# Tazarotene : A Potent Medication for Anti- Acne Effect

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***Abstract*** **- Acne vulgaris is a common pilosebaceous unit inflammatory chronic illness. It frequently necessitates long-term therapy, leading in increased demand for popular topical drugs in order to achieve long-term compliance. Tazarotene foam 0.1 percent is a new tazarotene formulation. The efficacy and tolerance tests of the novel formulation are reviewed, and a potential use for the medication in the treatment of acne vulgaris is suggested.**

***Index Terms*** **- Retinoids, Efficacy, Safety, Tolerability.**

## INTRODUCTION

Acne vulgaris is a common pilosebaceous unit inflammatory chronic illness. It's thought to be a complex disease caused by four basics pathophysiologic processes1:

- Abnormal follicular keratinization that leads to ductal obstruction.
- Increased and altered sebum production that is androgen induced.
- Follicular colonization and proliferation of Propionibacterium acnes.
- Altered adaptive immune response and inflammation2.

Despite the fact that it is commonly thought of as a self-limited and non-physically damaging adolescent condition, its incidence persists into adulthood, and its psychological impact can be significant, contributing to low self-esteem, anxiety, and despair3. As a result, there is a high demand from patients for effective acne treatments, such as prescription drugs and over the counter solutions1. Furthermore, given the requirement for long-term treatment, there is a greater demand for patient-friendly topical treatments in order to achieve long-term compliance4. As a result, agents are available in a variety of formulations. These include topical antibiotics, retinoids, and benzoyl peroxide in monotherapy or in combination products. Systemic medications also include antibiotics and retinoids, as well as hormonal agents5.

Pharmacology, mode of action, and Pharmacokinetics of Tazarotene foam6, 7

Tazarotene is a retinoid that belongs to the acetylenic family. Tazarotene is ethyl 6-([4,4-dimethylthiochroman-6-yl]ethynyl)nicotinate in chemical terms. Tazarotene is a retinoid prodrug that is easily converted to its active form, the homologous carboxylic acid of tazarotene, in both animals and humans. Tazarotene acid binds to all three members of the retinoic acid receptor (RAR) family – RAR, RAR, and RAR – but has a higher affinity for RAR and RAR and may influence gene expression.

Tazarotene is a drug that is used to treat psoriasis and acne. The US Food and Drug Administration (FDA) has only approved the 0.1 percent strength for acne therapy. For acne vulgaris, cream 0.1 percent is recommended, gel 0.1 percent is recommended for mild-to-moderate acne vulgaris, and foam 0.1 percent is recommended for moderate-to-severe acne vulgaris. Tazarotene, adapalene, and tretinoin have varied outcomes in comparison trials, with some researchers claiming equivalent efficacy and tolerability, while others claiming tazarotene has greater efficacy and irritation8.

The antihyperproliferative, normalizing-of-differentiation, and anti-inflammatory properties of tazarotene may be the basis of its therapeutic benefit in acne9. The following are some of the cellular pathways and inflammatory cascades that may be linked to acne aetiology and are regulated by topical tazarotene:

- Reduced expression of hyperproliferative keratins K6 and K16, which are increased during comedogenesis10.
- Suppression of activation of the activator protein 1, which results in reduced expression of several matrix metalloproteinases from keratinocytes, which have been shown to be increased in acne vulgaris.
- Decreased Toll-like receptor (TLR) 2 expression and ligand interaction with P. acnes, resulting in suppression of the TLR-2-induced innate response that causes acne inflammation11.
- Increased epidermal turnover, with reduction in post inflammatory hyperpigmentation.
- Normalization of epidermal cellular differentiation and decreased hyperkeratinization10.
- Downregulated expression of the epidermal growth factor receptor.7

In 2012, the FDA authorised Tazarotene foam 0.1 percent for the treatment of acne vulgaris in individuals aged 12 and up. It's the first time a retinoid has been used in a foam formulation12. The novel foam vehicle is hydrating, emulsion-based, and ethanol-free. It's made up of butylated hydroxytoluene, ceteareth-12, citric acid anhydrous, diisopropyl adipate, light mineral oil, potassium citrate monohydrate, potassium sorbate, purified water, and sorbic acid in an aqueous-based foam carrier13.

Tazarotene is a retinoid prodrug that undergoes de-esterification in the epidermis and plasma to become the physiologically active form of tazarotenic acid11. Tazarotene and tazarotenic acid are highly attached to human plasma proteins (greater than 99 percent). In the plasma, only a small amount of the parent molecule may be found. Tazarotenic acid's secondary metabolites (sulfoxide, sulfone, and an oxygenated derivative of tazarotenic acid) are excreted through the urine and fecal systems14.

The relative bioavailability of the active metabolite tazarotenic acid after topical administration of two distinct formulations of tazarotene – foam or gel – was assessed in a Phase I trial15. Twenty-nine individuals with moderate-to-severe acne vulgaris were given a once-daily dose of 3.7 g tazarotene foam 0.1 percent or gel 0.1 percent in a 13:16 ratio, applied to around 15% of the body surface area for 22 days (face, chest, upper back, and shoulders). Maximum plasma concentration (Cmax), time to Cmax, concentration in plasma, elimination half-life, and areas under the plasma concentration–time curve from time zero to time of last measurable concentration and during a dosage interval was used to determine systemic exposure to tazarotene and tazarotenic acid (AUCs). Statistical study of these pharmacokinetic parameters for tazarotene and its active metabolite revealed that tazarotene gel had a considerably greater AUC0–t and Cmax than tazarotene foam by an average of 1.8 to 2.2 times16. When compared to tazarotene gel 0.1 percent, the results of this study showed that tazarotene foam 0.1 percent delivers less tazarotenic acid systemic exposure and better safety for the treatment of acne vulgaris15.

Efficacy Studies17, 18, 19

The efficacy of tazarotene foam 0.1 percent against vehicle foam was evaluated in two Phase III multicenter, randomized, double-blind, vehicle-controlled, parallel-group investigations in acne vulgaris individuals. The research was conducted in 39 locations across Canada and the United States. The first trial enrolled 744 people, while the second enrolled 742 people between the ages of 12 and 45 who had moderate-to-severe acne vulgaris on the Investigator Static Global Assessment (ISGA) scale, with 25–50 inflammatory lesions on the face and 30–125 noninflammatory lesions at baseline. The following were the primary outcomes of these Phase III studies:

- Lesion reduction in two of three lesion counts (inflammatory, noninflammatory, and total) from baseline to week 12 (end of treatment).
- Percentage of subjects who had a score of 0–1 (clear or almost-clear skin) on the ISGA scale.
- A minimum 2-grade improvement at week 12.
- For 12 weeks, patients were randomly assigned to receive either tazarotene foam 0.1 percent or vehicle foam. The treatment arm that received tazarotene foam had positive results in both clinical trials. When comparing the tazarotene foam to the vehicle foam, the reduction in lesion counts was statistically larger (P0.001). On tazarotene foam, a higher percentage of individuals had an ISGA score of 0 or 1 than on vehicle foam. In both studies, the tazarotene foam group had a substantially higher (P0.001) proportion of patients who improved by at least

two grades on the ISGA scale by the conclusion of treatment than the control arm. Table 1 shows the reduction in lesion counts and improvement in the ISGA scale at week 12.

Table 1-Reductions in lesion counts and improvement in Investigator Global Assessment at week 12

| | Tazarotene foam, n=371 | Vehicle foam, n=372 | Tazarotene foam, n=373 | Vehicle foam, n=369 |
|---|---|---|---|---|
| Inflammatory lesions | | | | |
| Mean absolute reduction from baseline | 18.0 | 14.0 | 18.0 | 15.0 |
| Mean percentage reduction from baseline | 58% | 45% | 55% | 45% |
| Noninflammatory lesions | | | | |
| Mean absolute reduction from baseline | 28.0 | 17.0 | 26.0 | 18.0 |
| Mean percentage reduction from baseline | 55% | 33% | 57% | 41% |
| Total lesions | | | | |
| Mean absolute reduction from baseline | 46.0 | 31.0 | 43.0 | 33.0 |
| Mean percentage reduction from baseline | 56% | 39% | 56% | 43% |
| IGA, n (%) | | | | |
| Minimum 2-grade improvement and IGA of 0 or 1 | 107 (29%) | 60 (16%) | 103 (28%) | 49 (13%) |

Safety and Tolerability issues[20]

Table 2 shows the results of the Phase III trials on safety. The majority of the negative reactions were mild to moderate in severity. 3.0% of subjects had severe adverse responses, while 2.6 percent of patients stopped due to local skin reactions.

Table 2-Incidence of adverse reactions at the application site in 1% of patients treated with tazarotene foam 0.1%

| Adverse reactions at the application site | Tazarotene foam, n=744 | Vehicle foam, n=741 |
|---|---|---|
| Patients with any adverse reaction, n (%) | 163 (22) | 19 (3) |
| Irritation | 107 (14) | 9 (1) |
| Dryness | 50 (7) | 8 (1) |
| Erythema | 48 (6) | 3 (<1) |
| Exfoliation | 44 (6) | 3 (<1) |
| Pain | 9 (1) | 0 |
| Photosensitivity (including sunburn) | 8 (1) | 3 (<1) |
| Pruritus | 7 (1) | 3 (<1) |
| Dermatitis | 6 (1) | 1 (<1) |

Table 3 Analysis of patients lost to follow-up

| | Tazarotene foam | Vehicle foam |
|---|---|---|
| Started | 372 | 372 |
| Completed | 306 | 333 |
| Not completed | 66 | 39 |
| Adverse event | 11 | 1 |
| Lost to follow-up | 14 | 14 |
| Noncompliance with study product | 1 | 1 |
| Withdrawal by subject | 32 | 16 |
| Relocation | 0 | 4 |
| Pregnancy | 2 | 1 |
| Protocol violation | 2 | 0 |
| Took excluded medication | 2 | 0 |
| Did not meet eligibility criteria | 1 | 2 |
| Change in work situation | 1 | 0 |

There is no information on statistical analysis when assessing the impact of tazarotene foam treatment on quality of life using the Dermatology Life Quality Index on patients older than 17 years and the Children's Dermatology Life Quality Index on patients younger than 17 years. However, the findings show an early impact on patients' quality of life while using tazarotene foam during the first four weeks, which could be attributable to tazarotene irritation. At week 12, patients who used tazarotene had a higher improvement in quality of life than those who used the vehicle, which could be related to the efficacy of tazarotene foam in acne vulgaris (Table 4).

Table 4 -Impact on quality of life of patients applying tazarotene foam or vehicle in the 12-week studies using the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)

| | Tazarotene foam | Vehicle foam |
|---|---|---|
| DLQI | | |
| Number of participants analyzed | 171 | 165 |
| Change in DLQI score from baseline at weeks 2, 4, 8, and 12 in participants 17 years of age or older, mean ± standard deviation | | |
| Week 2, n=171,165 | −0.1±4.98 | −2.1±3.68 |
| Week 4, n=166,167 | −1.9±4.60 | −2.5±3.85 |
| Week 8, n=160,155 | −2.9±4.86 | −2.7±4.40 |
| Week 12, n=154,155 | −3.6±5.22 | −3.1±4.31 |
| CDLQI | | |
| Number of participants analyzed | 162 | 179 |
| Change of CDLQI from baseline at weeks 2, 4, 8, and 12 in participants 16 years old or younger, mean ± standard deviation | | |
| Week 2, n=162,179 | 1.1±4.16 | −1.4±3.21 |
| Week 4, n=153,180 | −0.6±3.45 | −1.4±3.23 |
| Week 8, n=148,171 | −1.2±3.53 | −1.9±3.11 |
| Week 12, n=146,169 | | |
| | −1.7±4.09 | −2.0±3.46 |

## CONCLUSION

Guidelines will never be able to cover every clinical scenario. However, recommendations based on a literature study increase the overall quality of acne treatment. Personal experiences should always be analysed critically, and therapeutic decisions should be based on agreed-upon therapeutic recommendations, as well as the type of acne and severity of the condition. The European evidence-based guidelines for the treatment of acne were developed with the purpose of increasing patient adherence and minimising severe conditions, scarring, and antibiotic resistance. They include a moderate-strength advice for comedonal acne patients to use topical retinoid monotherapy. Retinol monotherapy is also recommended by the German Society of Dermatology and the German Association of Dermatologists as the treatment of choice for comedonal acne. Topical retinoids should be the foundation of treatment for most acne patients, according to an international committee of physicians and researchers in the field. Retinoids target the microcomedo, the precursor to all acne lesions, and they also have intrinsic anti-inflammatory effects, thus targeting two pathogenic factors in acne. Based on level I evidence from literature accessible at the time of publication, the American Academy of Dermatologists treatment guidelines for acne propose a level A strength of recommendation for topical retinoids.

As a result, tazarotene should be considered the first-line treatment for comedonal acne, with an added effect on inflammatory acne lesions, especially after prolonged use. When tazarotene is compared to adapalene and tretinoin, there is no unambiguous conclusion concerning its efficacy and tolerability. As a result, while determining which topical retinoid to prescribe, the demands of the individual patient should be taken into account. Despite the fact that the foam is a new vehicle with good moisturising qualities, no studies have been conducted to evaluate efficacy and tolerability of the foam to the gel and cream formulations of tazarotene. When prescribing tazarotene-foam, doctors should warn patients about the likelihood of discomfort, especially during the first two weeks of treatment, and explain that this is due to the product's mechanism of action and will eventually contribute to favourable therapeutic effects. During the first few days, additional hydrating products, as well as short-contact application schedules, may be used to help the patient to gradually become used to the tazarotene effects.

In individuals with comedonal and papulopustular acne, combination therapy with retinoid/antimicrobial medicines has been advocated as the treatment of choice. Despite the fact that no studies have been done on the efficacy of tazarotene foam in combination with an antibacterial agent like benzoyl peroxide or clindamycin, common sense suggests that such a combination therapy could be beneficial. The likelihood of additional irritation induced by benzoyl peroxide, as well as the influence of using two medications on patient adherence, are also potential sources of worry.

In conclusion, the trials published reveal that tazarotene foam 0.1 percent has a great effectiveness and tolerability profile. Prescription experience, as well as comparison trials with other topical retinoids and tazarotene formulations, will provide significant information about its potential benefits and drawbacks in the future.

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