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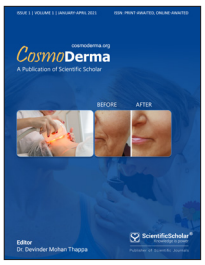

Focus

Trifarotene – A brief review in dermatology

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HISTORY AND INTRODUCTION

Tretinoin 0.05% solution (also known as all-trans retinoic acid [ATRA]; Vitamin A acid) was approved by the US Food and Drug Administration (FDA) in 1971 for the treatment of acne vulgaris and was the first topical retinoid. Poor adherence has been linked to the local irritation brought on by topical retinoids, which is particularly noticeable during the first few weeks of therapy. To increase efficacy and tolerability, new retinoids, formulations, and combinations were released in the years that followed. Over 50 years of study has produced new generations of retinoids that are more tolerable and have better stability (mostly due to structural modifications). Trifarotene is the only fourth-generation retinoid, which is selectively bound to the retinoic acid receptor-gamma (RAR-γ) receptor. In 2019, the FDA approved trifarotene, the first topical retinoid of its kind, for the treatment of acne vulgaris in patients who are 9 years of age or older.[1]

However, larger human studies and multiple perspectives of the drug are to be tested to assess its efficacy in other dermatological indications.

STRUCTURE

The intranuclear RAR or retinoic X receptor, each of which has three primary isotypes (alpha, beta, and gamma), represents the way retinoids exert their actions. The FDA has approved four topical preparations for the treatment of acne vulgaris: ATRA, often known as tretinoin (first generation), adapalene and tazarotene (third generation), and trifarotene (fourth generation). In the epidermis, RAR-γ is the most prevalent isoform. Trifarotene is the only topical retinoid that binds to it selectively.[1]

MECHANISM OF ACTION AND PHARMACOKINETICS

Mechanisms that have not been linked to other retinoids before, such as:

1. Cell adhesion: Trifarotene decreases dystonin, which weakens intercellular adhesions and hemidesmosomes and permits comedolysis and keratinocyte migration
2. Skin hydration: Trifarotene affects skin barrier function and improves cutaneous hydration by upregulating aquaporin 3 and peptidyl arginine deiminase 1
3. Proteolysis: Trifarotene efficiently promotes antiaging advantages in the skin by downregulating matrix metalloproteinases, which are proteins that break down collagen and elastin.

Ex vivo human keratinocytes have shown that trifarotene is very metabolically stable (>24 h), while hepatic microsomes rapidly metabolize it (half-life <5 min), leading to significant cutaneous activity and low systemic concentrations.

When administering trifarotene to large body surface regions, as in truncal acne, it is necessary for the liver to eliminate the medicine quickly. This minimizes potential safety concerns related to systemic absorption. Despite repeated administrations, its short half-life (2–9 h) prevented systemic accumulation. There were no hematologic or biochemical anomalies found.

METHOD OF APPLICATION

Providing the patient with instructions on how to apply trifarotene is crucial to reduce the chances of side effects. Before the treatment, the affected areas should be washed and pat dried using a light or soapless cleaner. The next step is to apply a thin coating of trifarotene cream in the evening. One pump for the face and two pumps for the chest, shoulders, and back are advised to ensure consistency. One can use moisturizer as often as necessary to reduce irritation and dryness. Sunscreen application is advised daytime.[2]

To date, every published study has looked at the use of trifarotene as a monotherapy and in a cream formulation with a single strength of 50 μg/g. Other topical retinoids are available in cream and gel formulations; therefore, future research examining different trifarotene formulations ought to be taken into consideration. Trifarotene cream use may be limited in cases with oily skin, which is a prevalent phenotype among acne patients and for which gel formulations are often recommended.[3]

GENETIC AND MOLECULAR PATHWAY OF TRIFAROTENE

A distinct group of 67 genes were modified by trifarotene, the most dominantly regulated of which were MMP12 and MMP13, CXCL13, XCL1, and SPP1/Osteopontin. Trifarotene affected T-cell migration, neutrophil chemotaxis, and proinflammatory responses. It also has a decrease in B-cells; in acne, larger B-cell counts have been linked to more severe cases of the condition.[4]

INDICATIONS

Acne

According to epidemiologic research, acne affects 9.4% of the world's population, making it the eighth most common disease globally. First of all, according to the American Academy of Dermatology's guidelines for managing acne, "retinoids are the core of topical therapy for acne because they are anti-inflammatory, comedolytic, and resolve the precursor micro-comedone lesion."[5] In the 50 years after tretinoin was first approved, topical retinoids, either by themselves or in combination with other agents, have established themselves as the cornerstone of acne treatment. In 2019, the FDA approved trifarotene, the first topical retinoid of its kind, for the treatment of acne vulgaris in patients who are 9 years of age or older.[1] Adherence to acne treatment is significantly hampered by topical retinoid irritation. The irritant potential of tazarotene 0.045% lotion in comparison to adapalene 0.3% gel and trifarotene 0.005% cream was evaluated in two investigations, according to the study by Draelos. Tazarotene 0.045% lotion was numerically less irritating than trifarotene 0.005% cream in the head-to-head comparisons shown here, and it was substantially less irritating than adapalene 0.3% gel, one of the best-tolerated topical retinoids for acne.[6]

Acne scars

Topical retinoids can thicken the epidermis by stimulating dermal fibroblasts to produce more procollagen. In addition, Dreno *et al*.'s transcriptome and gene expression research revealed that trifarotene specifically modulates genes related to cellular migration, inflammation, and cellular matrix remodeling while downregulating pro-fibrotic macrophages. Trifarotene's phase III trials showed comparable benefits in active acne on the face and trunk; hence, it stands to reason that trifarotene would also lessen truncal scarring. Truncal acne frequently results in long-lasting scarring, such as keloidal and macular atrophic scars.[7]

Autosomal recessive congenital ichthyosis

In 2014, the FDA granted topical trifarotene an Orphan Drug Designation in recognition of its safety and tolerability in the treatment of congenital ichthyosis. A 12-week topical trifarotene treatment for moderate-to-severe autosomal recessive lamellar ichthyosis in adults (≥18 years old) and adolescents (ages 12–17 years, inclusive), that was phase II, randomized, multicenter, double-blind, and vehicle-controlled. The treatment was followed by a 12-week open-label extension. The patients were split into two groups; one group was given trifarotene twice a day, and the other group was given a vehicle treatment for a period of 12 weeks. The study's findings are not yet available.

Malignancies

Among the treatments for cutaneous T-cell lymphoma (CTCLs) that the World Health Organization and European organization for research and treatment of cancer (EORTC) propose, retinoid therapy plays a critical role. The FDA has approved topical bexarotene 1% gel for chronic or refractory stage IA and IB CTCLs. In CTCL cell lines, it has been observed to induce apoptosis. There is currently only one phase I trial that has been published in the literature to assess the safety and tolerability of trifarotene in patients with early-stage CTCL; however, the results are not yet accessible.

In addition to oncohematology, retinoid use is predominant in cutaneous inflammatory, dyskeratotic, and viral disorders.

Trifarotene's safety and tolerability have been demonstrated through tests for the treatment of acne and congenital ichthyosis. There are yet no excellent randomized clinical trials assessing trifarotene treatment of primary cutaneous lymphomas. Unlike other retinoids, trifarotene operates specifically on RAR-γ, mitigating the negative effects of RAR-β. It also has a better clinical profile than medicines that act on both RAR-β and RAR-γ, such as tretinoin and its derivatives.

As has already been observed with earlier generation retinoids, there may be a reason to further research on the use of trifarotene in skin problems because RAR-γ is significantly more common in the skin than the other retinoid receptors.[8]

CONCLUSION

While research on mice has demonstrated that trifarotene has a stronger comedolytic impact than tazarotene and ATRA, no human studies have been conducted to support these results in clinical settings. Trifarotene's extremely selective activity, which may lower the likelihood of discomfort, makes it distinctive. Trifarotene's known side effect profile, however, appears to be comparable to other retinoids'. There are currently no comparison studies that demonstrate trifarotene's advantages in terms of side effects. According to the literature, retinoid's irritability is an extension of their therapeutic benefit. We still do not know if trifarotene's claims of reduced irritability are clinically meaningful or if efficacy suffers as a result. Hence, comparative human study should be conducted to establish its efficacy and safety as compared to other topical retinoids.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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