Trifarotene – The latest retinoid

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Introduction

Retinoids are an important class of drugs in dermatology, and include topical and systemic agents. They act through retinoid receptors which belong to the superfamily of nuclear ligand-activated transcriptional regulators.[1] There are two families of retinoic acid (RA) receptors - RAR (retinoic acid receptors α, β and γ) and RXR (retinoid X receptors α, β and γ), and their numerous isoforms. The main effect and side effects of retinoids are mediated through the RARs.[1,2] Based on the structural features and considering the time of introduction, retinoids are classified into four generations of topical and systemic agents.[2-8] [Tables 1 and 2].

The chief adverse effect of topical retinoids is local irritation. It was previously shown that RAR-γ receptors mediated retinoid-induced skin irritation in Rhino mouse and rabbit models.[9] However, recent research suggests that dermal RAR-β might significantly participate in retinoid-induced skin irritation. This suggests the possibility that a selective RAR-γ agonist drug may cause less irritation.[10,11]

Trifarotene is the latest entry into the retinoid family and is marketed as a topical agent. Trifarotene is a fourth-generation retinoid with potent and selective RAR-γ agonist activity, claimed to have an improved efficacy/safety ratio when compared with less or non-selective RAR agonists.[10] In October 2019, trifarotene received Food and Drug Administration (FDA) approval for the topical treatment of acne vulgaris in patients nine years of age and older, thus becoming the first retinoid approved in the past 20 years for management of acne.[12,13] However, so far there are no published head-to-head comparison studies of this new drug with other retinoids.

Structure and Mechanism of Action

Trifarotene is a pure and potent RAR-γ agonist. The chemical name is 3”-tert-butyl-4’-(2-hydroxy-ethoxy)-4”-pyrrolidin-1-yl-[1,1’,3’,1”]terphenyl-4-carboxylic acid. Structurally, it is a terphenyl acid derivative.[14] The clinical effects of retinoids in dermatology are through the ability to modify pathways involved in inflammation, cellular differentiation, apoptosis and sebaceous gland activity. RAR are always paired with an RXR, whereas RXR can exist as a homodimer with another RXR, or as a heterodimer with several other families of receptors. The genes regulated by retinoids contain a DNA sequence called retinoic acid response element which attaches itself with the RAR–RXR heterodimer. On binding of a ligand, the RAR–RXR heterodimer acts as a transcription factor, resulting in the expression of a number of proteins involved in growth and regulation. The retinoid–receptor complex can also act in an indirect fashion by antagonizing the action of other transcription factors.[1,2,4]

Trifarotene has no activity at RXRs, and significantly less activity at RAR-β and RAR-α (16- and 65-fold lower than activity at RAR-γ, respectively). Agonism at RARs results in dimerization, and the resultant receptor-ligand dimer binds to specific DNA regulatory sequences in the promotor regions of retinoid-responsible genes. This reduces the expression of various genes involved in retinoid metabolism, epidermal differentiation/proliferation, keratinization, epidermal response to stress, immune modulation and apoptosis.[14,15]

In addition to these, trifarotene may modulate retinoid-mediated pathways involved in cell adhesion, skin hydration and proteolysis, through the following mechanisms:[10,14-16]

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1. Cell adhesion: Trifarotene downregulates dystonin, and thus weakens hemidesmosomes, thereby interfering with cell adhesion. This induces migration of keratinocytes which facilitates comedolysis.
2. Transport/skin hydration: Trifarotene improves skin hydration by induction of aquaporin-3 channels and peptidyl arginine deiminase 1 in skin and thus promotes barrier function of the skin. Trifarotene may also maintain the cutaneous pH homeostasis by impacting the ammonium/ammonia (NH4+/NH3) balance.
3. Proteolysis: Membrane metallo-endopeptidase upregulation is associated with elastin degradation and wrinkling of skin. Trifarotene downregulates this enzyme, thereby improving the skin texture – a feature not seen with other retinoids.[10]

Actions

Trifarotene has demonstrated a marked comedolytic activity with reduction in the comedone count and increased epidermal thickness. Trifarotene produced the same comedolytic effect as other known retinoids such as tazarotene and all-trans-retinoic acid, at about ten times lower dose in mouse models. Trifarotene has also shown anti-inflammatory and depigmenting actions in *in vitro* studies.[10] At present, there are no human studies comparing the efficacy of trifarotene with other retinoids.

Table 1: Classification of retinoids[2]

Generation	Chemical structure	Members
First generation	Non-aromatics	Retinol Retinaldehyde Tretinoin Isotretinoin Alitretinoin
Second generation	Mono-aromatics	Etretinate Acitretin
Third generation	Poly-aromatics	Adapalene Tazarotene Bexarotene
Fourth generation	Pyranones	Seletinoid G Trifarotene

Pharmacokinetics

Absorption: Topically applied trifarotene is absorbed in low amounts. Peak plasma concentration occurs four hours after application. Clinical significance of this is unknown. It is not expected to show long-term accumulation.[17]

Distribution: Trifarotene penetrates the skin with an exponential distribution from the stratum corneum to the rest of the epidermis and dermis. It also penetrates the pilosebaceous unit. Trifarotene is greater than 99.9% bound to plasma proteins. Animal studies have shown high concentrations in the liver, kidney, preputial gland, adrenal cortex and salivary gland. It crosses the placental and blood-brain barrier in small amounts.[10,14,17-19]

Metabolism: Trifarotene is stable in human keratinocytes with a half-life of more than 24 hours, but very rapidly metabolized in human liver microsomes by CYP2C9, CYP3A4, CYP2C8 and to a lesser extent by CYP2B6.[10] The elimination half-life ranges from two to nine hours.[17]

Indications

The US FDA granted orphan drug status to trifarotene for the treatment of lamellar ichthyosis in 2014.[20] Trifarotene received FDA approval for the topical treatment of acne vulgaris in

Table 2: Topical retinoids used in acne[3-8]

Retinoid	Mechanism of action	Therapeutic effects	Indications	Remarks
All-trans retinol (retinol)	Gene transcription	Comedolysis Epidermal thickening, dermal regeneration, pigment lightening	Part of over-the-counter cosmetic products	First generation, weaker retinoid
All-trans retinoic acid (tretinoin)	Gene transcription normalizes follicular epithelial differentiation	Comedolysis Reduces fine wrinkling and roughness, mottled hyperpigmentation of skin	Acne vulgaris, photoaging, resurfacing peels, actinic keratosis/ precancers and actinic lentigines, melasma, warts, acanthosis nigricans	First generation
Adapalene	Normalizes follicular epithelial differentiation and reduces microcomedone formation	Comedolysis	Acne vulgaris, photodamage and skin aging, actinic keratosis/ precancers and actinic lentigines	Third generation RAR β/γ selective, potent More chemically stable, less photolabile and more lipophilic
Tazarotene	Blocks ornithine decarboxylase activity and reduces cell proliferation and hyperplasia. Normalization of keratinocyte differentiation in psoriasis	Comedolysis Reduces fine wrinkling, facial mottled hyper and hypopigmentation and lentigines	Mild to moderate acne Psoriasis photoaging	Prodrug of tazarotenic acid. Third generation. Selective to RAR-α and RAR-γ, but not to RXRs More potent comedolytic activity
Trifarotene	Reduce epidermal differentiation/proliferation, keratinization and apoptosis	Comedolysis increased epidermal thickness Improves skin texture Depigmenting effect Anti-inflammatory	Lamellar ichthyosis, acne vulgaris	Pure and potent RAR-γ agonist. No activity at RXRs

RAR: Retinoic acid receptor, RXR: Retinoid X receptor

patients nine years of age and older in October 2019.[13] It is mainly indicated for the management of moderate acne on the face and trunk.[12] The efficacy and safety were determined by two large scale phase III trials- PERFECT 1 and PERFECT 2.[12] They were double-blind, randomized, vehicle-controlled, 12-week studies of once-daily trifarotene cream versus vehicle in subjects aged nine years or older.[12,13] However, so far there are no published head-to-head comparison studies of this new drug with other retinoids on human subjects.

Dosage and Administration

Trifarotene is available as 50 mg/g (0.005%) cream. The manufacturer advises that it should be applied as a thin layer to clean and dry skin in the evening. It is marketed as a pump formulation.[19]

The use of a moisturizer before and after the application of trifarotene is recommended as frequently as needed from the initiation of treatment, while allowing sufficient time before and after the application of the drug to allow the skin to dry.[19]

Adverse Effects

Trifarotene exhibits the expected local tolerability profile of a topical retinoid. Even though it is expected that this drug causes significantly less irritation, the most commonly reported adverse effect is local irritation, including erythema, dryness, scaling, burning, pruritus and sunburn, as is with other retinoids. As photosensitivity is a concern, patients must be advised regarding sun protection and avoidance of phototherapy. The majority of the observed side-effects are mild to moderate, occur during the initial few weeks, and subside thereafter. Local tolerability on the trunk is better than on the face. Use of a non-comedogenic moisturizer and short contact therapy may be helpful in reducing local irritation. There are no human trials comparing the effect or side effects of this drug with other topical retinoids. PERFECT 1 and 2 are vehicle-controlled trials.[12,18,19]

Acne exacerbation, allergic contact dermatitis, discoloration, erosion, pain on the skin, rash and swelling have been reported less commonly.[14,18,19]

Animal studies of systemic exposure to trifarotene in rats have shown hypervitaminosis A, slight decrease in red cell mass with compensatory reticulocytosis, increased extramedullary erythropoiesis and/or increased granulocytopoiesis, increase in leukocyte counts, slight increases in cholesterol and triglycerides, decrease in albumin and albumin/globulin ratio, epiphyseal growth plate disorganization (femur/sternum), ossification of the epiphyseal cartilage, increased osteoclastic activity, hyperplasia, hyperkeratosis and ulcers of the forestomach mucosa, eye irritation, pre-neoplastic and neoplastic changes and fetal malformations.[17,19]

Safety

Studies till date have shown trifarotene to be well-tolerated and effective. Safety on long-term use up to 52 weeks for moderate facial and truncal acne has been demonstrated in patients between ages 9 and 54.[18]

Safety and efficacy in children below nine years, and in geriatrics above 65 years has not been established.[18,19] The systemic absorption following topical application of trifarotene has not been affected either by age or gender.[17] However, more studies in different population groups are needed to substantiate these findings. Post-marketing studies may shed more light on rarer side effects of this new retinoid during the next few years.

There are no adequate and well-controlled studies of trifarotene in pregnant or breastfeeding women. As is for other retinoids, it should be ensured before treatment initiation, and before each fresh prescription, that the patient is not pregnant. Although there may be less potential for systemic exposure, trifarotene is a teratogenic drug. The level of exposure required for teratogenicity in humans is not known. It is unknown whether trifarotene is excreted in human milk. Oral animal studies have shown that trifarotene can cross the placental barrier and is also excreted in the breast milk of lactating rats. Hence, trifarotene must be strictly avoided in pregnancy, breastfeeding and in women planning pregnancy.[15]

Contraindications

Pregnancy, active eczema and hypersensitivity to trifarotene are contraindications for using this drug.[14,19]

Drug Interactions

There are no reported clinically significant drug-drug interactions of trifarotene till date. Trifarotene neither induces nor inhibits hepatic microsomal enzymes.[17]

Questions to be Answered

Although mouse models have shown a greater comedolytic effect for trifarotene in comparison with tazarotene and all-trans retinoic acid, there are no human studies to substantiate these findings in clinical scenarios. The unique attribute of trifarotene is that it has a highly selective action which in turn may reduce chances of irritation.[10] However, the known side effect profile of trifarotene seems similar to that of other retinoids. There are no comparative trials yet to prove any superiority of trifarotene in terms of adverse effects.

There are studies which state that irritation by retinoids is an extension of their therapeutic effect.[21,22] It remains to be seen whether the claims of lesser irritability by trifarotene is clinically significant, and whether it comes at the cost of efficacy. Tretinoin still remains the gold standard topical medication for acne, and trifarotene needs to go on a head-to-head challenge with it to prove eminence, if any.

Conclusion

Trifarotene is the latest fourth generation retinoid with a selective action on RAR-γ receptor, and has been

demonstrated to be yet another congener in the management of acne. However, the existing topical retinoids have proven their mettle in the fight against acne, and the advantages of trifarotene over them are yet to be proven beyond doubt. More studies on large groups, and comparative trials with other retinoids are needed to establish where trifarotene lies in terms of efficacy, tolerability and long-term safety.

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Conflicts of interest
There are no conflicts of interest.

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