$) [27].

Gollnick et al. randomized 1670 subjects to A/BPO 0.1%/2.5% gel, adapalene 0.1% gel, BPO 2.5% gel or vehicle daily for 12 weeks. The primary endpoint was IGA success rate of clear or almost clear and percent change in TLC, IN, and NIN lesions at Week 12. A/BPO therapy was superior to adapalene monotherapy, BPO monotherapy, and vehicle in IGA success rate (75% vs 62.5% vs 58.8% vs 52.6%; $p < 0.001$). A/BPO therapy was more effective than adapalene monotherapy, BPO monotherapy, and vehicle in reducing TLC (65.4% vs 52.3% vs 48.2% vs 37.1%; $p < 0.001$), IN (70.3% vs 57.1% vs 61.9% vs 45.5%; $p < 0.001$), and NIN (62.2% vs 50.4% vs 48.8% vs 36.7%; $p < 0.001$) lesions [28].

An investigator-blinded, parallel-group study randomized 382 subjects to clindamycin/BPO 1%/5% with hydrating excipient or A/BPO 0.1%/2.5% daily for 12 weeks. The primary endpoint was percent change in IN lesion count from baseline to Week 12. There was no difference in efficacy between groups ($p = 0.076$) [29].

A multi-center, open-label study randomized 209 subjects to nano-emulsion gel or conventional gel formulation of adapalene/CLNP 0.1%/1% once daily for 12 weeks. The primary endpoints were change in TLC, IN, and NIN lesions at Week 12. Nano-emulsion therapy was superior to conventional formulation in reducing TLC (79.7% vs 62.7%), IN (88.7% vs 71.4%), and NIN (74.9% vs 58.4%; $p < 0.001$) [30].

A prospective clinical trial randomized 46 subjects with moderate-to-severe acne to photodynamic therapy for 6 weeks followed by adapalene 0.1% gel for 6 weeks or doxycycline 100 mg plus adapalene 0.1% gel once daily for 6 weeks followed by adapalene 0.1% gel monotherapy for 6 weeks. The primary endpoint was a reduction in TLC, IN, and NIN lesions at Week 6. There was no significant difference between groups [31].

An open-label, parallel group clinical trial randomized 38 subjects to nadifloxacin and BPO 1%/2.5% gel or adapalene 0.1% cream plus BPO 2.5% gel for 12 weeks. The primary endpoint was change in TLC. A/BPO significantly reduced TLC more than nadifloxacin/BPO (94.9% vs 83.2%; $p < 0.05$) [32].

An investigator-blinded, single-center study randomized 132 patients to A/BPO 0/1%/2.5% gel, adapalene 0.1% gel, or BPO 2.5% gel for 12 weeks. The primary endpoints were success rate defined as IGA of clear or almost clear and change in TLC, IN, and NIN lesions. At Week 12, combination therapy had a higher success rate than adapalene and BPO monotherapies (37.2% vs 23.3% vs 19.4%; $p < 0.05$). Adapalene/BPO was superior to adapalene and BPO monotherapies in reducing TLC (75.4% vs 60.5% vs 59.2%; $p = 0.0002$), IN (75.9% vs 58.6% vs 53.4%; $p = 0.008$), and NIN (74.8% vs 61.0% vs 57.6%; $p = 0.001$) [33].

A prospective trial randomized 120 subjects to clindamycin/adapalene 1%/0.1% gel or clindamycin/BPO 1%/2.5% gel daily for 12 weeks. The primary endpoint was percent reduction in TLC, NIN, and IN lesions. Clindamycin/adapalene was superior to clindamycin/BPO in reducing TLC (0.7 vs 0.51), NIN (0.68 vs 0.49), and IN (0.77 vs 0.57; $p < 0.001$) lesions [34].

3.2.2 Safety and Tolerability

The most common AEs were skin irritation, dryness, and erythema [14–20, 22, 25, 27–32, 34]. Most were mild to moderate, peaked in the first 2 weeks of therapy, and resolved without residual effects [14–20, 22, 23, 26, 28]. Around 10% of subjects with adapalene 0.3%/BPO 2.5% had to adopt an every-other-day application regimen [14–16]. Combination therapies with doxycycline or faropenem had common side effects of gastroenteritis and accounted for a majority of treatment-related AEs [18, 21, 23, 24]. Two subjects had worsening acne unrelated to product, and two subjects had an acute flare of atopic dermatitis [16, 17]. About 33.8% of subjects receiving oral isotretinoin presented with treatment-related AEs requiring medical intervention [21]. Dapsone and moisturizer was better tolerated than other treatments [19].

3.3 Tazarotene Monotherapy

3.3.1 Efficacy

Two randomized, double-blind, vehicle-controlled, parallel-group studies assessed the safety and efficacy of tazarotene 0.1% foam versus vehicle applied once daily in 1468 subjects for 12 weeks (Table 4). The primary endpoints were absolute change in TLC, IN, and NIN lesions, ISGA score of clear or almost clear, and a 2-grade improvement in ISGA from baseline to Week 12. In the first and second studies, tazarotene was superior to vehicle in reducing TLC (45.8 vs 30.8 and 43.3 vs 32.9, respectively), IN (18 vs 14.1 and 17.8 vs 14.7, respectively), and NIN (27.9 vs 16.7 and 25.6 vs 18.2, respectively; $p < 0.001$) lesion counts. In the first and second study, more tazarotene-treated patients had an ISGA of clear or almost clear compared with control (28.8% vs 16.1% and 27.6% vs 13.3%, respectively; $p < 0.001$). In the first and second study, more tazarotene-treated patients had a 2-point reduction in ISGA compared with vehicle (35.8% vs 23.9% and 32.2% vs 18.2%, respectively; $p < 0.001$) [35].

Another clinical trial of 74 subjects received tazarotene 0.1% cream daily for 12 weeks. The primary endpoint was grade 0 defined as complete response or remission; 53% of subjects achieved remission [36].

3.3.2 Safety and Tolerability

Of tazarotene-treated groups, 35% reported AEs compared with 20% in vehicle groups [35]. Most AEs were mild to moderate in intensity [35]. The most common adverse effects were application site irritation, erythema, and

Table 4 Tazarotene monotherapy

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Zakaria et al. [36]	Open clinical trial	Tazarotene 0.1% cream	67	12	Complete remission	Tazarotene: 53%	0
Feldman et al. [35]	Randomized, double-blind, parallel, vehicle controlled	Tazarotene 0.1% foam or vehicle daily	744	12	% Patients with 2-point reduction in ISGA	Tazarotene: 35.8% Vehicle: 23.9; $p < 0.001$	5
					% Patients with ISGA of clear or almost clear	Tazarotene: 28.8% Vehicle: 16.1%; $p < 0.001$	
					Reduction in inflammatory count	Tazarotene: 17.8 Vehicle: 14.7; $p < 0.001$	
					Reduction in noninflammatory count	Tazarotene: 25.6 Vehicle: 18.2; $p < 0.001$	
					Reduction in TLC	Tazarotene: 43.3 Vehicle: 32.9; $p < 0.001$	
Feldman et al. [35]	Randomized, double-blind, parallel, vehicle controlled	Tazarotene 0.1% foam or vehicle daily	742	12	% Patients with 2-point reduction in ISGA	Tazarotene: 32.2% Vehicle: 18.2%; $p < 0.001$	5
					% Patients with ISGA of clear or almost clear	Tazarotene: 27.6% Vehicle: 13.3%; $p < 0.001$	
					Reduction in inflammatory count	Tazarotene: 17.8 Vehicle: 14.7; $p < 0.001$	
					Reduction in noninflammatory count	Tazarotene: 25.6 Vehicle: 18.2; $p < 0.001$	
					Reduction in TLC	Tazarotene: 43.3 Vehicle: 32.9; $p < 0.001$	

ISGA Investigator's Static Global Assessment, *TLC* total lesion count

dryness. About 2.5% from the tazarotene group discontinued the study due to application-site-related AEs [35].

3.4 Tazarotene Combination Therapy

3.4.1 Efficacy

Tanghetti et al. randomized 171 subjects to dapsone 5% gel twice daily plus tazarotene 0.1% cream daily or tazarotene 0.1% cream daily for 12 weeks (Table 5). The primary endpoint was a change in IN lesion count from baseline to Week 12. There was no difference in IN lesion count between treatment groups (66.6% vs 60.9%; $p=0.17$). However, dapsone plus tazarotene was superior to tazarotene monotherapy in reducing NIN lesions (59.7% vs 46.5%; $p=0.01$) and TLC (63.3% vs 53.6%; $p=0.02$) at Week 12 [37].

A single-center, single-blind, parallel-group study randomized 40 subjects to CLNP/BPO 1.2%/5% or CLNP/BPO 1.2%/2.5% with tazarotene (TZ) 0.1% cream applied daily for 12 weeks. The primary endpoints were mean changes in IN, NIN, and TLC observed at Week 12. There was no significant difference between treatment groups [38].

3.4.2 Safety and Tolerability

Most AEs, including erythema and dryness, were mild to moderate and resolved without sequlae [37]. There were more adverse events associated with tazarotene monotherapy (9) than combination therapy (4) [37].

3.5 Tretinoin Monotherapy

3.5.1 Efficacy

A phase IV, open-label, non-randomized, multicenter trial of 544 subjects dissatisfied with current acne treatment received either tretinoin gel microsphere (TGM) 0.04% or 0.1% in a pump dispenser for 12 weeks (Table 6). Physicians chose which treatment regimen patients received based on skin sensitivity; 361 patients received TGM 0.04% and 183 patients received TGM 0.1%. The demographic characteristics were similar between the two groups. The primary endpoint was a change in modified Global Acne Grading System (mGAGS) from baseline to Week 12. Both TGM 0.1% and TGM 0.04% had a significant change in mGAGS from baseline to Week 12 (4.7 vs 4.2; $p<0.0001$) but no significant group differences were observed [39].

A double-blind, parallel-group study randomized 77 subjects to cortexolone 17α-propionate 1% cream (CB-03-01), tretinoin 0.05%, or placebo once daily for 8 weeks. The primary endpoints were change in TLC, IN lesions, Acne Severity Index (ASI), and IGA. There was no difference between tretinoin and CB-03-01 or placebo in TLC, ASI, and IGA. CB-03-01 was superior to tretinoin in reducing IN lesions (54% vs 35%; $p<0.05$) at Week 6 [40].

3.5.2 Safety and Tolerability

Most AEs were mild to moderate [39, 40]. The most common AEs were dry skin, erythema, and skin exfoliation with tretinoin. Skin irritation worsened from baseline in tretinoin treatment groups but was transient [39, 40]. Only one patient discontinued from the TGM 0.04% group due to skin peeling [39]. There were more AEs in the tretinoin treatment group than the CB-03-01 treatment group [31].

3.6 Tretinoin Combination Therapy

3.6.1 Efficacy

A multicenter, double-blind study randomized 66 subjects with mild-to-moderate acne vulgaris to Treatment A consisting of an over-the-counter formulation containing BPO 5.5% with lipohydroxyl acid applied twice daily and tretinoin 0.025% cream applied nightly or Treatment B consisting of prescription clindamycin/BPO 1%/5% gel applied twice

Table 5 Tazarotene combination therapy

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Tanghetti et al. [37]	Randomized, single-blind, parallel, vehicle controlled	Dapsone 5% + tazarotene 0.1% or tazarotene 0.1%	171	12	Reduction in inflammatory count	No significant difference	3
Dhawan and Gwazdauskas [38]	Randomized, single-blind	Tazarotene 0.1% + either CLNP/BPO 1.2%/5% or CLNP/BPO 1.2%/2.5%	40	12	% Reduction in TLC, inflammatory count, and noninflammatory count	No significant difference	3

CLNP/BPO clindamycin phosphate/benzoyl peroxide, *TLC* total lesion count

Table 6 Tretinoin monotherapy

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Eichenfield et al. [39]	Phase IV, open-label, multi-center	TGM 0.04% or TGM 0.1%	544	12	Mean mGAGS	TGM 0.1%: 4.7 TGM 0.04%: 4.2	1
Trifu et al. [40]	Randomized, double-blind	CB-03-01 1% cream or tretinoin 0.05% cream or placebo	77	8	% Reduction in TLC	No significant difference between tretinoin and CB-03-01 or placebo	5
					% Reduction in inflammatory count	CB-03-01: 54% Tretinoin: 35%; $p < 0.05$	
					Reduction in ASI	No significant difference between tretinoin and CB-03-01 or placebo	
					Change in IGA	No significant difference between tretinoin and CB-03-01 or placebo	

ASI Acne Severity Index, *CB-03-01* cortexolone 17α-propionate 1% cream, *IGA* Investigator Global Assessment, *mGAGS* Modified Global Acne Grading System, *TGM* tretinoin gel microsphere, *TLC* total lesion count

daily and tretinoin 0.025% cream nightly for 12 weeks. The primary endpoints were change in lesion counts, skin tone, skin smoothness, skin brightness, appearance of pores, overall appearance, and global acne assessment from baseline to Week 12 (Table 7). Both treatment regimens resulted in significant improvement in lesion counts and skin appearance at Week 12 compared with baseline ($p < 0.05$). There was no significant difference in lesion count and skin appearance between the two treatments [41].

A 12-week, multicenter, double-blind, parallel-group study randomized 1656 subjects to clindamycin-tretinoin (CT) 1.2%/0.025% gel, clindamycin 1.2% gel, tretinoin 0.025% gel or vehicle gel. The primary endpoints were a 2-grade or greater improvement of ISGA and absolute change in TLC, IN, and NIN lesion counts from baseline to Week 12. CT gel was superior to clindamycin, tretinoin, and vehicle in ISGA improvement (36.3% vs 26.6% vs 26.1% vs 20.2%; $p < 0.001$). CT gel was superior to clindamycin, tretinoin, and vehicle in reducing TLC (38.7 vs 34 vs 36 vs 28.1), IN (15.5 vs 14.5 vs 13.9 vs 11.1), and NIN (23.2 vs 19.5 vs 22.1 vs 17.0; $p < 0.05$) lesions [42].

Pariser et al. randomized 240 subjects to receive TGM 0.04% pump and BPO 5% either both in the morning (morning/morning regimen) or BPO in the morning and TGM in the evening (morning/evening regimen) for 12 weeks. The primary endpoint was change in TLC from baseline to Week 12. Both morning/morning and morning/evening treatment regimens reduced TLC from baseline (39 vs 41.2, $p < 0.001$) but there was no significant difference between regimens [43].

A single-blind trial randomized 42 subjects with mild-to-moderate acne to clindamycin 1% lotion twice daily, CT 1%/0.025% lotion nightly, or clindamycin/salicylic acid 1%/2% lotion twice daily for 12 weeks. The primary endpoints were change in TLC and ASI. Clindamycin plus salicylic acid lotion was superior to clindamycin monotherapy in reducing TLC (78% vs 56%; $p = 0.039$) but there was no difference between combination therapies. Clindamycin plus salicylic acid lotion was superior to clindamycin monotherapy in reducing ASI (81.8% vs 37.87%; $p = 0.02$), but there was no difference between combination therapies [44].

A 12-week, single-blinded study randomized 40 subjects to tretinoin/CLNP 0.025%/1.2% either with BPO 6% cleansing cloth in the evening or a non-medicated cleanser. The primary endpoint was Physician's Global Assessment (PGA) score of clear or almost clear. There was no significant difference in treatment groups [45].

A phase IV, multicenter, open-label, single-arm study of 97 patients with moderate-to-severe acne received triple combination therapy of oral minocycline HCL, 6% BPO foaming cloths, and CLNP/tretinoin 1.2%/0.025% gel daily for 12 weeks. The primary endpoints included IGA of at least 1-grade improvement, Global Aesthetic Improvement Score (GAIS), and change in lesion counts from baseline to week 12. About 89% of patients showed at least a 1-grade IGA improvement while 96% showed a 1-grade

Table 7 Tretinoin combination therapy

Authorship	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Draelos et al. [41]	Randomized, double-blind	OTC BPO 5.5% with lipohydroxyl acid + tretinoin 0.025% or clindamycin 1% + BPO 5% + tretinoin 0.025%	66	12	Lesion count and skin appearance	No significant difference between groups	3
Jarratt and Brundage [42]	Randomized, double-blind	CT 1.2%/0.025%, clindamycin 1.2%, tretinoin 0.025%, or vehicle	1656	12	Reduction in TLC	CT: 38.7 Clindamycin: 34 Tretinoin: 36 Vehicle: 28.1; $p < 0.05$	5
					Reduction in inflammatory count	CT: 15.5 Clindamycin: 14.5 Tretinoin: 13.9 Vehicle: 11.1; $p < 0.05$	
					Reduction in noninflammatory count	CT: 23.2 Clindamycin: 19.5 Tretinoin: 22.1 Vehicle: 17.0; $p < 0.05$	
					% Patients with 2-point reduction in ISGA	CT: 36.3% Clindamycin: 26.6% Tretinoin: 26.1% Vehicle: 20.2%; $p < 0.001$	
Pariser et al. [43]	Randomized, investigator-blind	TGM pump 0.04% + 5% BPO morning/morning or morning/evening	240	12	Reduction in TLC	No significant difference	2
Zeichner et al. [45]	Randomized, single-blind	CT 0.1.2%/0.025% with BPO 6% or non-medicated cleanser	40	12	PGA of clear or almost clear	No significant difference	1
Babayeva et al. [47]	Randomized, single-blind	Salicylic acid/CLNP 3%/1% or tretinoin/CLNP 0.05%/1%	46	12	% Reduction in TLC, inflammatory and noninflammatory count	No significant difference	2
Kircik [49]	Randomized, investigator-blind	C/BPO 1%/5% plus tretinoin 0.04% or CLNP/tretinoin 1.2%/0.025% plus BPO 5% wash	147	12	% Reduction in inflammatory lesion count	No significant difference	2
NilFroushzadeh et al. [44]	Randomized, single-blind	CT 1%/0.025%, clindamycin 1% + salicylic acid 2%, or clindamycin 1%	42	12	% Reduction in TLC	No difference between combination therapies Clindamycin + salicylic acid: 78% Clindamycin: 56%	2
					% Reduction in ASI	No difference between combination therapies Clindamycin + salicylic acid: 81.8% Clindamycin: 37.87%	

Table 7 (continued)

Authorship	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Jackson et al. [48]	Randomized, investigator-blind	CLNP/BPO 1%/5% gel or CLNP/tretinoin 1.2%/0.025% gel	54	16	Change in *P. acnes* colonies	CLNP/BPO: 1.84 CLNP/tretinoin: 0.78; $p = 0.0030$	2
					Change in TLC, inflammatory, noninflammatory lesions, IGA and overall disease severity	No significant difference	
Zaenglein et al. [46]	Phase IV, open-label, single-arm	Minocycline HCL + CT 1.2%/0.025%	97	12	% Patients with 1-grade IGA improvement	Minocycline + CT: 89%; $p < 0.011$	1
					% Patients with 1-grade improvement in GAIS	Minocycline + CT: 96%; $p < 0.001$	
					% Reduction in inflammatory count	Minocycline + CT: 62%; $p < 0.001$	
					% Reduction in noninflammatory count	Minocycline + CT: 49%; $p < 0.001$	
					% Reduction in TLC	Minocycline + CT: 57%; $p < 0.001$	

ASI Acne Severity Index, *BPO* benzoyl peroxide, *CLNP* clindamycin phosphate, *CT* clindamycin/tretinoin, *GAIS* Global Acne Severity Index, *IGA* Investigator Global Assessment, *ISGA* Investigator's Static Global Assessment, *P. acnes Propionibacterium acnes*, *PGA* Physician Global Assessment, *TGM* tretinoin gel microsphere, *TLC* total lesion count

improvement in GAIS at Week 12 ($p < 0.001$). By Week 12, IN lesion counts decreased by 61.8%, NIN lesion counts decreased by 48.8% and TLC decreased by 56.6% from baseline ($p < 0.001$) [46].

A single-blind, parallel-group study randomized 46 subjects to salicylic acid 3% plus CLNP 1% lotion or tretinoin 0.05% cream plus CLNP 1% lotion twice daily for 12 weeks. The primary endpoints were percent change in TLC, NIN, and IN lesions. There was no difference between groups [47].

Jackson et al. randomized 54 subjects to CLNP/BPO 1%/5% gel or CLNP/tretinoin 1.2%/0.025% gel once daily. The primary endpoints were number of *Propionibacterium acnes* (*P. acnes*) colonies, lesion counts, IGA, and overall disease severity. At Week 16, CLNP/BPO was superior to CLNP/tretinoin in reducing *P. acnes* colonies (1.84 vs 0.78, $p = 0.0030$). There was no difference between the two groups in lesion counts, IGA, and overall disease severity. However, CLNP/BPO had a faster onset of action in reducing IN and TLC compared with CLNP/tretinoin beginning at Week 4 [48].

A multi-center, investigator-blinded study randomized 147 subjects to clindamycin/BPO 1%/5% gel plus tretinoin 0.04% gel or CLNP and tretinoin 1.2%/0.025% gel plus BPO 5% wash for 12 weeks. The primary endpoint was reduction in IN lesions. More subjects using clindamycin/BPO plus tretinoin had > 75% reduction in IN lesions than with CLNP/tretinoin plus BPO wash (36.5% vs 19.4%; $p = 0.0266$) at Week 8, but there was no significant difference at Week 12 [49].

3.6.2 Safety and Tolerability

Dryness, erythema and irritation were common application site AEs [42–47]. Most AEs were mild to moderate in intensity [49]. Tretinoin-treated groups had a higher frequency of AEs than clindamycin-treated groups [42, 44].

3.7 Comparison Trials

3.7.1 Adapalene versus Tazarotene

Thiboutot et al. randomized 171 subjects to either adapalene 0.3% gel or tazarotene 0.1% gel once daily for 12 weeks (Table 8). The primary endpoint was percent change in TLC from baseline to Week 12. The adapalene and tazarotene treatment groups displayed a similar percent reduction in IN lesions (67% and 59%, respectively; $p = 0.066$) and NIN lesions (55% each; $p = 0.307$) at Week 12. At Week 1 and 4, adapalene reduced IN lesion count more than tazarotene (27% vs 14%; $p = 0.02$ and 40% vs 22%; $p = 0.003$, respectively) [50].

Table 8 Adapalene versus tazarotene

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Thiboutot et al. [50]	Phase IIIb, randomized, evaluator-blinded, parallel	Adapalene 0.3% or tazarotene 0.1% daily	172	12	Reduction in TLC	No significant difference	2
Gold et al. [51]	Phase IV, randomized, evaluator-blinded, parallel	Adapalene 0.1% daily for 12 wk or adapalene 0.1% for 6 wk + tazarotene 0.1% for 6 wk	201	12	Reduction in TLC	Adapalene was noninferior to tazarotene (LCL −11.25)	1
Pariser et al. [52]	Phase IV, randomized, evaluator-blinded, parallel	Adapalene 0.1% or tazarotene 0.1% daily	202	12	Reduction in TLC	Adapalene was noninferior to tazarotene (LCL −9.25)	2
Tanghetti et al. [53]	Randomized, investigator-blinded	Adapalene 0.3% or tazarotene 0.1%	180	16	Reduction in noninflammatory count	No significant difference	2
Maiti et al. [54]	Randomized, open-label	Tazarotene 0.1% + clindamycin 1% or adapalene 0.1% + clindamycin 1%	60	4	Reduction in TLC	Tazarotene + clindamycin: 17.54 Adapalene + clindamycin: 11.03; $p = 0.007$	3

LCL lower confidence limit, *TLC* total lesion count

A phase IV, randomized, investigator-blinded, parallel-arm study of 201 subjects received either adapalene 0.1% gel applied once daily for 12 weeks or adapalene 0.1% gel applied once daily for 6 weeks followed by tazarotene 0.1% cream for 6 weeks. The primary endpoint was percent change in TLC from baseline to Week 12. The adapalene arm was noninferior to switch arm for percent change in TLC (median difference −3.57%; lower confidence limit [LCL] −11.25) [51].

Pariser et al. randomized 202 subjects to receive either adapalene 0.1% gel or tazarotene 0.1% cream applied once daily for 12 weeks. The primary efficacy was percent change in TLC from baseline to Week 12. Adapalene 0.1% gel was noninferior to tazarotene 0.1% cream (median difference −1.18; LCL −9.26) [52].

Tanghetti et al. randomized 180 moderate acne subjects to receive either adapalene 0.3% gel or tazarotene 0.1% cream once daily. The primary endpoint was percent change in NIN lesion count at Week 12. Tazarotene treatment led to a greater percent decrease in NIN lesion count than adapalene but was statistically significant ($p = 0.107$). Other efficacy measures showed a greater decrease in TLC for tazarotene than adapalene (82% vs 64%; $p < 0.02$). Tazarotene decreased post-inflammatory hyperpigmentation (PIH) index from baseline to week 16 (47.2%; $p = 0.014$); there was no significant decrease in the adapalene group [53].

A randomized, open-label trial of 60 subjects received either tazarotene 0.1% gel plus clindamycin 0.1% gel or adapalene 0.1% gel plus clindamycin 0.1% gel for 4 weeks. The primary endpoint was a change in TLC at Week 4. Tazarotene plus clindamycin was superior to adapalene plus clindamycin in reducing TLC (17.54 vs 11.03; $p = 0.007$) [54].

3.7.2 Adapalene versus Tretinoin

A single-center, randomized, double-blinded study of 171 subjects with FST III–IV received either adapalene 0.1%, adapalene 0.3%, tretinoin 0.05%, or placebo once daily for 12 weeks. The primary endpoint was change in TLC (Table 9). At Week 12, tretinoin 0.05% had a greater reduction in TLC compared with adapalene 0.3%, adapalene 0.1%, and placebo (76.7% vs 66.4% vs 57.8% vs 21.8%; $p < 0.001$) [55].

3.7.3 Tretinoin versus Tazarotene

A 12-week, single-center, investigator-blinded, randomized study of 40 subjects received either tretinoin gel 0.04% or tazarotene cream 0.05% daily for mild-to-moderate acne (Table 10). The primary endpoint was change in IGA, IN lesions, NIN lesions, and TLC from baseline to Week 12. There was no difference between treatment groups. Tretinoin

Table 9 Tretinoin versus adapalene

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Tirado-Sanchez et al. [55]	Randomized, double-blinded	Tretinoin 0.05%, adapalene 0.3%, adapalene 0.1%, or vehicle	171	12	% Reduction in TLC	Tretinoin: 76.7% Adapalene 0.3%: 66.4% Adapalene 0.1%: 57.8% Vehicle: 21.8%; $p < 0.001$	3

TLC total lesion count

Table 10 Tretinoin versus tazarotene

Study	Study design	Intervention	No. of subjects	Duration (wk)	Primary outcome	Result	Jadad score
Kircik [56]	Randomized, investigator-blind	TGM 0.04% pump vs tazarotene 0.05%	40	12	Reduction in inflammatory count, noninflammatory count, IGA, and TLC	No significant difference	1

IGA Investigator Global Assessment, *TGM* tretinoin gel microsphere, *TLC* total lesion count

produced a more rapid reduction in IN lesions from baseline to Week 4 than tazarotene (4.41 vs 3.95; $p < 0.001$). There was a reduction in NIN lesion count from baseline to Week 12 for groups treated with tretinoin (92.65%; $p = 0.002$) and tazarotene (79.55%; $p = 0.0078$) [56].

3.7.4 Safety and Tolerability

Common AEs in the comparison trials were erythema, dryness, scaling, stinging, and burning [50–56]. Most were mild to moderate in severity and peaked by Week 2 with resolution [50–52]. Adapalene was primarily associated with skin irritation, while scaling, stinging, and burning were associated more with tazarotene [51–53]. The tazarotene arm experienced more severe treatment-related AEs than adapalene [50]. Tazarotene had increased skin dryness, peeling, and pruritus compared with tretinoin [56]. More patients receiving adapalene were tolerant of the AEs compared with tazarotene (55.4% vs 24.4%; $p < 0.0012$) and more subjects were cosmetically satisfied with adapalene than tazarotene (92.8% vs 71.8%; $p < 0.001$) [50]. Tretinoin 0.05% resulted in 62% of patients experiencing AEs compared with adapalene 0.1% (19%) and adapalene 0.3% (40%) [55].

4 Discussion

A topical retinoid is an efficacious first-line treatment for acne vulgaris (Tables 2-10). Topical retinoid monotherapies can be effective and dose-dependent increases lead to greater efficacy [57–59]. Combination therapy of topical retinoid and antimicrobial agents including clindamycin, BPO, and salicylic acid are superior to monotherapies, supporting the synergistic effect of anti-inflammatory agents [60, 61]. Combinations with other anti-inflammatory agents such as dapsone can be used as an alternative [62].

It is difficult to rank the various topical retinoids based on the limited number comparative trials. Therefore, it is important to consider both the type and strength of a particular topical retinoid as well as the severity of acne to help choose the right agent for a particular patient. In mild acne vulgaris, any of the three topical retinoids would be suitable to use. For more severe forms of acne, the strength of the topical retinoid and combining it with other antimicrobial agents appears more important than the type of topical retinoid in improving disease severity. Subjects with severe acne improved with a topical retinoid and either BPO or oral antibiotic combination therapy, providing favorable alternative options to oral isotretinoin [17, 63]. BPO is an effective bactericidal agent so a topical retinoid/BPO combination is preferred for initial and maintenance therapy over topical or oral antibiotic monotherapy in order to reduce antibiotic resistance [64].

Tretinoin worked more rapidly than tazarotene in reducing inflammatory lesions, which may be important in clinical practice for increased patient satisfaction.

Furthermore, a few studies reported diverse, multiethnic populations of subjects, increasing the generalizability of these results to the diverse US population [12, 15, 16, 55], and supporting the benefit of topical retinoid therapy in people of color who are prone to PIH [56, 65].

The safety and tolerability profile of topical retinoids is favorable. Most patients experienced transient application site reactions, making topical retinoids feasible for long-term use. In the study assessing dapsone and adapalene combination therapy, subjects with just moisturizer and dapsone had a lower incidence of tolerability, possibly due to the alleviating effects of the moisturizer on skin irritation and discomfort most commonly reported [19]. Adapalene has a superior tolerability profile compared with tazarotene and tretinoin, which may be more conducive to better adherence to treatment.

Other ways to improve adherence were assessed in a few trials. A simplified regimen using both combination therapies in the morning may lead to better adherence. Patients may have a preference for the type of vehicle used for topical retinoids. Those using topical retinoids in a foam vehicle had fewer tolerability side effects compared with gel counterpart [66].

Limitations of clinical trials include small sample sizes, lack of blinding, potential for investigator grading bias, and duration of clinical trials. There was a 3-fold rate of discontinuation in the tazarotene group of one trial while another trial only treated 60 subjects over the course of 4 weeks, making it difficult to provide definite comparisons of topical retinoids [50]. The lack of double-blinding in comparison trials may lead to potential bias and uncertainty of the conclusions from these studies. In a study stratifying patients based on Fitzpatrick skin types, there was a lack of significance for IGA success rate in darker skin types that may have been attributed to fewer subjects in vehicle and PIH interfering with investigator grading bias. Topical retinoids are rarely curative and they appear to be more efficacious in the short-term.

5 Conclusion

Topical retinoids are efficacious and well tolerated as monotherapies and combination therapies. They are most efficacious with BPO and such a combination is recommended over topical or oral antibiotic monotherapy as first-line therapy for acne. The difference in efficacy of topical retinoids appears minor; therefore, the type of topical retinoid is not as important as choosing a particular strength of topical retinoid and combining it with an antimicrobial agent. Adapalene has a superior tolerability profile amongst topical retinoids, which may be more conducive to better long-term maintenance therapy in acne patients. A topical retinoid in combination with an antimicrobial agent is an effective alternative therapy to oral isotretinoin in those with severe acne and shows promise in diverse populations to offer physicians more options and flexibility in acne treatment regimens.

Compliance with Ethical Standards

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