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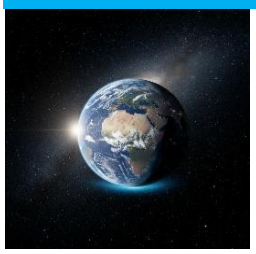

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Trifarotene in the Treatment of Acne Vulgaris: Current Evidence and Place in Clinical Practice

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Abstract

Background: Acne vulgaris is a highly prevalent chronic inflammatory skin disease that significantly affects quality of life and psychological well-being. Topical retinoids remain a cornerstone of acne therapy due to their comedolytic and anti-inflammatory properties.

Trifarotene, a selective retinoic acid receptor-γ agonist, is a recently developed fourth-generation retinoid introduced for the treatment of both facial and truncal acne.

Aim: This review aims to summarize current evidence on the pharmacology, clinical efficacy, safety, and role of trifarotene in the management of acne vulgaris.

Materials and Methods: A narrative literature review was conducted using PubMed and Embase, including clinical trials, meta-analyses, case reports, systematic reviews, post-marketing studies, and international treatment guidelines published up to 2026.

Results: Randomized controlled trials demonstrate that trifarotene effectively reduces both inflammatory and non-inflammatory lesions on the face and trunk, with a generally favorable safety and tolerability profile, predominantly characterized by mild, localized adverse reactions. Long-term data support sustained efficacy and improvement in quality of life. However, comparative evidence, including network meta-analyses and tolerability studies, suggests that trifarotene may be less effective, associated with higher rates of treatment discontinuation, and exhibit a greater propensity for local irritation compared with other topical retinoids. Emerging evidence, including a case report, indicates potential benefit in combination therapy, particularly in treatment-resistant acne.

Conclusions: Trifarotene is an effective and generally well-tolerated treatment for acne vulgaris, demonstrating efficacy in both facial and truncal acne. However, its precise role in clinical practice remains to be established, given the lack of clear superiority over existing therapies and its higher cost.

Key words: acne vulgaris; trifarotene; topical retinoids; RAR-γ agonist; retinoid

Introduction

Acne vulgaris is a prevalent chronic inflammatory disease of the pilosebaceous unit, affecting nearly 85% of the adolescent population in the USA. It can occur in any area abundant in sebaceous glands, but the face remains the most frequent site of involvement. Nearly half of patients with facial acne also exhibit truncal lesions. Active acne is clinically characterized by a range of cutaneous manifestations, such as comedones, papules, pustules, nodules, and cysts.[1,2] The pathogenesis is multifactorial, involving the interplay of increased sebum production, inflammation, colonization with Cutibacterium acnes, and follicular hyperkeratinization, thereby promoting comedone formation. Recent evidence suggests that inflammation is present throughout all stages of acne lesion formation, with keratinocytes producing pro-inflammatory cytokines, including interleukin (IL)-1 and tumor necrosis factor (TNF)-α.[3,4] Multiple studies have demonstrated an association between acne and dietary

patterns, particularly high glycemic index diet and dairy consumption. Additionally, genetic susceptibility and environmental factors are involved.[5,6] Acne may result in persistent sequelae, including scarring, which affects up to 20% of teenagers and psychological distress, potentially leading to depression and anxiety.[2,7] Effective treatment is often associated with substantial enhancement of self-esteem.[4] Current guidelines from the American Academy of Dermatology (AAD) and the European Dermatology Forum emphasize the central role of retinoids in acne management, as they influence multiple key components of acne vulgaris pathophysiology.[8,9] According to the AAD guidelines "retinoids are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedone lesion, and are anti-inflammatory".[9] Retinoids, a group of vitamin A analogues, are currently classified into four generations, with tretinoin as the first topical agent, followed by newer compounds such as adapalene and tazarotene.[10] Topical retinoids are widely recognized as a cornerstone in the management of acne vulgaris due to their established efficacy and favorable safety profile.[11] Trifarotene (Aklief), a novel fourth-generation retinoid and a first to specifically act as a RAR-γ agonist, was developed by Galderma Research and Development LLC, and approved by the FDA in 2019 for the treatment of acne vulgaris. Initially granted orphan drug status in 2014 for the management of congenital ichthyosis, trifarotene is now indicated for the topical therapy of facial and truncal acne in patients aged 9 years and older.[12–14] Contrary to expectations based on its RAR-γ selectivity, results from a network meta-analysis suggest that trifarotene may demonstrate lower tolerability and efficacy. In the absence of comparative data showing a distinct benefit over existing topical retinoids, its role in acne treatment appears limited, although it remains a potentially useful therapeutic option.[15,16] This review aims to summarize the pharmacology, efficacy, safety and clinical data on trifarotene, as well as its current role in the management of acne vulgaris.

Pharmacodynamics

Trifarotene is a highly potent and selective RAR-γ agonist, with a half maximal effective concentration (EC_{50}) of 7.7 nmol L^{-1}, exhibiting over 20-fold selectivity compared with RAR-α (EC_{50} of 498 nmol L^{-1}) and RAR-β (EC_{50} of 125 nmol L^{-1}).[17] In contrast, earlier-generation retinoids lack RAR-γ selectivity: first-generation compounds bind all retinoic acid receptors, while third-generation agents (adapalene and tazarotene) primarily target RAR-β and RAR-γ (Table 1).[17] By selectively activating RAR-γ—the predominant subtype in the skin—trifarotene modulates gene expression regulating epidermal differentiation, proliferation and stress response, as demonstrated in both *ex vivo* and *in vivo* studies.[17,18] Through its strong anti-

comedogenic, anti-inflammatory and antipigmenting properties, trifarotene exhibits clinical efficacy in patients with acne vulgaris. In a rhino mouse model, it demonstrated dose-dependent comedolytic activity, achieving full efficacy at a concentration 10-fold lower than that needed for tazarotene to produce comparable effects. Moreover, trifarotene exhibited superior antipigmenting activity compared with adapalene.[17] Although the exact mechanism of trifarotene in acne remains unclear, studies indicate it modulates both classical retinoid-induced pathways, as well as novel processes not previously associated with other retinoids, including cell adhesion, transport/skin hydration and proteolysis.[17,1]

Table 1. Pharmacological Comparison of Topical Retinoids[10,17]

Retinoid	Generation	RAR selectivity EC_{50} (nmol L^{-1})	t1/2: Human keratinocytes	t1/2: Human hepatic microsomes
Trifarotene	fourth-generation	RAR-α: 498 RAR-β: 125 RAR-γ: 7.7	>24 Hours	5 Minutes
Adapalene	third-generation	RAR-α: 22 RAR-β: 2 RAR-γ: 9	>24 Hours	>60 Minutes
Tazarotenic acid*	third-generation	RAR-α: 11 RAR-β: 2.5 RAR-γ: 11	>24 Hours	57 Minutes

Abbreviations: EC_{50}, half maximal effective concentration; RAR, retinoic acid receptor.
*the active compound of tazarotene

Pharmacokinetics

In a preclinical study, trifarotene demonstrated high stability in human keratinocytes (>24 h), while undergoing rapid metabolism in hepatic microsomes, with half-life (t1/2) of only 5 minutes. Conversely, adapalene and the active metabolite of tazarotene, tazarotenic acid, exhibited substantially longer hepatic half-lives (>60 minutes and 57 minutes, respectively; Table 1).[17] This pharmacokinetic profile allows trifarotene to maintain high local cutaneous activity with minimal systemic exposure, even when applied to large skin areas, such as those affected by truncal acne.[19,20]

Two maximal usage pharmacokinetic trials (MUsT) assessed the pharmacology and safety of trifarotene in adults (18-34 years) and pediatric patients (9-17 years) with moderate to severe acne. Under maximal-use conditions, systemic absorption was minimal, with quantifiable plasma concentrations observed in 37% of adults and 18% of children treated with the 50 μg/g formulation, compared with 61% of adults and 69% of children receiving 100 μg/g. In the 50

μg/g group, maximum plasma concentrations (C_{max}) ranged from 5 to 10 pg/mL in adults and from 7 to 9 pg/mL in children, with a time to reach the maximum concentration (t_{max}) of approximately 4 hours, indicating limited yet rapid absorption. Trifarotene showed no evidence of systemic accumulation after repeated application. Most adverse events were localized and mild, primarily erythema and skin irritation, with no hematologic or biochemical abnormalities reported. Overall, the drug demonstrated favorable local and systemic tolerability in both age groups.[19,21] In vitro, trifarotene is primarily metabolized by CYP2C9, CYP3A4, CYP2C8, and CYP2B6, and excreted mainly via feces.[12,22]

Clinical Trials

12-week PERFECT Trials

Two phase III, multicenter, double-blind, randomized, vehicle-controlled studies (PERFECT 1 and PERFECT 2) were conducted over 12-weeks to evaluate the safety and efficacy of once-daily trifarotene 50 μg/g cream versus vehicle cream.[23] A total of 2,420 patients aged ≥9 years with moderate facial and truncal acne were enrolled. Moderate severity was defined as a score of 3 on both the Investigator's Global Assessment (IGA) and the Physician's Global Assessment (PGA). Patients presenting with severe acne manifestations, acne cysts, or more than one facial or truncal nodule were excluded from participation.[23] The evaluation of efficacy was based on primary endpoints, including the percentage of patients achieving treatment success on the face, defined as an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a two-grade improvement from baseline, together with the absolute change in inflammatory and noninflammatory lesion counts at week 12. Secondary endpoints assessed similar parameters on the trunk using the Physician's Global Assessment (PGA), along with corresponding changes in truncal lesion counts from baseline to week 12. Safety evaluation included monitoring of adverse events, local tolerability, vital signs, and standard laboratory parameters.[23] In both studies, at week 12, trifarotene demonstrated significantly higher Investigator's Global Assessment success rates compared with the vehicle group (29.4% vs 19.5% in PERFECT 1 and 42.3% vs 25.7% in PERFECT 2; P<0.001; Table 2). Reductions in mean absolute inflammatory lesion counts were greater with trifarotene, reaching –19.0 in PERFECT 1 and –24.2 in PERFECT 2 (vs –15.4 and –18.7 with vehicle; P<0.001), as were reductions in noninflammatory lesions (–25.0 vs –17.9 in PERFECT 1 and –30.1 vs –21.6 in PERFECT 2; P<0.001). Similar results were observed on the trunk, with higher Physician's Global Assessment success rates for trifarotene versus vehicle group (35.7% vs 25.0% in PERFECT 1 and 42.6% vs 29.9% in PERFECT 2; P<0.001; Table 2). Improvements in both

inflammatory and noninflammatory truncal lesions were statistically significant as early as week 2 in PERFECT 2 and week 4 in PERFECT 1.[23] Trifarotene was generally well tolerated, with local tolerability manifestations predominantly mild to moderate in severity and resolving within the first weeks of treatment. The most common symptoms included erythema, scaling, dryness, and stinging/burning. Local tolerability was better on the trunk than on the face. Severe cutaneous adverse events (AEs) occurred in nine patients overall (skin irritation, sunburn, allergic dermatitis, and application-site pain, erosion, or irritation), but no serious AEs were reported. Treatment discontinuation due to AEs was infrequent—1.9% in PERFECT 1 and 1.2% in PERFECT 2—and no clinically meaningful changes in laboratory findings, vital signs, or physical examination were demonstrated.[23]

Table 2. Efficacy Results for Phase III Trifarotene Clinical Trials: PERFECT 1 and PERFECT 2[23]

	PERFECT 1		PERFECT 2	
	Trifarotene cream (n=612)	Vehicle cream (n=596)	Trifarotene cream (n=602)	Vehicle cream (n=610)
IGA success (face)	29.4%	19.5%	42.3%	25.7%
PGA success (trunk)	35.7%	25.0%	42.6%	29.9%

Abbreviations: IGA, Investigator's Global Assessment; PGA, Physician's Global Assessment.

52-week Clinical Trial

A 52-week, multicenter, open-label, phase III study assessed the long-term safety and efficacy of trifarotene 50 μg/g cream in patients aged 9 years and older with moderate facial and truncal acne.[24] Overall, 453 patients were enrolled and 348 completed the trial. Moderate severity was defined as a score of 3 on both the Investigator's Global Assessment (IGA) and the Physician's Global Assessment (PGA). In accordance with criteria applied in the PERFECT studies, treatment success required an IGA or PGA score of 0 (clear) or 1 (almost clear) with a minimum two-grade improvement from baseline. Quality of life was assessed using the 0-30 Dermatology Life Quality Index (DLQI) and the Children Dermatology Life Quality Index (C-DLQI), for patients aged ≤16 at baseline, with higher scores indicating greater quality of life impairment. Patients completed a QoL standardized form at baseline and subsequently at weeks 12, 26 and 52/ET.[24] Progressive clinical improvement was observed throughout the study period. IGA success rates escalated from 26.6% (week 12) to 65.1% (week 52), while PGA success

rates increased from 38.6% (week 12) to 66.9% (week 52; Table 3). By the end of the trial, overall success (overall percent IGA and PGA success in the same patient) reached 57.9% (Table 3).[24] At week 12, 41.4% of patients experienced substantial or complete improvement of facial acne, with this proportion rising to 54.8% by week 26 and reaching 66.6% at week 52. Among those with completed evaluations at week 52 visit, 53.8% (92/171) achieved DLQI values from 0 to 1, indicating no impact of acne on their quality of life, compared with 22.6% (47/208) at baseline visit. According to C-DLQI assessments, 54.2% of pediatric patients reported no effect of acne on quality of life at week 52, compared with 30.9% at baseline.[24] Trifarotene demonstrated a favorable safety and tolerability profile throughout the 52-week study. Cutaneous adverse events occurred in approximately 12.6% of patients, mainly pruritus, irritation, and sunburn at application sites. Severe treatment-related reactions were uncommon (0.7%) and included application site irritation, pruritus and erythema. Treatment discontinuation due to adverse events was infrequent (3%). No clinically relevant laboratory abnormalities were detected throughout the study. When tolerability issues arose, investigators reduced application frequency or temporarily discontinued treatment on affected regions.[24]

Table 3. Key Results for 52-week Trifarotene Clinical Trial[24]

	52-week Study Visits				
	Week 12	Week 20	Week 26	Week 38	Week 52
IGA success (face)	26.6%	43.3%	50.1%	57.6%	65.1%
PGA success (trunk)	38.6%	54.1%	58.4%	62.5%	66.9%
Overall IGA and PGA success in the same patient	22.0%	36.8%	43.3%	49.9%	57.9%

Abbreviations: IGA, Investigator's Global Assessment; PGA, Physician's Global Assessment.

Trial of Trifarotene Plus Doxycycline for Severe Acne Vulgaris

A randomized, controlled, 12-week, double-blind trial (n=202) comparing once-daily trifarotene 50 μg/g cream plus enteric-coated doxycycline 120 mg (n=133; T+D) with a vehicle formulation of trifarotene and placebo doxycycline (n=69; V+P), assessed the efficacy and safety of combining topical trifarotene with oral doxycycline in acne.[25] Patients aged ≥12 years with severe facial acne (characterized by at least 20 inflammatory lesions, 30-120 non-inflammatory lesions, and no more than 4 nodules) were enrolled. Efficacy was evaluated by changes in lesion counts from baseline and by achievement of IGA success, defined as a score

of 0 or 1 with a ≥2-grade improvement.[25] Reductions in lesion counts from baseline were substantially greater among subjects receiving T+D treatment than among those receiving V+P (-69.1 vs -48.1 for total lesions, -29.4 vs -19.5 for inflammatory lesions, and -39.5 vs -28.2 for non-inflammatory lesions; all P<0.0001; Table 4). Overall IGA success was accomplished by 31.7% of participants receiving T+D compared with 15.8% in the V+P group (P=0.0107).[25] Safety and tolerability were similar across treatment arms, with adverse events reported in 13.5% of patients in the T+D group, and 15.9% in the V+P group. Treatment emergent adverse events were predominantly mild and subsided over the course of the study. Overall, trifarotene plus oral doxycycline combination proved to be both safe and clinically effective for severe acne, providing significantly greater clinical improvement than vehicle plus placebo.[25]

Table 4. Absolute Change in Lesion Counts from Baseline at Each Visit of Trifarotene plus Doxycycline Trial[25]

	12-week Study Visits									
	Week 1		Week 2		Week 4		Week 8		Week 12	
	T+D	V+P	T+D	V+P	T+D	V+P	T+D	V+P	T+D	V+P
Total lesion count*	-16.1	-14.6	-28.0	-24.5	-43.6	-33.1	-55.0	-44.1	-69.1	-48.1
Inflammatory lesion count*	-7.6	-6.8	-12.7	-10.6	-19.6	-14.2	-22.9	-18.2	-29.4	-19.5
Non-inflammatory lesion count*	-8.6	-7.7	-15.3	-13.8	-24.0	-18.8	-32.1	-25.9	-39.5	-28.2

Abbreviations: T+D, Topical Trifarotene 50 μg/g Cream + Oral Doxycycline 120mg; V+P, Topical Trifarotene Vehicle Cream + Oral Doxycycline Placebo.
*mean absolute change in lesion count from baseline

Subject Satisfaction with Trifarotene in the Treatment of Acne Vulgaris

In a case series derived from a 12-week evaluation of a larger 24-week trial, three patients with moderate facial and truncal acne were managed with trifarotene 50 μg/g cream applied to the face, shoulders, upper back, and upper anterior chest. Patient satisfaction was evaluated through standardized questionnaires.[26] At baseline, moderate severity required the presence of at least 20 inflammatory and 25 non-inflammatory lesions on the face, as well as 20-100 inflammatory and ≥20 non-inflammatory lesions on truncal areas.[26] A decrease in both inflammatory and non-inflammatory lesion counts was observed. In the first subject, the percentage reductions in lesions on the face and trunk were 90% and 47% for inflammatory and non-inflammatory lesions, respectively. The second subject achieved a 20% reduction in inflammatory lesions and

22% reduction in non-inflammatory lesions. The third subject reached a reduction of 66% and 34% in inflammatory and non-inflammatory lesions, respectively, after 12 weeks of treatment.[26] All participants reported overall satisfaction with trifarotene 50 μg/g cream for both facial and truncal application, including ease of use and time to onset of effect. A quality of life improvement was observed in one case based on DLQI questionnaire score reduction over 12 weeks, though overall quality of life analysis was limited by incorrect questionnaire use in one adolescent and minimal baseline quality of life impairment in another.[26,27] Although constrained by a small number of subjects, the analysis draws attention to the significance of patient-perceived outcomes, particularly for truncal acne, an area with relatively limited evidence.[19]

Place of Trifarotene in Clinical Practice

Trifarotene 0.005% cream, a fourth-generation topical retinoid selectively targeting retinoic acid receptor-γ, has received FDA approval within the past decade for the management of acne vulgaris. Long-term clinical studies have demonstrated its efficacy in reducing both facial and truncal lesions, particularly comedonal acne, along with a favorable safety and tolerability profile.[15,18,28] Post-marketing data further support its predominantly local and mild safety profile, with a recent disproportionality analysis indicating that the majority of reported adverse events were non-serious (96.8%), in contrast to other topical retinoids. These observations are consistent with findings from clinical trials, although the relatively small number of reports limits the precision of the estimates.[29] Despite these favorable safety findings, emerging evidence raises questions regarding its relative position among topical retinoids. A 2023 network meta-analysis suggests that trifarotene may be less effective and associated with higher rates of treatment discontinuation due to adverse events compared with other agents in this class.[16] Additionally, two double-blind tolerability studies demonstrated significantly greater local irritation with trifarotene than with tazarotene 0.045% lotion.[30] However, another meta-analysis indicates that trifarotene, tazarotene, and clascoterone exhibit comparable efficacy in the management of moderate-to-severe acne vulgaris.[31] Notably, a recent case report described the use of oral dapsone in combination with topical trifarotene in severe, recalcitrant, isotretinoin-resistant nodulocystic acne, resulting in marked and sustained clinical improvement, with the Investigator's Global Assessment score decreasing from 4 to 1 and minimal residual scarring. The combination was well tolerated, with no significant adverse effects reported. Following discontinuation of dapsone after 3 months, continued trifarotene therapy maintained remission without recurrence of cystic lesions. Whereas trifarotene has

previously been studied in combination with doxycycline, this case presents a novel therapeutic approach involving oral dapsone, suggesting a potential therapeutic option in treatment-resistant acne that warrants further investigation.[32] A notable limitation of trifarotene is its high cost, with a 45-g formulation priced at over $500, which is considerably higher than that of other topical retinoids. This raises concerns about its cost-effectiveness in the absence of clear evidence of superior efficacy and tolerability.[18,33] Although its receptor selectivity and potency may offer advantages in selected or treatment-resistant cases, the lack of clear superiority, combined with higher cost and potential tolerability concerns, may limit its role in routine clinical practice. Further comparative studies are needed to better define its efficacy and safety relative to existing standard therapies.[15,34,35]

Conclusions

Acne vulgaris is a common, multifactorial inflammatory skin disease that can significantly impair quality of life and negatively affect psychological well-being. Trifarotene, a selective fourth-generation topical retinoid targeting RAR-γ, represents a novel therapeutic option for the management of both facial and truncal acne. Clinical trials have demonstrated its efficacy in reducing both inflammatory and non-inflammatory lesions, along with an overall favorable safety and tolerability profile characterized predominantly by mild, localized adverse reactions. However, comparative data remain limited, and emerging evidence from network meta-analyses and tolerability studies suggests that trifarotene may not demonstrate clear superiority over established topical retinoids, with some data indicating relatively lower efficacy and increased local irritation. In addition, its substantially higher cost raises concerns regarding cost-effectiveness in routine clinical practice. While its receptor selectivity and pharmacological properties may be beneficial in selected or treatment-resistant cases, its overall position within current acne treatment algorithms remains to be fully defined. Future studies, particularly well-designed head-to-head trials and real-world analyses, are needed to better clarify the comparative effectiveness, long-term safety, and cost-effectiveness of trifarotene, thereby helping to establish its optimal role in clinical practice.

Disclosure

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Declaration of the Use of Generative AI and AI-assisted technologies in the Writing Process

During the preparation of this work, the authors used Google Gemini and ChatGPT for the purpose of language improvement, readability enhancement, and text formatting. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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