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Tazarotene

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Contents

Summary

▲ Tazarotene is a topical retinoid that appears to exert its effects via retinoic acid receptors. It normalises differentiation and proliferation of keratinocytes and has an anti-inflammatory effect.

▲ Topical tazarotene 0.05% or 0.1% gel was effective in the treatment of plaque psoriasis in clinical trials and its therapeutic effect was maintained for at least 12 weeks after treatment discontinuation in some patients.

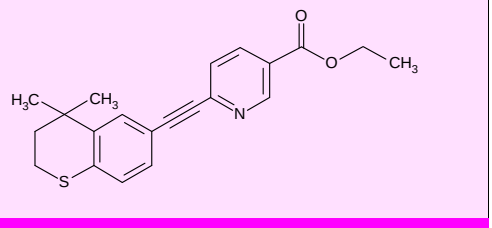
▲ In one study in patients with psoriasis, tazarotene had similar efficacy to fluocinonide in reducing plaque elevation, but not erythema. In another study, tazarotene was reported to be less effective than fluocinonide.

▲ Combination treatment with tazarotene plus a mid- or high-potency corticosteroid was more effective in the treatment of psoriasis than tazarotene alone.

▲ Topical tazarotene 0.1% gel significantly reduced lesion counts in patients with mild to moderate facial acne vulgaris.

▲ Skin irritation is a common adverse event with topical tazarotene, but it is mainly of mild to moderate severity. Tazarotene is not recommended for use in women who are, or may become, pregnant.

Features and properties of topical tazarotene (AGN 190168)	
Indications	
Plaque psoriasis	Launched
Acne vulgaris	Launched
Mechanism of action	
Retinoid	Normalises keratinocyte differentiation, reduces keratinocyte proliferation and decreases expression of inflammatory markers
Dosage and administration	
Usual concentration in clinical trials	0.05 *or* 0.1%
Frequency of application	Once daily
Pharmacokinetic profile	
Systemic bioavailability after topical administration	≈5%
Metabolism	Rapid and extensive metabolism to tazarotenic acid occurs in blood and liver microsomes
Plasma elimination half-life of tazarotenic acid	20h
Adverse events	
Erythema, pruritus, burning and other skin irritation occur commonly. Use in women who are, or may become, pregnant is contraindicated	



Tazarotene (AGN 190168)

Tazarotene (AGN 190168) is a topical retinoid that is indicated for the treatment of psoriasis and acne vulgaris.

Psoriasis is an inflammatory and proliferative skin disorder most commonly associated with chronic, sharply demarcated, dull-red scaly plaques.[1] Current treatments suppress, but do not cure, psoriasis.[2] For patients with mild to moderate stable plaque psoriasis affecting <20% of the body surface area, topical therapies are the first line of treatment. However, use of many of the available topical therapies is limited by inadequate long term efficacy, adverse effects and/or a lack of cosmetic acceptability. In particular, investigative use of topical retinoids in psoriasis has been limited by variable efficacy and unacceptable irritation.[3]

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous units. The four major contributing factors are increased sebum production, microbial flora abnormalities, cornification of the pilosebaceous duct and inflammation.[4]

1. Pharmacodynamic Profile

Retinoids exert their pharmacological effects through retinoic acid receptors (RARα, β and γ) and retinoid X receptors (RXRα, β and γ), which are ligand-dependent transcription factors.[5] In the skin, RARs predominate.

RARs and RXRs down-regulate certain genes by antagonising the effect of transcription factors such as AP1 and interferon-γ. They up-regulate expression of other genes by binding to retinoid-responsive elements in the promoter region.[5,6]

- Tazarotene down-regulates AP1-dependent gene expression through RARα, β and γ.[7] In transactivation assays, it acts as an agonist at RARβ and RARγ, but not RARα.[7]

Effects on Markers of Cell Differentiation, Proliferation and Inflammation

- As a result of changes in gene expression, tazarotene normalises keratinocyte differentiation, reduces keratinocyte proliferation and decreases expression of inflammatory markers.[5]

- The effects of topical tazarotene 0.05% gel on markers of cell differentiation, proliferation and inflammation have been assessed in 7 patients with plaque-type psoriasis who applied the drug twice daily for 2 weeks.[8] In biopsy samples of psoriatic lesions, expression of keratinocyte transglutaminase, keratin 16, involucrin and epidermal growth factor receptor was decreased in, respectively, 5, 5, 5 and 3 patients. Expression of filaggrin increased towards normal in 4 patients. Expression of intercellular adhesion molecule type 1 and HLA-DR in both the epidermis and dermis was reduced in most patients.

- Tazarotene inhibited expression of migration inhibitory factor-related protein 8 (MRP-8) and skin-derived anti-leukoproteinase (SKALP) in psoriatic lesions[6] and stromelysin-1 in cultured human keratinocytes.[7] Expression of the hyperproliferation-associated keratin K6 was reduced in psoriatic lesions after topical treatment with tazarotene 0.1%.[5]

- In female hairless mice, ornithine decarboxylase activity induced by 12-*O*-tetradecanoylphorbol-14-acetate was inhibited by topical tazarotene, indicating antiproliferative activity.[7]

- The antiproliferative effect of tazarotene may partly result from up-regulation of newly identified RAR-responsive genes, including tazarotene-induced gene-1 (TIG-1) and gene-2 (TIG-2).[5,9,10]

- Treatment with topical tazarotene 0.1% gel once or twice daily for 2 weeks increased expression of TIG-1[9] and TIG-2[10] mRNA in lesional biopsy samples from patients with plaque-type psoriasis.

2. Pharmacokinetic Profile

• Topically applied tazarotene 0.1% gel (50mg gel/≈7cm^2) rapidly penetrated through the stratum corneum into the epidermis in shaved minipigs.[11] The mean concentration of drug recovered on day 1 was 6 μg-eq from the stratum corneum, 41.2 μg-eq/g from the epidermis and 0.14 μg-eq/g from the dermis. Metabolism was limited; approximately 75 to 90% of the dose recovered from the epidermis and dermis was the parent drug. There was only a minor degree of accumulation after 7 days' administration.

• After topical administration of tazarotene 0.1% gel (2.5 μg/cm^2; total tazarotene dose 2mg) under occlusion for 10 hours, approximately 6% of the applied dose was distributed in the stratum corneum in healthy volunteers.[12,13] An additional 2% of the dose partitioned into the epidermis and dermis, indicating minimal bioavailability. Only about 5% of the tazarotene dose was systemically absorbed. There was no significant reservoir of drug in the skin when tested 7 days after the single application.

• Tazarotene was rapidly and extensively metabolised to tazarotenic acid (AGN 190299) in human blood and liver microsomes *in vitro*.[14]

• No unchanged tazarotene was detectable in plasma after administration of 0.05% or 0.1% gel to 20% of the body surface area for 10 hours in healthy male volunteers; the limits of detection were not stated.[15] The mean maximum plasma concentrations of tazarotenic acid were 0.33 and 0.47 μg/L, respectively, after application of tazarotene 0.05% and 0.1%. The mean area under the plasma drug concentration-time curves were, respectively, 10.6 and 14.6 μg/L · h and the time to maximum plasma concentration was approximately 15 hours. The mean plasma elimination half-life was approximately 20 hours.

• Plasma concentrations of tazarotene were detectable (0.05 to 0.15 μg/L) in only 6 of 283 patients (2%) with psoriasis who applied tazarotene 0.05% or 0.1% gel once daily for up to 12 weeks in phase III trials.[13] 61% of patients had detectable but low plasma concentrations of tazarotenic acid (0.05 to 6.1 μg/L).

• Tazarotene is eliminated equally by the urinary and faecal routes.[12]

3. Therapeutic Trials

Psoriasis

• Two dose-ranging trials of topical tazarotene gel were conducted in patients with mild to moderate plaque psoriasis. In one study, tazarotene 0.05% twice daily was significantly more effective than 0.01% twice daily in reducing induration and scaling.[16] The other study found no significant difference in global efficacy between tazarotene 0.05% or 0.1% applied once or twice daily; 48 to 63% of patients in each dosage group had a good, excellent or complete clearing response.[16,17]

• In small placebo-controlled trials, most patients with plaque psoriasis treated with topical tazarotene demonstrated clinical improvement,[8,18,19] including those with scalp psoriasis in a 15-week study in which tazarotene 0.1% gel was applied daily for 2 weeks and then every other week for the remainder of the study.[19]

• Tazarotene was significantly more effective than placebo in a multicentre double-blind trial in 318 evaluable patients with mild to moderate plaque psoriasis.[3,20,21] Patients were randomised to apply a gel that contained tazarotene 0.1% or 0.05% or vehicle only (placebo) once daily for 12 weeks. Significant improvement in plaque elevation was seen in tazarotene recipients within 1 week. The rate of treatment success (good, excellent or complete clearing response) by week 12 for trunk/limb target lesions was 70% in the tazarotene 0.1% group and 59% in the 0.05% group, compared with 35% in the placebo group. The success rate for knee and elbow lesions (which are traditionally viewed as more difficult to treat) was approximately 60% with both concentrations of tazarotene.

• In the above study, treatment success rates were significantly greater with 0.1% than 0.05% taza-

rotene at several observation points, and the onset of beneficial effect was more rapid with the higher concentration. However, response was maintained after cessation of treatment in more patients who received the lower concentration. Response was maintained for up to 12 weeks after treatment in approximately half of the patients.

• No tachyphylaxis was evident in 227 patients with stable plaque psoriasis who applied tazarotene 0.05% or 0.1% gel on an 'as needed' basis for 1 year.[22]

Comparisons with Other Agents

• Once-daily application of tazarotene gel 0.05% or 0.1% was as effective as twice-daily fluocinonide cream 0.05% in reducing plaque elevation of target lesions after 12 weeks' treatment in an investigator-blinded study in 340 evaluable patients with plaque psoriasis.[21,23] However, fluocinonide reduced erythema more effectively than tazarotene. Fluocinonide also tended to be more effective in reducing scaling in the first 4 weeks of treatment. The rates of global treatment success (good, excellent or complete clearing response) at week 12 for knee and elbow lesions were 65% with tazarotene 0.1%, 52% with tazarotene 0.05% and 66% with fluocinonide.

• Psoriasis recurred more rapidly after completion of treatment in fluocinonide than in tazarotene recipients in the above study; this was particularly evident in the first 4 weeks after treatment discontinuation. A successful response was maintained for at least 12 weeks after treatment in 59% of patients who achieved treatment success with tazarotene and 40% of those who achieved treatment success with fluocinonide.

• The results of the above study were not replicated in another study in which the efficacy of tazarotene gel 0.05% or 0.1% once daily was compared with that of fluocinonide cream 0.05% twice daily in 331 patients with plaque psoriasis. Details of the results of this study have not yet been published, but it has been reported that fluocinonide was superior to tazarotene during treatment, and tazarotene did not demonstrate any advantage in the post-treatment period.[24]

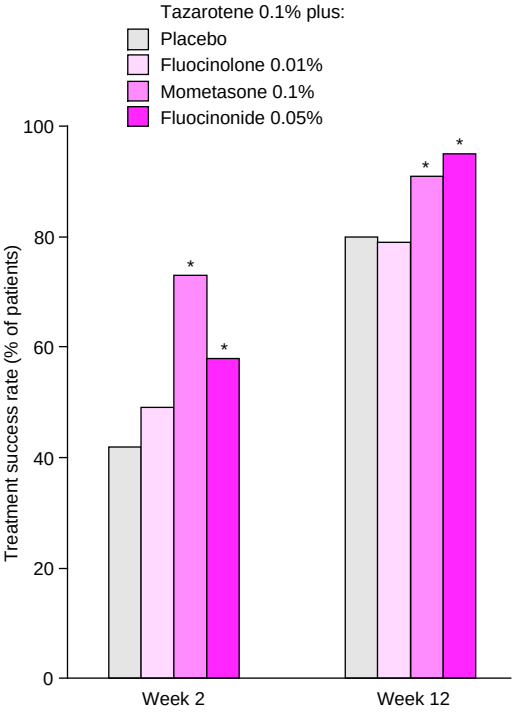


Fig. 1. Treatment success rates of tazarotene plus corticosteroids in plaque psoriasis.[25] 284 evaluable patients with stable plaque psoriasis were randomised to apply tazarotene 0.1% gel plus fluocinolone acetonide 0.01%, mometasone furoate 0.1%, fluocinonide 0.05% or placebo cream, each once daily, for 12 weeks. Treatment success was defined as ≈50% (moderate) to 100% improvement (complete clearing). * $p < 0.05$ *vs* tazarotene plus placebo.

• Once-daily application of tazarotene gel 0.05% or 0.1% was not more effective overall than twice-daily application of calcipotriol ointment 0.005% in 369 patients with psoriasis.[24]

Combination Treatment

• Combination treatment with tazarotene 0.1% gel plus a mid- or high-potency corticosteroid cream produced significantly higher treatment success rates than treatment with tazarotene 0.1% plus placebo in an investigator-blinded 12-week study in 284 evaluable patients with stable plaque psori-

asis (fig. 1).[25] The addition of a mid- or high-potency corticosteroid increased efficacy against scaling and erythema, and reduced the skin irritation associated with tazarotene use (see section 4). The corticosteroid creams used were fluocinolone acetonide 0.01% (low potency), mometasone furoate 0.1% (medium potency) or fluocinonide 0.05% (high potency). The corticosteroid or placebo cream was applied once daily in the morning, and tazarotene was applied once daily in the evening.

- The results of an interim analysis of the first 10 patients in a study evaluating the benefits of applying tazarotene 0.1% in combination with ultraviolet B (UVB) phototherapy suggest that tazarotene reduces plaque elevation and scaling and reduces the time to response to UVB therapy.[26] Patients applied tazarotene or vehicle once daily, or received no treatment, for 2 weeks before initiation of UVB therapy. UVB therapy was then administered 3 times weekly for 10 weeks and patients applied tazarotene, vehicle or no treatment after each exposure to UVB.

Acne

- The efficacy of tazarotene in mild to moderate facial acne vulgaris has been assessed in a multicentre, double-blind study in 375 evaluable patients.[27,28] Vehicle alone produced a response in 32% of patients after 8 weeks, but tazarotene 0.05% or 0.1% gel applied once daily was significantly more effective (response rates 43 and 48%, respectively; fig. 2). Only the 0.1% gel was significantly more effective than placebo at week 12, producing a response rate of 68%.

- The non-inflammatory lesion count was reduced by ≈55% and the inflammatory lesion count by ≈42% at week 12 in tazarotene 0.1% gel recipients in the above study. These reductions were significantly greater than those seen in placebo recipients (≈35 and 29%, respectively). Tazarotene 0.05% gel significantly reduced the non-inflammatory, but not the inflammatory, lesion count compared with placebo.

- These results were supported by a further 12-week, vehicle-controlled study involving a similar number of patients with mild to moderate facial acne vulgaris; details of the results of this study have not yet been published.[24]

4. Tolerability

- Adverse effects on bone morphology (e.g. a narrowing zone of proliferation in the sternum, chondrolysis, and a widening zone of maturation in the femur) were observed with oral administration of tazarotene to animals, but only after prolonged exposure to high doses (≥0.125 mg/kg/day).[13]

- Topically applied tazarotene was nonmutagenic, noncarcinogenic and did not affect fertility in preclinical studies.[13]

- Teratogenicity occurred with oral administration of tazarotene 0.25 mg/kg in rats and with 0.2 mg/kg in rabbits, but not with topical administration.[13] On the basis of these data, the US FDA has classified tazarotene as category X, meaning that it is contraindicated in women who are, or may

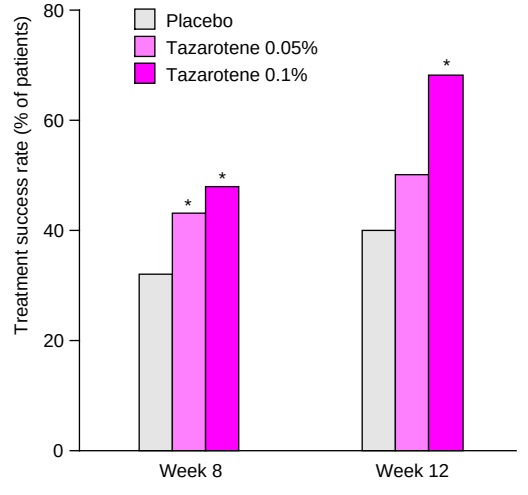


Fig. 2. Efficacy of tazarotene in facial acne vulgaris.[28] Treatment success rates after 8 and 12 weeks of once-daily treatment with tazarotene 0.05% or 0.1% or placebo gel in 375 evaluable patients. Treatment success was defined as a good, excellent or complete clearing response. * $p < 0.05$ *vs* placebo.

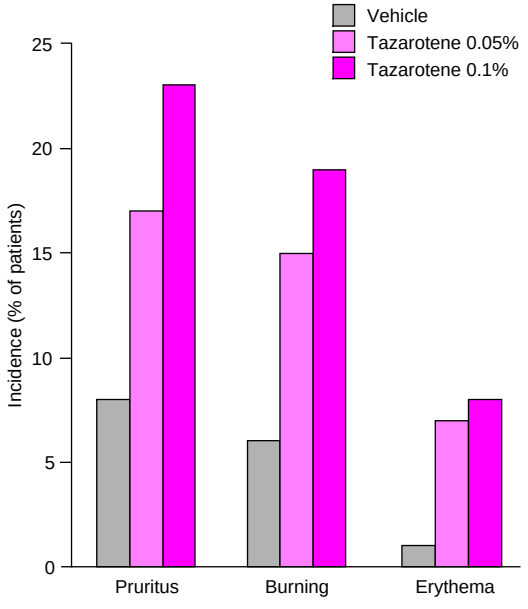


Fig. 3. Local irritation associated with topical tazarotene treatment for psoriasis.[20] Incidence of local irritation in 324 patients with stable plaque psoriasis involving <20% of total body surface who were treated with tazarotene 0.05% or 0.1% gel or vehicle once daily for 12 weeks.

become, pregnant.[24] In clinical trials, 6 women treated with tazarotene who became pregnant gave birth to healthy infants.[24]

- With repeated exposure to tazarotene 0.05% or 0.1% gel (fifteen 24-hour semioccluded applications), moderate skin irritation was observed in healthy volunteers.[29] The cumulative irritation potential was similar to or marginally less than that of tretinoin 0.1% cream. No contact sensitisation, phototoxicity or photosensitivity were evident in healthy volunteers.[29]

- The most common adverse events associated with topical tazarotene gel treatment for psoriasis or acne are erythema, pruritus and burning or other skin irritation.[3,13,16,20,23,25,28,29] These events are mainly mild or moderate in severity and are concentration related. The incidence of local irritation is exemplified by the study results shown in figure 3.

- In a 12-week clinical trial in 324 patients with psoriasis, 12% of those treated with tazarotene 0.1% gel, 10% of those treated with 0.05% gel and 3% of those treated with vehicle discontinued treatment because of adverse events (mainly local irritation).[20]

- The incidence of adverse events (erythema, pruritus, burning) associated with tazarotene 0.1% gel tended to be reduced by combined treatment with mometasone furoate 0.1% or fluocinonide 0.05% cream in patients with psoriasis.[25]

- No serious systemic adverse events were reported among the ≈2000 patients who received tazarotene 0.05% or 0.1% gel in clinical trials, some of whom were treated for as long as 1 year.[13] Furthermore, haematology, blood chemistry and urinalysis tests did not identify any consistent, clinically significant effects. No clinically significant tazarotene-related bone changes in the ankle, cervical spine or thoracic spine were detected in radiographic evaluation of 96 patients treated with tazarotene 0.05% or 0.1% gel for up to 1 year.[13]

- The majority of patients in a study in patients with facial acne vulgaris found tazarotene to be cosmetically acceptable.[28]

5. Tazarotene: Current Status

Tazarotene is a topical retinoid that has shown promising efficacy in the treatment of mild to moderate plaque psoriasis and facial acne vulgaris. It is available for these indications in a number of countries and is in late phase clinical development in many others. Tazarotene is cosmetically acceptable, but commonly causes mild to moderate skin irritation. It is not recommended for use in pregnant women.

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