Review Article - New Drug Approval

Trifarotene for the Treatment of Facial and Truncal Acne

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Abstract

Objective: This article reviews clinical trials to assess the efficacy, safety, and clinical application of trifarotene 0.005% cream (Aklief). **Data Sources:** A systematic review of the literature was performed using the terms *trifarotene* OR *Aklief* OR *CD5789* in MEDLINE (PubMed) and EMBASE databases. Articles prior to May 2020 were considered for inclusion. Bibliographies and ClinicalTrials.gov were also searched to identify further studies. **Study Selection and Data Extraction:** Relevant English language and human studies related to pharmacology, clinical trials, and safety were considered. **Data Synthesis:** In the 52-week phase III trial, treatment success rates for facial acne (Investigator Global Assessment [IGA] rating of no or almost no acne) and truncal acne (Physician's Global Assessment [PGA] rating of no or almost no acne) were 65.1% and 66.9%, respectively. Overall success rates (IGA and PGA success in the same patient) were 57.9%; 52.8% of patients had a Dermatology Quality of Life Index score of 0 or 1, compared with 22.6% at baseline. Trifarotene was well tolerated, with pruritus, irritation, and sunburn as the most common adverse effects. **Relevance to Patient Care and Clinical Practice:** Trifarotene is a newly Food and Drug Administration–labeled fourth-generation topical retinoid that shows particular promise in the treatment of facial and truncal acne vulgaris. It is an effective and safe addition to currently available retinoids. **Conclusion:** Trifarotene is effective and safe for treatment of facial and truncal acne. Future trials should compare its efficacy and tolerability with that of the older, clinically established retinoids. Despite efficacy, cost may be a prohibitive factor.

Keywords
acne vulgaris, trifarotene, retinoid, facial acne, truncal acne

Introduction

Acne vulgaris is a disease of the pilosebaceous unit with complex pathogenesis involving hyperkeratinization of the hair follicle, increased sebum production, and overgrowth of *Cutibacterium acnes*.[1] Topical retinoids are vitamin A analogues and have been long established as a mainstay in the treatment of inflammatory and noninflammatory acne vulgaris.[1] First-generation (tretinoin) and third-generation (tazarotene and adapalene) retinoids exert their activity by binding nonselectively to intranuclear retinoic acid receptors (RAR)-β and RAR-γ, which results in downstream normalization of follicular keratinization.[2-5] Subsequent decreased cohesion between keratinocytes reduces follicular occlusion, a primary mechanism by which comedones develop.[4] Topical retinoids also have immunomodulatory functions, which mitigate inflammation of active lesions and improve postinflammatory hyperpigmentation.[4] Additionally, retinoids act synergistically with other acne medications, enhancing their penetration of the epidermis and, thus, overall efficacy.[4] Second-generation retinoids (acitretin) are only available in oral formulations and are predominantly used in the treatment of psoriasis.[6]

Trifarotene 0.005% cream (Aklief) is the first-in-class fourth-generation topical retinoid, and as of October 2019 has been labeled by the US Food and Drug Administration (FDA) for the treatment of acne in patients 9 years and older. Trifarotene is the first new retinoid to join the market in more than 20 years and is selective for RAR-γ, which is highly prevalent in epidermal tissue.[7] The purpose of this review is to examine the pharmacology, clinical trials, safety, and efficacy of trifarotene in the treatment of acne vulgaris.

Methods

A systematic review of the literature was performed using the terms *trifarotene* OR *Aklief* OR *CD5789* in MEDLINE (PubMed) and EMBASE databases. All available studies

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Table 1. Comparison of Retinoids.[10]

Retinoid	Receptor selectivity EC_{50} (nmol L^{-1})	$t_{1/2}$ Keratinocytes	$t_{1/2}$ Hepatic microsomes	Comedolytic activity	Anti-inflammatory activity	Antipigmenting activity
Adapalene	RAR-α: 9 RAR-β: 2 RAR-γ: 22	>24 Hours	>60 Minutes	✓	✓	×
Tazarotenic acid	RAR-α: 11 RAR-β: 2.5 RAR-γ: 11	>24 Hours	57 Minutes	✓	✓	N/A
Trifarotene	RAR-α: 7.7 RAR-β: 125 RAR-γ: 498	>24 Hours	5 Minutes	✓	✓	✓

Abbreviations: EC_{50}, half maximal effective concentration; RAR, retinoic acid receptors.

written in English related to pharmacology, clinical trials, adverse events (AEs), and safety prior to May 2020 were considered for inclusion. Bibliographies of the articles were also searched to identify additional studies for inclusion. The website ClinicalTrials.gov was searched to identify ongoing or unpublished studies.

Results

Drug Pharmacology

Mechanism of Action. The 3 main subtypes of RAR— α, β, and γ—are nuclear hormone receptors whose activation causes regulation of cell growth, differentiation, and apoptosis.[8,9] RAR-γ is the predominant subtype found in the skin.[8,9] It is hypothesized that a drug selective for RAR-γ could preferentially act on the skin and effectively treat acne while mitigating adverse effects of skin irritation; however, the clinical significance of this selectivity is not currently known.[8,10] Trifarotene is a potent RAR-γ selective agonist because it binds to RAR-γ with a much higher affinity (half maximal effective concentration [EC_{50}] of 7.7) than to RAR-α or RAR-β (EC_{50} of 125 and 498, respectively).[10]

Pharmacokinetics. Trifarotene has a long elimination half-life in the skin and remains in keratinocytes for >24 hours, whereas it is quickly metabolized by the liver, with an elimination half-life of only 5 minutes.[10] In contrast, adapalene and tazarotenic acid (the active metabolite of tazarotene) have prolonged half-lives in hepatic microsomes of >60 minutes and 57 minutes, respectively (Table 1).[10] Trifarotene produces a total of 5 metabolites in in vitro assays, 3 of which are active; however, none of these active metabolites produce detectable plasma levels in humans.[11]

Comedolytic, Anti-inflammatory, and Antipigmenting Properties. Trifarotene is a potent comedolytic, resulting in a 98% reduction in comedones.[10] Its efficacy in comedone reduction is similar to that of tazarotene; however, it requires only one-tenth of the concentration to yield similar results.[10] Like other retinoids, trifarotene has anti-inflammatory properties.[10] Additionally, antipigmenting activity on ultraviolet radiation–induced pigmentation was significant after 6 weeks of treatment with trifarotene.[10] In contrast, adapalene did not have significant antipigmenting effects (Table 1).[10]

Summary of Clinical Trials for Acne Treatment

Shorter-Term PERFECT Trials. Two 12-week, multicenter, double-blind, randomized, vehicle-controlled phase 3 trials evaluated the safety and efficacy of daily 50 μg/g trifarotene cream versus vehicle cream.[12] Patients older than 9 years with moderate facial and truncal acne, defined as an Investigator Global Assessment (IGA) and Physician's Global Assessment (PGA) score of 3 (0, no acne; 4, severe acne), were enrolled.[12] The IGA scale, an assessment tool used by investigators, was used to evaluate facial acne, whereas the PGA scale, an assessment tool used by clinicians, was used to evaluate truncal acne.[12] End points included IGA and PGA success, defined as an IGA or PGA score of 0 or 1 (no acne or almost no acne, respectively) and a 2-grade or more improvement from the patient's baseline score.[12] In the first trial, PERFECT1 (NCT02566369), 612 participants were treated with trifarotene, and 596 patients received vehicle.[12,13] In the second trial, PERFECT2 (NCT02556788), 602 participants were treated with trifarotene, and 610 patients received vehicle.[12,14] Patients treated with trifarotene had higher IGA success rates than the vehicle group (29.4% vs 19.5% in PERFECT1 and 42.3% vs 25.7% in PERFECT2 [$P < 0.001$]).[12] The trifarotene group also demonstrated a greater decrease in inflammatory lesions (54.4% vs 44.8% in PERFECT1 and 66.2% vs 51.2% in PERFECT2 [$P < 0.001$]) and noninflammatory lesions (49.7 vs 35.7% in PERFECT1 and 57.7 vs 43.9% in PERFECT2 [$P < 0.001$]) versus the vehicle group (Table 2).[12]

Similar success was achieved in the treatment of truncal acne.[12] By week 12, patients treated with trifarotene had

Table 2. Trifarotene Phase III Clinical Trials.[12,15]

Study	Study design	Primary end point	Patients enrolled and initiated treatment (n)	Patients completed treatment (n)	IGA success rate[a] (%)	PGA success rate[b] (%)	Overall success rate[c] (%)	Patients who report DLQI score of 0 or 1[d] (%)	Percentage decrease in inflammatory lesions from baseline (%)	Percentage decrease in noninflammatory lesions from baseline (%)	AE (%)	Types of SAE (n)	Discontinuation as a result of AE (%)
Tan et al,[12] 2019; PERFECT1	Phase III, DB, randomized, vehicle controlled	12 Weeks	612 T vs 596 VC		29.4 T vs 19.5 VC	35.7 T vs 25.0 VC			Face: 54.4 T vs 44.8 VC Trunk: 57.4 T vs 50.0 VC	Face: 49.7 T vs 35.7 VC Trunk: 49.1 T vs 40.3 VC	Erythema: 23.7 Scaling: 21.4 Dryness: 23.0 Stinging/burning: 16.3	Irritation (1) Sunburn (1) Allergic dermatitis (1)	1.9
PERFECT2			602 T vs 610 VC		42.3 T vs 25.7 VC	42.6 T vs 29.9 VC			Face: 66.2 T vs 51.2 VC Trunk: 65.4 T vs 51.1 VC	Face: 57.7 T vs 43.9 VC Trunk: 55.2 T vs 45.1 VC	Erythema: 33.2 Scaling: 32.9 Dryness: 36.4 Stinging/burning: 24.9	Pain (1) Erosion (1) Irritation (1)	1.2
Blume-Peytavi et al,[15] 2019	Phase III, open label, noncomparative	52 weeks	453	348	65.1	66.9	57.9	52.8			Overall: 48.1 Cutaneous: 12.6 Pruritus: 4.6 Irritation: 4.2 Sunburn: 1.8	Irritation (1) Pruritus (1) Erythema (1)	3.5

Abbreviations: AE, adverse event; DB, double blind; IGA, Investigator Global Assessment; PGA, Physician's Global Assessment; SAE, severe adverse event; T, trifarotene; VC, vehicle controls.
[a]IGA success rate defined as score = 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline at week 52 compared with baseline.
[b]PGA success rate defined as score = 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline at week 52 compared with baseline.
[c]Overall success rate defined as IGA and PGA success in the same patient.
[d]Dermatology Life Quality Index (DLQI; score of 0 or 1 means acne having no effect on quality of life).

higher PGA success rates than the vehicle group (35.7% vs 25% in PERFECT1 and 42.6% vs 29.9% in PERFECT2 [$P < 0.001$]).[12] Trifarotene-treated patients also had a greater decrease in inflammatory lesions (57.4% vs 50% in PERFECT1 and 65.4% vs 51.1% in PERFECT2 [$P < 0.001$]) and noninflammatory lesions (49.1% vs 40.3% in PERFECT1 and 55.2% vs 45.1% in PERFECT2 [$P < 0.001$]) versus the vehicle group (Table 2).[12]

In both trials, trifarotene demonstrated early success, with significant reductions in inflammatory and noninflammatory lesions as early as week 1 posttreatment on the face and week 2 on the trunk.[12]

Trifarotene was overall well tolerated and had a favorable safety profile.[12] Common AEs included erythema, scaling, dryness, and stinging/burning.[12] Severe AEs were seen in 6 PERFECT1 patients and 3 PERFECT2 patients and included skin irritation, sunburn, allergic dermatitis, and application site pain, erosion, and irritation.[12] There were no significant abnormalities in vital signs, physical examinations, or laboratory findings (Table 2).[12]

Longer-Term 52-Week Trial. A 52-week, multicenter, open-label, noncomparative, phase 3 trial (NCT02189629) evaluated the safety and efficacy of 50 µg/g trifarotene cream in patients with moderate acne on the face and trunk.[15,16] Patients ≥9 years old with moderate facial and truncal acne, defined as a score of 3 (0, no acne; 4, severe acne) on the IGA and PGA scales, respectively, met criteria for inclusion.[15] A total of 453 patients were enrolled, 348 of whom completed the study.[15] Treatment success was defined in the same fashion as the PERFECT trials, with an IGA or PGA score of 0 or 1 and a 2-grade or more improvement from the patient's baseline score.[15] Quality of life was also measured on a scale of 0 to 30 using the Dermatology Life Quality Index (DLQI), in which a higher score corresponds to acne causing greater impairment in quality of life.[15]

IGA success rates at weeks 12, 20, 26, 38, and 52 were 26.6%, 42.3%, 50.1%, 57.6%, and 65.1%, respectively.[15] At the same time points, PGA success rates were 38.6%, 54.1%, 58.4%, 62.5%, and 66.9%.[15] Overall success rate (IGA and PGA success in the same patient) was 57.9% by week 52.[15] Percentage of patients with a DLQI of 0 or 1, meaning acne has little to no effect on quality of life, was 52.8% by week 52 compared with 22.6% at baseline.[15] Trifarotene was well tolerated, with 12.6% of patients experiencing cutaneous AEs.[15] The most common AEs included mild pruritus, irritation, and sunburn predominantly on treated areas.[15] There were 3 severe AEs (rated on a 0 to 3 scale [0, no symptoms; 3, severe symptoms]), which included more significant irritation, pruritus, and erythema.[15] Discontinuation rates resulting from AEs were low at 3.5% (Table 2).[15]

Relevance to Patient Care and Clinical Practice

As the first medication in the fourth-generation class of retinoids, trifarotene acts by binding selectively to the epidermis-predominant RAR-γ.[10] Prior retinoids, including adapalene and tazarotenic acid, are selective agonists of both the RAR-β and RAR-γ receptors.[5,17] Action at the RAR-β receptor has been shown to induce human dermal fibroblasts[18] as well as glandular metaplasia in animal studies.[19] Although the clinical significance of these findings is uncertain, it is postulated that they may contribute to retinoid-induced skin irritation, and thus, the RAR-γ selectivity of trifarotene may avoid these β-mediated effects.[10] Direct comparisons between trifarotene and older-generation retinoids may potentially validate trifarotene's theorized superiority with respect to drug tolerability and should, therefore, be considered.

Trifarotene is stable in keratinocytes for more than 24 hours, and compared with adapalene and tazarotenic acid, it is more quickly metabolized by hepatic microsomes.[10] These factors allow it to exert excellent activity in the skin while minimizing blood concentrations,[10] theoretically allowing for an improved safety profile in conditions that require diffuse skin applications, such as in truncal acne. Importantly, however, this benefit is purely hypothetical because topical retinoids have not been shown to produce important increases in blood concentrations.[20]

Like other retinoids, trifarotene is an excellent comedolytic and has substantial anti-inflammatory activity; however, it is unique in its superior antipigmenting activity on ultraviolet radiation–induced pigmentation when compared with adapalene.[10] This property may prove efficacious in the treatment of postinflammatory hyperpigmentation in inflammatory acne, seen more predominantly in skin of color.[10]

Prior topical retinoids available for the treatment of acne include tretinoin, available as a cream or gel; adapalene available as a cream, gel, or lotion; and tazarotene available as cream, gel, or foam.[21] A potential drawback of trifarotene is its limitation to a cream formulation.[10] Some guidelines have recommended the use of gel formulations in patients with oily skin while reserving creams for dry and sensitive skin.[22] This could render trifarotene suboptimal for patients with oily skin.

In pivotal and long-term clinical trials, trifarotene has demonstrated its efficacy as an acne treatment and has established a favorable safety profile with limited adverse effects.[12,15] In the PERFECT1 and PERFECT2 trials, trifarotene exhibited early success, with a significant reduction in lesion number on the face and trunk compared with vehicle cream as early as week 1 and week 2 post–treatment initiation, respectively.[12] The additional 52-week phase III trial reinforced these results, with significant

decreases in inflammatory and noninflammatory acne lesions as well as improvements in patient-reported quality of life.[15] A continuous increase in IGA and PGA success rates from initial measurement at week 12 onward[15] suggests that efficacy may improve with prolonged use. The adverse effects reported in these trials were congruent with the recognized tolerability profile of older-generation retinoids, which includes pruritus, irritation, sunburn, erythema, scaling, dryness, and stinging/burning localized to the sites of application.[12,15] Adverse effects were typically transient, and there were no serious AEs attributed to the application of trifarotene.[12,15] Future studies comparing efficacy and tolerability of trifarotene with the older retinoids are warranted.

A major drawback to trifarotene is cost, with one 45-g pump costing more than $500.[23] The pharmaceutical company that developed trifarotene offers a discount program for commercially insured and uninsured patients, enabling purchase of a 45-g pump for $0 and $75, respectively; however, this discount program is not available to patients enrolled in government-run or government-sponsored health care plans.[24] For comparison, costs of a 45-g tube of adapalene 0.1% gel and tretinoin 0.025% cream are around $34 and $47, respectively, whereas a 30-g tube of tazarotene 0.1% cream is around $68.[25] Despite the manufacturer's reductions in price for qualifying patients, treatment still may not be feasible for many patients. Additionally, trifarotene is currently only available by prescription, whereas the retinoid adapalene 0.1% gel can be purchased over the counter.[1]

Conclusion

Acne vulgaris is a common, chronic inflammatory skin disorder with a negative impact on quality of life and self-esteem.[26] Tretinoin, adapalene, and tazarotene are topical retinoids that have been the cornerstone for treatment of comedonal and inflammatory acne.[4] Trifarotene, a newly FDA-labeled fourth-generation topical retinoid, maintains a favorable safety profile and shows particular promise in the treatment of facial and truncal acne vulgaris. Future head-to-head trials are needed to compare its efficacy and tolerability with that of the older, clinically established retinoids. Additionally, cost may be a significant barrier for many patients.

Declaration of Conflicting Interests

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