ijlpr 2022; doi 10.22376/ijpbs/lpr.2022.12.6.P207-219

International Journal of Life science and Pharma Research

ISSN 2250-0480

Review Article

A Review on TAZAROTENE

TAZAROTENE: A Concise Review of Mechanism of Action and Therapeutic Benefits

Chahat Khanna[1], Peeyush Sharma[2], Simranjit Kaur[2], Sukhdeep Singh[1], Lavish Kumar[1], Sandeep Rahar[2], Varinder Soni[1], Charanjeet Kaur[4], Parminderjit Kaur[3] and Charanjit Kaur*[5]

[1]*Department of Pharmaceutical Analysis, Khalsa College of Pharmacy, Amritsar.*

[2]*Department of Pharmaceutical Chemistry, Khalsa College of Pharmacy, Amritsar.*

[3]*Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar.*

[4]*Department of Medical Lab Technology, Khalsa College of Pharmacy and Technology, Amritsar.*

[5]*Department of Pharmaceutical Chemistry, Lovely Faculty of Applied Medical sciences, Lovely Professional University, Phagwara, Punjab*

Abstract: Tazarotene is the first topical receptor-selective retinoid prodrug derived from vitamin A, used for managing plaque psoriasis, and effective in *acne vulgaris*, and photoaging. The aim and objective of writing this article were to recapitulate the information from the literature regarding every aspect of tazarotene, recent research including clinical trials and analytical methods of detection along with general characteristics uses and information about the physicochemical characteristics, pharmacokinetics properties, mechanisms of action, treatment strategies, dosage and administration, drug interactions, safety profile, potential for teratogenicity and, use in special populations like paediatrics and pregnant women. We have also mentioned the analytical methods like hyphenated and conventional chromatographic techniques such as LC–MS/MS and HPTLC, HPLC respectively used to estimate this drug both qualitatively and quantitatively in pharmaceutical formulations for quality control purposes. The clinical data considered in this study concludes the effect of tazarotene in psoriasis, *acne vulgaris*, and in the condition of brittle nails in different regimens, conditions, and dosage forms, providing good insights for clinicians. The data compiled in this review contain all the information related to tazarotene already published in the literature, but the scattered form and recent studies, including clinical trials, new composition of lotions as well as cream forms, were not mentioned in previous reviews. This review focussed on the updated use of tazarotene as a viable option for treating psoriasis and other skin conditions alone and in combination with corticosteroids or phototherapy as approved by regulatory bodies. Due to minimum side effects, convenient once-daily application, rapid and sustained response, tazarotene is an optimum choice for various diseased skin conditions in combination with a corticosteroid in the treatment of psoriasis than tazarotene alone, as per the literature and clinical data summarized in this article.

Keywords: Tazarotene, retinoid, psoriasis, acne vulgaris and photoaging.

***Corresponding Author**

Charanjit Kaur , Department of Pharmaceutical Chemistry, Lovely Faculty of Applied Medical sciences, Lovely Professional University, Phagwara, Punjab

Received On 11 May, 2022

Revised On 12 September, 2022

Accepted On 21 September, 2022

Published On 1 November, 2022

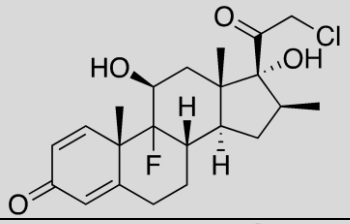
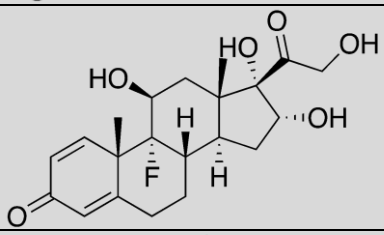
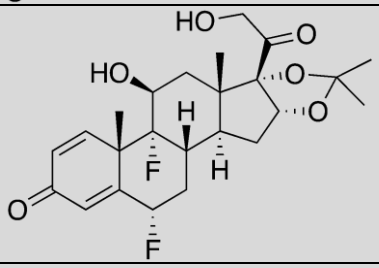
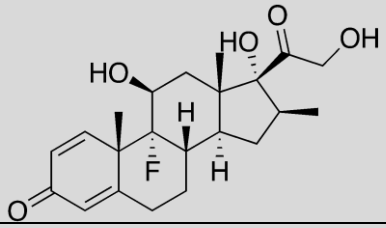
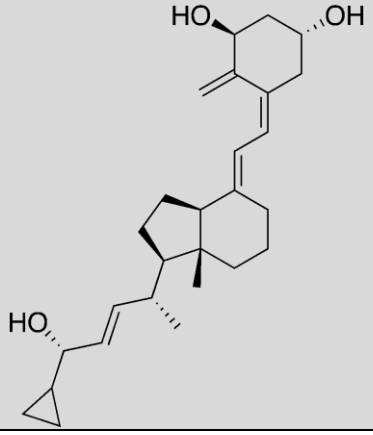
Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

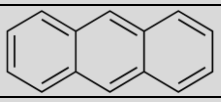
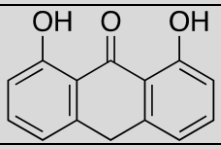
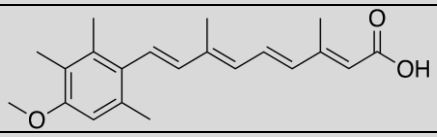
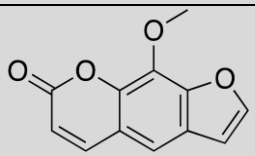
Citation Chahat Khanna, Peeyush Sharma, Simranjit Kaur, Sukhdeep Singh, Lavish Kumar, Sandeep Rahar, Varinder Soni, Charanjeet Kaur, Parminderjit Kaur and Charanjit Kaur , TAZAROTENE: A Concise Review of Mechanism of Action and Therapeutic Benefits.(2022).Int. J. Life Sci. Pharma Res.12(6), P207-219 http://dx.doi.org/10.22376/ijpbs/lpr.2022.12.6.P207-219

1. INTRODUCTION

Psoriasis is a dreadful agitating condition imparted by immune irregularities, which affects mostly youngsters (0.1%), and adults (3%)[1,2]. It exhibits minimal occurrence in Asian and a few African inhabitants and up to 11% in Scandinavian and Caucasian inhabitants[3-5]. It is recognized by silvery-white scales casing erythematous plaques in an equilibrium pattern from the trunk, elbows, scalp, and knees. The cycle of chronic inflammation starts with activating plasmacytoid dendritic cells by environmental and/or genetic factors, which stimulate the release of pro-inflammatory cytokines followed by stimulation of the hyperproliferation of keratinocyte, causing inflammation[6-10]. The various types of psoriasis are inverse, guttate, plaque, pustular and erythrodermic. It is a genetic skin disease related to HLA in which there is a reversible alteration in the differentiation of the epidermis[10]. The systemic treatment is not recommended due to side effects, and topical therapy is associated with a lower efficacy. This disease is inoperable, but many therapeutics options are available to help treat the syndrome. Topical treatment is preferred for psoriasis patients as the emollients in topical formulations reverse the upper skin layer damage and inflammatory response after corneum penetration. The topical formulations also incorporate keratolytic agents like salicylic acid to enhance active drug absorption and soften the plaques associated with psoriasis[11]. There are numerous drugs available in the market which are clinically recommended in psoriasis-like oral retinoids[12] (vitamin A derivatives), topical corticosteroids[13] and a few other drugs along with their structures[14,15] are mentioned below in Table 1

Table 1: Structure and therapeutic uses of drugs used in psoriasis

Drugs	Structure	Uses
Corticosteroids		
Clobetasol [1]		Eczema, Psoriasis and Dermatitis
Triamcinolone		Allergies and Rash
Fluocinolone Acetonide		Inflammation and Itching
Betamethasone		Skin Infection and Skin Irritation
Vitamin-D		
Calcipotriene		Plaque Psoriasis

Tar Containing Preparations		
Coal Tar (Anthracene)		Psoriasis and Eczema
Topical Agents		
Anthralin		Decreasing inflammation and slowing down the growth of skin cells
Retinoids		
Acitretin		Pain, Swelling or Peeling of your Skin
Psoralens		
Methoxsalen		Premature Aging or Skin Cancer

Topical corticosteroids are widely used due to the absence of local irritation and staining problems associated with other topical treatments. But tachyphylaxis, hypertrichosis, and cutaneous atrophy occur with excessive use. Other topical options include coal tar, anthralin alone or combined with phototherapy, and calcipotriene. Topical treatment is opted in mild to moderate conditions. In moderate to severe conditions, systemic therapies are recommended in topically non-responsive conditions, as mentioned in Table 1. The clinicians choose the type of treatment as per the patient's condition and response to a particular dose[16]. Tazarotene regulates the expression of genes associated with nuclear retinoic acid receptors with minimum systemic absorption and rapid elimination, reducing the chances of systemic side effects. Therefore, it is specifically recommended for plaque psoriasis and acne vulgaris. Tazorac® 1 is the first topical retinol approved for plaque psoriasis[16] and was found to be efficient at controlling symptoms of the disease and reported to possess lower recurrence rates than fluocinonide cream. The tazarotene (TZR) is chemically, ethyl 6-[(4,4-dimethyl-3,4-dihydro-2H-thiochromen-6-yl) ethynyl] nicotinate (Fig. 1), is the choice of drug for the dermatological ailments. The molecular formula and molecular Mass of TZR are $C_{21}H_{21}NO_2S$ and 351.5 g/mol, respectively[17].

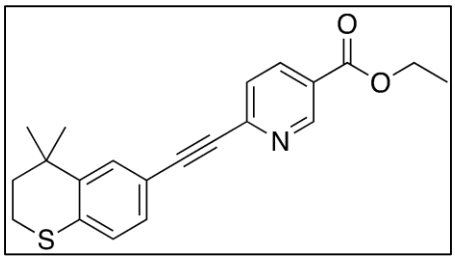


Fig. 1 Structure of Tazarotene

2. PHYSIOCHEMICAL CHARACTERISTICS

The physicochemical properties of drug are mentioned in the following Table-2[18].

Table 2: Physicochemical properties of drug

S No	Property	Value
1	XLogP3-AA	4.9
2	Acceptor Count of H Bond	4
3	No. of Rotatable Bonds	5
4	Polar Surface Area (Topological)	64.5 A^2
5	Formal Charge	0
6	Heavy Atom Count	25
7	Isotope Atom Count	0
8	Complexity	547
9	Compound Is Canonicalized	Yes
10	Covalently-Bonded Unit Count	1

Table 2 illustrates the physiochemical properties of tazarotene, including its different structural parameters like number of rotatable bonds, hydrogen bonds, topological surface area, formal charge, and heavy atom count, indicating the complete structure.

3. PHARMACOKINETICS

Matsumoto *et al*., 1994, reported the rapid penetration of topically applied TZR as 0.1% (50mg) gel through epidermis in minipigs. This group reported the 75-90% unaltered drug passage through dermis and epidermis with minimal drug deposition after 7 days of application[19]. Franz et al found that when the dose of 0.1% gel used was 2mg, only 6% of drug got accumulated in *stratum corneum* and 5% of TZR got systemically absorbed[20]. Tang-Liu *et al* found that TZR gets partially metabolized into the tazarotenic acid (TA), the active metabolite by esterase present in the skin on the topical application and was reported in *corneum stratum* (4-6%), after ten hours and in epidermis (2%)[21]After two weeks of therapeutics, the bioavailability of TA was increased from <1% (single use) to 2.6% and 5.3% sequentially for 0.05% and 0.1% TZR, once tested in 24 inmates suffered with psoriasis. However, for 12 weeks of treatment, the systemic bioavailability was found to be 1.8% for 0.05% and 3.9% for 0.1% TZR, while steady-state systemic bioavailability was found to be ≈1% after topical administration of drug for 7 days in healthy volunteers[19]. In plaque psoriasis, low plasma concentrations was observed i.e. ≤0.15 μ g/L in patients (1–3%) when studied for 12-week under phase III clinical trials[22, 23,24]. In a study conducted on five psoriatic patients, TZR gel (dose-2mg gel/$cm^{2,}$ BSA-13%) was applied on 2 hr air dried skin. The increase in bioavailability was noted from 2.7 to 11.9 to 14.8% after one dose, at 1 and 2 weeks respectively[25]. Moreover, with respect to $AUC_{24,}$ with mean body surface area involvement 7% (n=12) for 12 weeks of study, AUC_{24} (TA) was 5.7 and 11.8 μ g h/ L for both 0.05 and 0.1% gel, respectively, while the C_{max} was 0.45 and 0.83 μ g/L and; time reported to C_{max} values were 8.7 and 6.82 hours respectively for both gels. Plasma metabolism is more intense than percutaneous metabolism, 99% of tazarotenic acid was bound to plasma as well as V_d (Volume of distribution) of IV infusion of drug was 15 μ g/kg/20mins, which was found to be more as compared to topical i.e. 0.75L/Kg, when studied in eight healthy volunteers, indicates that the drug is not extensively allotted extra-vascularly[21]. The plasma concentrations of TZR remained < 1 μ g/L in both facial acne patients and healthy volunteers after percutaneous absorption. The drug does not accumulate in the body due to hydrophilic nature of metabolic product i.e. tazarotenic acid (TA) by esterase through hepatic metabolism to sulfones and sulfoxide. After intravenous and topical administration, the half-life of TZR was found to be 6.2 hours and 2.3 to 4.6 hours, respectively with a mean half-life of 18 hrs in both normal and psoriatic patients[23,24]. In both healthy and psoriatic skin types, it achieves steady-state concentrations within 2 weeks of topical treatment and get rapidly and equally eliminated from the body through faeces and urine. Franz *et al*.,1992, conducted a study to understand the excretion pattern of TZR using radiolabelled TZR with and without occlusion in healthy and psoriatic patients. 2.7% and 2.6% of the dose was recovered in stool and urine respectively in healthy volunteers. However, in psoriasis patients, 0.33% and 0.43% of dose was recovered in the urine and faeces with excretion $t_{1/2}$ was found to be 15.6 and 7.3 hrs respectively[20]. Madhu *et al*., 1997, reported TZR metabolic similarities between Japanese-Americans and Caucasians[26]. It does not induce/inhibit metabolic enzymes as per literature[27].

4. PHARMACODYNAMICS

TZR causes downregulation of AP1-dependent gene expression after binding to the three RAR (Retinoic acid receptors), i.e., α , β and γ [28] and shows its effect on markers of inflammation, differentiation and proliferation of keratinocyte. It acts as an agonist of β and γ receptors and also impacts genes such as TIG-1, 2 and 3 (TZR-induced gene). RARs can induce the expression of certain genes in a ligand-dependent manner by binding to the retinoic acid-responsive elements in their promoter region. Moreover, the antiproliferative activity of TZR is because of the up-regulation of these genes[29].

5. MOLECULAR MECHANISM OF ACTION

A research group reported a decrease in expression of keratin 16, keratinocyte transglutaminase, epidermal growth factor receptor, intercellular adhesion molecule type 1, involucrin and HLA-DR in biopsy samples of psoriatic lesions in a study conducted on 7 patients with twice daily application of 0.05% gel for 2 weeks[30]. Nagpal *et al*., 1996, found TZR mediated inhibition of MRP-8 (inhibitory migration factor related rotein-8) and SKALP (skin-derived anti-leukoproteinase) expression[31]. The molecular mechanism of TZR was elucidated and the reduced expression of keratin K6 associated with hyperproliferation in psoriatic lesions was found after 0.1% topical application. Tgase-k which is overexpressed in psoriatic lesions is known to be involved in the formation of cross-linked envelope. Marked upregulation of TGase-K at baseline was observed in psoriatic skin sections. Seven patients suffering from psoriasis were treated with topical tazarotene gel (0.05% twice daily) for 14 days, biopsy specimens were taken from five patients, which showed decreased TGase-K expression as measured by anti-TGase-K antibody staining. During the study, no significant difference was observed in the two patients with psoriasis in a control group's TGaseK expression to confirm the effect of tazarotene on TGase-K, RT-PCR was used to compare the RNAs of pooled controls with the RNAs of psoriatic lesions. Downregulation of tgase-k in those lesions exposed to tazarotene was seen. Epidermal keratinocyte proliferation is thought to be stimulated by EGF-R and its ligand, transforming growth factor-alpha, and are increased in psoriatic epidermis. EGF-R was stained in all layers of the epidermis in lesional psoriatic skin, whereas it was limited to the basal layer and the lowest spinous layer in normal control biopsy specimens and non-lesional psoriatic skin. After the treatment of tazarotene, 3 out of 7 patients showed a decrease in the expression of EGF-R in the lesions marked by Immunohistochemical staining. Transcription factor AP1 consists of c-Jun and c-Fos, expressed in response to mitogens and tumor promoters. AP1 plays a critical role in the pathogenesis of psoriasis, which is associated with cell proliferation and inflammatory signal transduction pathways. Ornithine decarboxylase is an early marker of hyperproliferation which was observed to be elevated in the hyperplastic epidermis of psoriasis. In various *in vitro* cell culture systems, TZR antagonizes the effect of AP1 and ornithine decarboxylase activity *in vivo* in mouse skin. Compared with normal skin or non-lesional psoriatic skin, HLA-DR and ICAM-1 expression in untreated psoriatic skin was increased. In the recruitment of T cells to the epidermis in psoriasis ICAM-I called as the adhesion molecule is thought

to be involved. Treatment with tazarotene in seven patients with psoriasis was performed, and five patients had decreased ICAM-1 expression in the dermis. No epidermal ICAM-1 expression was observed in 6 patients, and decreased epidermal ICAM-1 expression was observed in the other patient. The same study demonstrated a marked decrease in HLA-DR positive epidermal cells; however, no significant effect on dermal HLA-DR expression was seen[32]. The overall mechanism of action of TZR has been shown in Fig. 2.

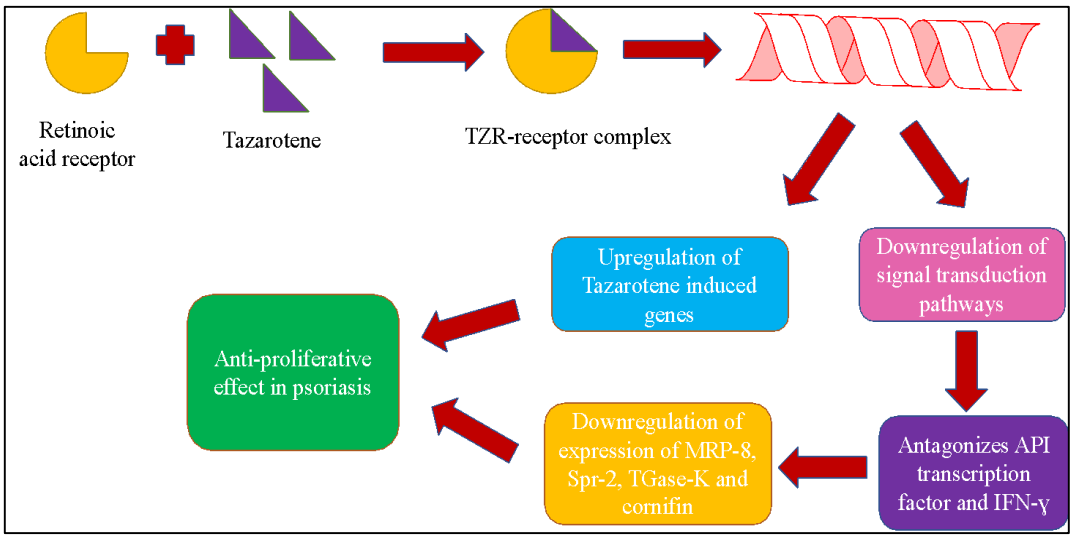


Fig. 2 Mechanism of action of tazarotene

6. CLINICAL EFFICACY

Topical tazarotene has proven clinical efficacy for treating moderate to severe plaque psoriasis, refractory mycosis fungoides lesions, steroid-induced epidermal atrophy, acne and photoaging, as shown by randomized clinical trials[33]. In addition, there are reports demonstrating its activity in rare diseases of keratinization and skin cancers[33].

6.1 In Psoriasis

In psoriasis, three major pathogenic causes are tackled by TZR in keratinocytes due to its antiproliferative effect, normalization of abnormal differentiation, and reduction of the expression of markers of inflammation[34]. As far as pharmacological effects are concerned, when 0.05% TZR gel is regularly applied for 14 days leads to an improvement of a granular layer in the form of a decline in acanthosis and hyperkeratosis[35]. With respect to the histochemical study, reduction of epidermal differentiation markers like involucrin, keratinocyte transglutaminase, calgranulin A/migration-inhibitory related factor 8 (MRP-8) and elafin/skin-derived anti-leukoproteinase) has been reported[35, 36]. As per reports, in case of phototherapy treatment of psoriasis, MED (mean minimal erythema dose) for UVA and UVB exposure needed to produce instant orpiment blacken were decreased upto 56.25 mJ/cm^2 in control and 42.50 mJ/cm^2 in tazarotene by pre-treatment with TZR 0.1% gel thrice weekly in 12 healthy participants for 2 weeks[37]. However, when antibiotics and tazarotene is used to heal the skin disorder like hyperpigmentation, mottling, defaced skin, sallow skin, and fine wrinkling as well as leads to depletion in epidermal cells as well as collagen productions is increased. In a dose ranging trial conducted in mild-moderate plaque psoriasis, the dose of 0.05% was found more effective than 0.01% TZR applied twice daily in reducing scalping[38]. In another study, no difference in global efficacy was observed between a dose of 0.05% and 0.1% TZR[38,39]. In one placebo controlled 15-week study in psoriasis patients, 0.1% TZR gel showed improvement in scalp psoriasis applied for 14 days daily and then after every 7 days[40]. In a multicentric double blind trial, 318 plaque psoriasis patients were randomized and were given treatment with gel containing 0.1%/0.05% TZR/vehicle once a day for 12 weeks. The success rates of treatment and onset of action were greater with larger dose but a decrease in lesions on trunk, limb, knee and elbow was observed with both doses. The response lasted for twelve weeks in 50% of patients after treatment with no reports of tachyphylaxis even after 1 year[41,42]. Xi *et al*., 2021, found an increased level of MMP13 in the samples of skin lesions and serum from the patients with psoriasis. They reported a decrease in the level of MMP13 expression and cell proliferation after treatment with acitretin and NB- UVB irradiation alone or in combination in HaCaT cells. In a mouse model, the same results were obtained after tazarotene treatment or NB- UVB irradiation in imiquimod-induced psoriasis - like dermatitis[43].

6.2 In Refractory Mycosis Fungoides Lesions

In an open labelled pilot study conducted by Apisarnthanarax et al., 2004, topical tazarotene 0.1% gel was evaluated for its efficacy and safety as adjuvant in refractory mycosis fungoides lesions (MFL) in 20 adult patients. The treatment was given for 4 weeks once daily, along with topical corticosteroids. 58% patients attained greater than 50 % improvement in body surface area. Histopathological results revealed a decrease in CD45RO(+) lymphocytes percentage, lymphocytic infiltrates and, the elevation of CD8(+) lymphocytes percentage during the study. Thus, TZR 0.1% gel was found safe and effective in MFL[44].

6.3 In Photodamaged Skin

Lowe et al. (2006), studied the efficiency of TZR 0.1% cream compared to a combination of TZR 0.1% cream and hydroquinone 4% cream in the treatment of photodamaged facial skin in a double blind randomized study of 24-week in 131 patients. 87% of patients completed the study due to the reports of adverse effects. The results suggested greater clinical improvement with the use of hydroquinone in

combination with TZR in photodamaged patients with dyspigmentation compared to TZR alone[45]. Kang et al., 2001. assessed the safety and efficacy of different concentrations of tazarotene cream on facial photodamage in a multicentric, randomized, investigator-masked, parallel-group study. Three hundred forty-nine subjects with facial photodamage were selected and treated with (0.01%, 0.025%, 0.05%, and 0.1%) TZR cream topically, and daily in comparison to its vehicle and 0.05% tretinoin emollient cream. Both TZR and tretinoin creams effectively improved mottled hyperpigmentation and fine wrinkles. Based on global responses, the success rates of treatment with 0.1%, 0.05%, 0.025% and 0.01% TZR were 67%, 52%, 36% and 41% of 58 subjects respectively in comparison to 0.05% tretinoin with 55%, and vehicle with 22% success rate. Mild to moderate local side effects were reported at higher concentrations with TZR but found safe and effective in treating photodamaged facial skin [46].

6.4 In Steroid-Induced Epidermal Atrophy

Kaidbey et al., 2001. Investigated the use of TZR as an adjuvant to prevent steroid-induced epidermal atrophy in 24 subjects. The treatment was given 6 days per week for 4 weeks to 6 groups (TZR vehicle, diflorasone diacetate (DFD) 0.05% ointment, TZR vehicle + TZR gel 0.1%, DFD 0.05% ointment + TZR gel 0.1% or DFD 0.05% ointment + TZR vehicle, no treatment). TZR gel 0.1% with DFD did not prevent atrophy completely but was reported to improve 37% of the epidermal atrophy induced by DFD alone. Thus, TZR gel 0.1% significantly reduces DFD 0.05% ointment-induced epidermal atrophy [47].

6.5 In Acne Vulgaris

According to the clinical studies, 0.1% TZR gel was found more effective, than tretinoin (Retin-A®) 0.025% gel[48,49], tretinoin (Retin-A Micro®) 0.1%[50] and adapalene 0.1% gel in comedo reduction[51]. The reduction in open comedo count was statistically more significant after treatment with TZR than tretinoin[49]. Compared with adapalene gel applied once daily, TZR was found to be more helpful in decreasing inflammatory and non-inflammatory lesions with an overall improvement in disease severity. Dr Bershad developed a short contact method to decrease the discomfort caused by TZR due to skin irritation, in which the application of TZR starts from initially 2 min and progresses till 5 min with a progression of 1 minute after every 3 days[52]. In a 12-week investigator-blind study, a minimum of 50% improvement was observed with short contact therapy in patients (64% and 61%) after twice and once daily application, respectively, compared to 15% on vehicle only. Inflammatory lesions were reduced by 38, 34 and 9%, respectively, and non-inflammatory lesions decreased by 46, 41, and 2%, respectively[52].

7. TREATMENT STRATEGIES

In mild to moderate plaque psoriasis, tazarotene gel was found effective in monotherapy in two dose-ranging studies in clinical trials[35, 53] and cream formulations (0.05 and 0.1%) have been found useful in psoriasis in terms of safety and efficacy in a vehicle-controlled phase 3 studies[24]. In order to achieve patient's compliance, TZR is clinically used along with glucocorticoids/PUVA and UVB phototherapy.

7.1 TZR and Corticosteroids

For psoriasis, topical steroids are the agents of choice because of their antiproliferative, anti-inflammatory and immunosuppressive effects[54]. Green and Sadoff[55] studied the use of corticosteroids and concomitant tazarotene gel topically in the morning and evening, respectively, in various formulations. The efficacy and tolerability were evaluated in different treatments in approximately 200 volunteers with plaque psoriasis for 12 weeks. The treatments given to the volunteers in different groups as TZR 0.1% gel only or TZR with betamethasone dipropionate 0.05% cream, diflorasone diacetate 0.05% cream or fluticasone propionate 0.005% ointment (a mid-high-potency steroid) or with diflorasone diacetate 0.05%, mometasone furoate 0.1%, fluocinonide 0.05% (a high-potency steroid ointment). The most effective treatment was TZR with steroid ointment in combination rather than monotherapy (efficiency: diflorasone diacetate 0.05% <mometasone furoate 0.1% ointments < betamethasone dipropionate 0.05% cream) administered twice daily[55-57-]. These results conclude that TZR and mometasone furoate act synergistically and patient can recover early from psoriasis than monotherapy.

7.2 TZR and Phototherapy

TZR can potentiate the impact of PUVA or UVB phototherapy in psoriatic patients. Numerous studies have reported the enhanced anti-psoriatic effect in terms of reduction in erythema, scaling, plaque elevation and recovery time of this combination therapy[58-560]. In a clinical broad-band UVB trial, TZR 0.1% gel/ vehicle gel/ no emollient was applied once daily for two weeks to psoriatic lesions and followed by three days a week along with phototherapy for the next 67 days. The 50% clinical improvement time was less in the TZR/UVB group than in UVB and vehicle gel or only phototherapy treatments. In addition, it was observed during the study that the extent of UV radiation necessary to treat psoriasis get significantly reduced with TZR from 1,644 mJ/cm^2 in phototherapy alone to 390 mJ/cm^2 in combination therapy[61]. Thus, a combination regimen was found beneficial regarding long-term hazards (a high chance of cutaneous cancer and augmented skin aging) of phototherapy[62-63].

8. DOSAGE AND ADMINISTRATION

Topical tazarotene has been approved in several countries to treat plaque psoriatic patients[29, 64-66] in two concentrations: 0.05% (initially) and 0.1% (if necessary) once daily, as detailed in Table 3

Table 3: TZR formulations approved in US and UK for plaque psoriasis

Country	Formulation	Condition
US	Cream	plaque psoriasis[64]
	Gel	stable plaque psoriasis with 20% body surface area (BSA) affected[29]
UK	Gel	mild-to-moderate plaque psoriasis (10% BSA affected)

9. TOLERABILITY

In preclinical studies, the adverse effects on bone morphology has been reported after oral, high dose (≥0.125 mg/kg/day), long-term administration and, teratogenic at 0.25 mg/kg in rats and 0.2 mg/kg in rabbits, but found non-carcinogenic, non-mutagenic with no effect on fertility after topical application. In healthy subjects, moderate skin irritation, no contact sensitization, phototoxicity or photosensitivity has been reported after multiple applications (TZR gel 0.05%/0.1%). Marks *et al*., 1997, conducted a study involving 2000 patients to observe clinical safety of TZR with 0.05% and 0.1% gel for 1 year. No serious side effect was reported in any patient and 96 patients did not observe any clinically significant bone-associated change after drug treatment. A large number of patients of facial *acne vulgaris* approved TZR cosmetically during the study[67].

10. SAFETY AND OVERDOSE

Depending upon dose, systemic adverse effects of TZR therapy are increased serum lipids, skeletal changes, pruritus, erythema, stinging/burning in psoriasis[22,23] and desquamation, erythema, dryness, and a burning sensation in patients with acne[67-68]. Topical TZR treatment does not cause phototoxicity/photoallergic reactions or contact sensitization, as reported in Phase I safety studies[69]. It is non-mutagenic and causes no clastogenic effects in preclinical studies, on topical application conducted in 21 months and after oral administration in a 2-year study [70]. Moreover, in a study involving 20 patients suffering from basal cell carcinoma(BCC), it has recently been found to have an anticarcinogenic effect on daily application for eight months and gave a complete response in 53% and a partial response in the remaining 47% of lesions [71]. Excessive topical use of TAZORAC Cream, may lead to peeling, discomfort or redness[64].

10.1 Potential for Teratogenicity

In animal studies, TZR (topically applied-0.25 mg/kg/day) has shown teratogenic effects like fall in the body weights of foetus, ossification of skeletal tissues in rats (used during gestation days), and in the foetuses of rabbits: retinoid-related abnormalities such as hydrocephalus, spina bifida, and heart malfunctions. Oral TZR has shown delays in development, losses after implantation, and counts of live foetuses in rabbits and/or rats. However, according to clinical data, humans do not know teratogenic dose. Thus, topical TZR therapy is not recommended in pregnant women as a precaution[64].

10.2 Regulatory Affairs

The first drug Application for tazarotene gel was accepted by the USFDA in June 1997 as 'Tazorac'. It was approved for mild to moderate plaque psoriasis and topically for facial *acne vulgaris* treatment. 'Zorac' is presently approved in Canada, Argentina, Ireland, UK, Australia, Bioglan, NSW, Europe, Warriewood, and Germany for psoriasis[72]. TZR gel is available in the market (0.05 and 0.1%) to treat psoriasis and (0.1%) acne. It was approved to be used as cream (0.05 and 0.1%) in US for psoriasis in September 2000, and 0.1% for *acne vulgaris* in October 2001. 0.1% TZR cream was approved as an adjuvant to other topical retinoids to reduce the signs of facial photodamage in September 2002[42].

10.3 Warnings and Precautions

As the skin penetration of TZR is < 6% of the applied dose along with low systemic absorption and rapid systemic elimination, topical tazarotene causes minimum systemic side effects, however, photosensitivity, local irritation, the risk for sunburn, hypersensitivity reactions, and embryofoetal toxicity has been reported. The US FDA has classified tazarotene as category X and is contraindicated in women liable to get pregnant. Females should be warned about the potential risk when TAZORAC Cream is to be used before conception and use of appropriate birth-control procedures. Prior to TAZORAC therapy, a lack of pregnancy report should be obtained prior to treatment[64]. However, in clinical trials, six women gave birth to healthy infants after TZR treatment during the pregnancy period[42,68].

10.4 Drug Interactions

The tazarotene interacts with the following drugs: Aminolaevulinic acid, Methoxsalen, Methyl amino levulinate topical, Salicylic acid topical, Sulphur topical, Verteporfin. Aminolaevulinic acid is a major drug interaction, while others are moderate interactions[72]. Abatacept, Adalimumab, Anakinra, Betamethasone, Canakinumab, Cyclophosphamide, dexamethasone, Ifosfamide, Infliximab, Hydrocortisone increase the metabolism of TZR[72]. Abiraterone, Almotriptan, Alpelisib, Aminophenazone, Amiodarone, Amitriptyline, Amodiaquine, Anastrozole, Antipyrine, Apomorphine, Atazanavir, Atorvastatin, Benzyl alcohol, Bezafibrate, Bosutinib, Cabazitaxel, Diclofenac, Gemfibrozil, Fosphenytoin, Fluticasone propionate, Fluorouracil, ketoconazole decrease the metabolism of TZR[72]. In combination with demeclocycline, the risk of pseudotumor cerebri increases. The therapeutic efficacy of dienogest, diethylstillbestrol, estradiol decreases when used in combination with TZR[73].

10.5 In Pregnancy, Lactation, Paediatric and Geriatric Use

As mentioned in teratogenicity section, TAZORAC cream may result in lethal distress to a pregnant woman and is not recommended throughout pregnancy. In the U.S., the approximate risk of miscarriage and congenital disabilities is 2-4% and 15-20%, respectively[64]. There are no reports of the passage of TZR in human milk and any effect on infants fed with breast milk. However, radioactivity was observed in rat milk on a single application of a topical dose of ^{14}C-tazarotene gel to the lactating rat's skin[64]. The safety and efficacy of TAZORAC Cream have not been established in patients with psoriasis under the age of 18 years, 65yrs older, or in acne under the age of 12 years[64].

11. ANALYTICAL METHODS FOR ESTIMATION

A review of literature shows numerous systematic procedures for the quantitative determination of TZR in topical formulations like ointment, foam, cream and gel with chromatographic, spectrophotometry, and hyphenated techniques like LC–MS/MS[74]. Some of the analytical techniques used for the estimation of TZR in bulk and in the pharmaceutical formulation are shown in Fig. 3.

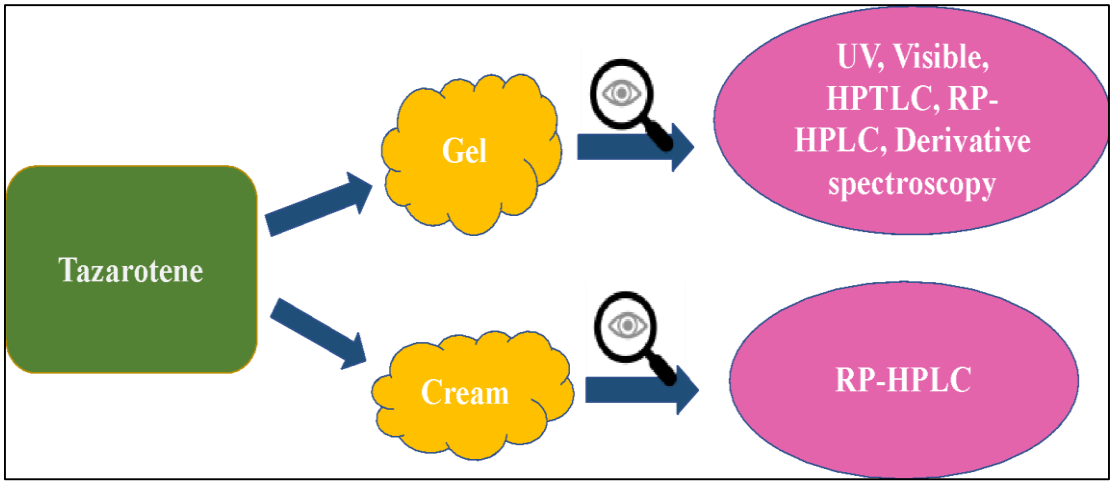


Fig. 3 Analytical techniques used to estimate tazarotene

12. CLINICAL TRIALS

The findings of some of the clinical trials of TZR have been summarised in Table 4.

Table 4: Details of the clinical trials of tazarotene in various diseased states

S.No	Study Title	No. of Patients	Condition	Interventions	Inference	Ref
1.	'Efficacy and Safety Study of Tazarotene (Tazorac) for the Treatment of Brittle Nails'	19	Brittle Nails	Tazorac	Improvement in brittle nails and minimal to no irritation	75
2.	'Acitretin or Tazarotene Gel and Excimer Laser for Treatment of Psoriasis'	13	Psoriasis	Acitretin 25Mg Oral Capsule; Tazarotene 0.1% Gel, Device: Excimer laser; Sham excimer laser	Lack of efficacy of TZR gel	76
3.	'Topical Tazarotene in Treating Patients With Basal Cell Skin Cancer and Basal Cell Nevus Syndrome on the Face'	36	Neoplastic Syndrome	tazarotene	Only 6% of patients had a chemo-preventive response in BCC but not in Basal Cell Nevus Syndrome	77
4.	'Combination Therapy With Imiquimod Cream 5% and Tazarotene Cream 0.1% for the Treatment of Lentigo Maligna	90	Cancer Lentigo Maligna	Imiquimod Cream; Tazarotene Cream 0.1%	Topical imiquimod can enhance the risk of recurrence as an alternative to surgery.	78
	Comparison of Tazarotene and Minocycline Therapies for Maintenance of Facial *Acne Vulgaris*'	189	*Acne Vulgaris*	Tazarotene 0.1% gel + placebo capsule, Oral minocycline (100 mg capsule) + vehicle gel	Improvement in moderately severe to severe acne with topical retinoid monotherapy.	79
5.	'A Bioavailability Study of DFD-03 (Tazarotene, Lotion 0.1 %) Compared to Tazorac® (Tazarotene), 0.1% in Patients With Moderate *Acne Vulgaris*'	58		Tazarotene Lotion and cream, 0.1%	Cmax, AUC, tmax of DFD-03 lotion was reported lesser than cream	80
6.	'A Study to Assess the Safety and Local Tolerability of DFD-03 (Tazarotene) Lotion, 0.1% Compared to Tazorac®	155		Tazarotene Lotion, 0.1%; Tazarotene Cream, 0.1%; Vehicle Lotion 0%; Vehicle Cream 0%	Frequency count of adverse events were reported more in Tazorac	81

	(Tazarotene) Cream, 0.1% in the Topical Treatment of *Acne Vulgaris*'				Cream groups than DFD-03 Lotion group.	
7.	'A Study To Evaluate The Safety And Therapeutic Equivalence of Tazarotene Foam 0.1% in Subjects With *Acne Vulgaris*'	894		Tazarotene (Fabior™);Tazarotene (Actavis); Vehicle foam	Formulation was reported as effective and tolerable in the test condition	82
8.	'A Study To Evaluate The Contact Sensitization Potential Of Tazarotene Foam On Skin In Healthy Volunteers'	254		Tazarotene Foam; Vehicle Foam	A low potential for contact-sensitization reaction	83
9.	'A Study to Evaluate the Safety and Efficacy of Tazarotene Foam, 0.1%, in Subjects With Common Facial Acne - W0260-301'	744		Tazarotene foam; Vehicle Foam	a safe and acceptable tolerability profile	84
10.	'A Phase 4, Single-Blind, Randomized, Study to Compare the Tolerability and Efficacy of 0.1% Tazorac Cream When Used in Combination With Either Duac Gel or Acanya Gel for the Treatment of Facial *Acne Vulgaris*'	40		Clindamycin(CLNP) 1%/Benzoyl Peroxide 5%(BPO5) and 0.1% tazarotene; clindamycin phosphate 1.2%/benzoyl peroxide 2.5%(BPO2.5) and 0.1% tazarotene	CLNP-BPO5 or CLNP-BPO2.5 fixed-dose gels with TZR cream 0.1% were well-tolerated and effective treatments	85
11.	'Dapsone Gel 5% and Tazarotene Cream 0.1% Versus Tazarotene Cream 0.1% Monotherapy for Facial *Acne Vulgaris*'	171		Dapsone; Tazarotene	Overall improvement in terms of decrease in both non-inflammatory and inflammatory lesion count, and acne severity	86
12.	'Safety and Efficacy of Tazarotene Cream 0.1% Compared With Adapalene Gel 0.3% in the Treatment of Moderate to Severe Facial *Acne Vulgaris*'	165		Tazarotene Cream 0.1%; Adapalene	more effective and nearly as well tolerated as adapalene 0.3% gel	87
13.	Tazarotene/Betamethasone Dipropionate Cream in Patients with Plaque Psoriasis: Results of a Prospective, Multicenter, Observational Study	2,299	Plaque psoriasis	Tazarotene/betamethasone dipropionate (Taz/BD) cream	effective and well tolerated in mild-to-moderate plaque psoriasis and, demonstrates efficacy and safety during retreatment.	88
14.	Fixed combination of tazarotene and betamethasone dipropionate for treatment of psoriasis vulgaris: The result of a phase 3, multicenter, randomized controlled trial	600	*Psoriasis vulgaris*	TAZ/BM cream, TAZ gel or BM cream groups for 6 weeks with an 8-week follow up	The combination proved superior over TAZ and, BM in terms of efficacy, rapid onset, reduced local stimulation and, longer relief time along with reduced clinical relapse rate, respectively.	89
15.	Efficacy of Tazarotene in Treatment of Verruca Plana	80	Warts Flat	Drug: Tazarotene 0.1% Gel,Top, Imiquimod,	Phase 2	90

				Fluorouracil Cream, Petrolatum		
16	Tazarotene 0.045% Lotion for Females With Acne: Analysis of Two Adult Age Groups	18 years aged (n=744) or 25 years aged (n=335)	Acne	Tazarotene 0.045% Lotion	At week 12, both age groups had greater reductions from baseline versus vehicle in inflammatory and non-inflammatory lesions.	91

Recently, Lindsey et al., 2022 evaluated the efficacy and tolerability of tazarotene 0.045% lotion by evaluating the data generated after two studies and reported that in 12-week phase III clinical trials, tazarotene 0.045% lotion had higher rates of treatment success than individuals who received the vehicle. There was greater reduction in inflammatory and non-inflammatory acne lesions than vehicle. Tazarotene 0.045% lotion was found well tolerated and the first retinoid to be utilized with polymeric emulsion technology (PET) to efficiently distribute the medication across the skin, reducing side effects while maintaining efficacy[92].

13. MARKETED FORMULATION

The manufacturers of tazarotene are Tazorac, Fabior, Avage, Zorotene, Tazret Forte, LA-Tez, Arazlo and fabrior. These medications are either in the form of gel, cream, foam or aerosol via cutaneous and topical route. The formulation is prescribed depending upon the state or condition of the patient and the site of psoriasis, acne or other specified skin conditions. It is also available in the market with other drugs, like Duobrii (halobetasol/tazarotene topical), Ethoxia (niacinamide/tazarotene topical) etc[93].

14. CONCLUSION

The preclinical and clinical studies conducted by different research groups suggested the use of tazarotene topically either in monotherapy or in combination with topical steroids or phototherapy in psoriasis, *acne vulgaris,* steroid-induced epidermal atrophy, photodamaged skin, and refractory mycosis fungoides lesions as a viable treatment option due to minimum percutaneous absorption and hence the least number of side effects after topical application as compared to other retinoids in the market. Furthermore, in combination with steroids/phototherapy, it has been found less irritating and more effective than either therapy given alone as maintenance therapy to treat psoriasis.

15. LIST OF ABBREVIATIONS

LC–MS: Liquid chromatography–mass spectrometry; MS: mass spectrometry; HPTLC: High-performance thin-layer chromatography; HPLC: High-performance layer chromatography; TZR: Tazarotene; TA: Tazarotenic acid; IV: Intravenously; Vd: Volume of distribution; AUC: Area under curve; RAR: Retinoic acid receptors; TIG: Tazarotene induced gene; MED: Mean minimal erythema dose; MRP-8: Migration-inhibitory related factor 8; BSA: Body surface area; BCC: Basal cell carcinoma; USFDA: United States Food and Drug Administration; BPO5: Benzoyl Peroxide 5%, spr-2: Suppressor of presenilin-2; TGase-K: Transglutaminase K; CLNP: Clindamycin; BPO2.5: benzoyl peroxide 2.5%; IFN©: Interferon gamma; API: (c-Jun/c-Fos)-mediated gene expression; RP: Reverse phase

16. ACKNOWLEDGEMENT

All Authors are grateful to Dr. R.K. Dhawan, Director-Principal, Khalsa College of Pharmacy, Amritsar, Punjab for encouragement and research facilities in the department.

17. AUTHORS CONTRIBUTION STATEMENT

Dr. Charanjit Kaur and Mr. Chahat Khana conceptualised the study. Parminderjit Kaur and Peeyush Sharma curated the data and prepared the draft. Dr. Sandeep Rahar , Dr. Charanjeet Kaur and Dr. Varinder soni provided valuable inputs towards designing of paper. Simranjit Kaur, Sukhdeep Singh and Lavish Kumar contributed toward data analysis.

18. CONFLICT OF INTERESTS

Conflict of interest declared none.

19. REFERENCES

1. Christophers E. Psoriasis-Epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26(4):314-20. doi: 10.1046/j.1365-2230.2001.00832.x, PMID 11422182.
2. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-85. doi: 10.1038/jid.2012.339, PMID 23014338.
3. Gibbs S. Skin disease and socioeconomic conditions in rural Africa: Tanzania. Int J Dermatol. 1996;35(9):633-9. doi: 10.1111/j.1365-4362.1996.tb03687.x, PMID 8876289.
4. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the united states. J Am Acad Dermatol. 2014;70(3):512-6. doi: 10.1016/j.jaad.2013.11.013, PMID 24388724.
5. Danielsen K, Olsen AO, Wilsgaard T, Furberg AS. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. Br J Dermatol. 2013;168(6):1303-10. doi: 10.1111/bjd.12230, PMID 23374051.

6. Di Meglio P, Villanova F, Nestle FO. Psoriasis. Cold Spring Harb Perspect Med. 2014;4(8):6. doi: 10.1101/cshperspect.a015354, PMID 25085957.
7. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of psoriasis: A comprehensive review. J Autoimmun. 2015;64:66-73. doi: 10.1016/j.jaut.2015.07.008, PMID 26215033.
8. Liang Y, Sarkar MK, Tsoi LC, Gudjonsson JE. Psoriasis: A mixed autoimmune and autoinflammatory disease. Curr Opin Immunol. 2017;49:1-8. doi: 10.1016/j.coi.2017.07.007, PMID 28738209.
9. Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2022;5:1465-858. doi: 10.1002/14651858.CD011535.pub2.
10. Zhou X, Chen Y, Cui L, Shi Y, Guo C. Advances in the pathogenesis of psoriasis: from keratinocyte perspective. Cell Death Dis. 2022;13(1):81. doi: 10.1038/s41419-022-04523-3, PMID 35075118.
11. Segaert S, Calzavara-Pinton P, de la Cueva P, Jalili A, Lons Danic D, Pink AE et al. Long-term topical management of psoriasis: the road ahead. J Dermatolog Treat. 2022;33(1):111-20. doi: 10.1080/09546634.2020.1729335, PMID 32091278.
12. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CEM, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: A European consensus. Arch Dermatol Res. 2011;303(1):1-10. doi: 10.1007/s00403-010-1080-1, PMID 20857129.
13. Chat VS, Uppal SK, Kearns DG, Wu JJ. Clinical management of psoriasis patients during the COVID-19 pandemic. J Dermatolog Treat. 2022;33(2):1166-7. doi: 10.1080/09546634.2020.1781045, PMID 32568009.
14. Available from: https://www.emedicinehealth.com/understanding_psoriasis_medications/article_em.htm#medical_treatment_of_psoriasis.
15. Prussick R, Ebaugh BK. Psoriasis: an overview. Trauma. 2003;45(4):73-84.
16. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Tazarotene.
17. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Tazarotene#section=Computed-Properties.
18. Matsumoto RM, Sun H, Duff SB, Tang-Liu D. Skin distribution and metabolism of 14C-AGN 190168 in minipigs. Pharm Res. 1992;9;Suppl:289.
19. Franz TJ, Lehman PA, Franz S, LEWKAYA D, Matsumoto R, Tangliu D. Percutaneous-absorption of AGN 190168, A new synthetic retinoid, through human skin in vivo. [350 main st, malden, ma 02148 usa: Blackwell Publishing Inc]. J Invest Dermatol. 1992;98(4):650-.
20. Tang-Liu DD-S, Matsumoto RM, Usansky JI. Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. Clin Pharmacokinet. 1999;37(4):273-87. doi: 10.2165/00003088-199937040-00001, PMID 10554045.
21. Lebwohl M, Ast E, Callen JP, Cullen SI, Hong SR, Kulp-Shorten CL, et al. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. J Am Acad Dermatol. 1998;38(5 Pt 1):705-11. doi: 10.1016/s0190-9622(98)70594-8, PMID 9591815.
22. Weinstein GD, Krueger GG, Lowe NJ, Duvic M, Friedman DJ, Jegasothy BV, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. J Am Acad Dermatol. 1997;37(1):85-92. doi: 10.1016/s0190-9622(97)70216-0, PMID 9216528.
23. Weinstein GD, Koo JY, Krueger GG, Lebwohl MG, Lowe NJ, Menter MA, et al. Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. J Am Acad Dermatol. 2003;48(5):760-7. doi: 10.1067/mjd.2003.103, PMID 12734506.
24. Study Report PK-95-048. Pharmacokinetics of AGN 190168 following single dose and multiple dose topical administration of 0.1% gel or 0.05% gel to subjects with stable plaque psoriasis. Irvine, (CA): Allergan; 1995.
25. Madhu C, Duff S, Baumgarten V, Rix P, Small D, Tang-Liu D. Metabolic de-esterification of tazarotene in human blood and rat and human liver microsomes. J Pharm Sci. 1997 Aug 1;86(8):972-4. doi: 10.1021/js9700558, PMID 9269878.
26. (Study Report PK-94-091. Effect of AGN 190168 on hepatic drug metabolising enzymes in Sprague-Dawley rats. Irvine, (CA): Allergan; 1995).
27. Marks R. Pharmacokinetics and safety review of tazarotene. J Am Acad Dermatol. 1998;39(4 Pt 2);Suppl(2):134-8. doi: 10.1016/s0190-9622(98)70310-x, PMID 9777791.
28. Allergan (US). Tazorac (tazarotene topical gel): prescribing information. Irvine, (CA); 2003.
29. Esgleyes-Ribot T, Chandraratna RA, Lew-Kaya DA, Sefton J, Duvic M. Response of psoriasis to a new topical retinoid, AGN 190168. J Am Acad Dermatol. 1994 Apr 1;30(4):581-90. doi: 10.1016/s0190-9622(94)70066-4, PMID 7512583.
30. Nagpal S, Patel S, Asano AT, Johnson AT, Duvic M, Chandraratna RA. Tazarotene-induced gene 1 (TIG1), a novel retinoic acid receptor-responsive gene in skin. J Invest Dermatol. 1996 Feb 1;106(2):269-74. doi: 10.1111/1523-1747.ep12340668, PMID 8601727.
31. Duvic M, Nagpal S, Asano AT, Chandraratna RAS. Molecular mechanisms of tazarotene action in psoriasis. J Am Acad Dermatol. 1997;37(2 Pt 3):S18-24. doi: 10.1016/S0190-9622(97)80396-9, PMID 9270552.
32. Christophers E. Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26(4):314-20. doi: 10.1046/j.1365-2230.2001.00832.x, PMID 11422182.
33. Menter A. Pharmacokinetics and safety of tazarotene. J Am Acad Dermatol. 2000;43(2 Pt 3):S31-5. doi: 10.1067/mjd.2000.108321, PMID 10898827.
34. Esgleyes-Ribot T, Chandraratna RA, Lew-Kaya DA, Sefton J, Duvic M. Response of pso- riasis to a new topical retinoid, AGN 190168. J Am Acad Dermatol. 1994;30(4):581-90. doi: 10.1016/s0190-9622(94)70066-4, PMID 7512583.
35. Nonomura K, Yamanishi K, Yasuno H, Nara K, Hirose S. Up-regulation of elafin/SKALP gene expression in psoriatic epidermis. J Invest Dermatol. 1994;103(1):88-91. doi: 10.1111/1523-1747.ep12391802, PMID 8027586.

36. Hecker D, Worsley J, Yueh G, Kuroda K, Lebwohl M. Interactions between tazarotene and ultraviolet light. J Am Acad Dermatol. 1999;41(6):927-30. doi: 10.1016/s0190-9622(99)70248-3, PMID 10570375.
37. Krueger GG, Drake LA, Elias PM, Lowe NJ, Guzzo C, Weinstein GD, et al. The safety and efficacy of tazarotene gel, a topical acetylenic retinoid, in the treatment of psoriasis. Arch Dermatol. 1998 Jan 1;134(1):57-60. doi: 10.1001/archderm.134.1.57, PMID 9449910.
38. Weinstein GD, Green L, Drake LA, Elias PM, Krueger GG, Lazarus GS, et al. New topical retinoid gel for therapy of psoriasis-dose-ranging study of AGN 190168. J Invest Dermatol. 1993;100(4):544-.
39. Hager C, Mays S, Chandraratna R. Tazarotene: a topical retinoid with efficacy in psoriasis vulgaris and scalp psoriasis. Australas J Dermatol. 1997;2:149-50.
40. Weinstein GD, Krueger GG, Lowe NJ, Duvic M, Friedman DJ, Jegasothy BV, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. J Am Acad Dermatol. 1997 Jul 1;37(1):85-92. doi: 10.1016/s0190-9622(97)70216-0, PMID 9216528.
41. Weinstein GD. Tazarotene gel: efficacy and safety in plaque psoriasis. J Am Acad Dermatol. 1997 Aug 1;37(2 Pt 3):S33-8. doi: 10.1016/S0190-9622(97)80398-2, PMID 9270554.
42. Xi C, Xiong C, Wang H, Liu Y, Luo S. Combination of retinoids and narrow-band ultraviolet B inhibits matrix metalloproteinase 13 expression in HaCaT keratinocytes and a mouse model of psoriasis. Sci Rep. 2021 Jun 25;11(1):13328. doi: 10.1038/s41598-021-92599-w, PMID 34172768.
43. Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol. 2004 Apr;50(4):600-7. doi: 10.1016/j.jaad.2003.09.005, PMID 15034511.
44. Lowe N, Horwitz S, Tanghetti E, Draelos Z, Menter A. Tazarotene versus tazarotene plus hydroquinone in the treatment of photodamaged facial skin: a multicenter, double-blind, randomized study. J Cosmet Laser Ther. 2006 Sep;8(3):121-7. doi: 10.1080/14764170600895237, PMID 16971360.
45. Kaidbey K, Kopper SC, Sefton J, Gibson JR. A pilot study to determine the effect of tazarotene gel 0.1% on steroid-induced epidermal atrophy. Int J Dermatol. 2001 Jul;40(7):468-71. doi: 10.1046/j.1365-4362.2001.01234.x, PMID 11679006.
46. Kang S, Leyden JJ, Lowe NJ, Ortonne JP, Phillips TJ, Weinstein GD, et al. Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks. Arch Dermatol. 2001 Dec;137(12):1597-604. doi: 10.1001/archderm.137.12.1597, PMID 11735710.
47. Kakita L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. J Am Acad Dermatol. 2000;43(2 Pt 3):S51-4. doi: 10.1067/mjd.2000.108322, PMID 10898831.
48. Webster GF, Berson D, Stein LF, Fivenson DP, Tanghetti EA, Ling M. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. Cutis. 2001 Jun 1;67(6);Suppl:4-9. PMID 11499329.
49. Leyden JJ, Tanghetti EA, Miller B, Ung M, Berson D, Lee J. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis. 2002 Feb 1;69(2);Suppl:12-9. PMID 12095064.
50. Webster GF, Guenther L, Poulin YP, Solomon BA, Loven K, Lee J. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. Cutis. 2002 Feb 1;69(2);Suppl:4-11. PMID 12095066.
51. Bershad S, Kranjac Singer GK, Parente JE, Tan MH, Sherer DW, Persaud AN, et al. Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. Arch Dermatol. 2002 Apr 1;138(4):481-9. doi: 10.1001/archderm.138.4.481, PMID 11939810.
52. Krueger GG, Drake LA, Elias PM, Lowe NJ, Guzzo C, Weinstein GD, et al. The safety and efficacy of tazarotene gel, a topical acetylenic retinoid, in the treatment of psoriasis. Arch Dermatol. 1998;134(1):57-60. doi: 10.1001/archderm.134.1.57, PMID 9449910.
53. Katz HI. Topical corticosteroids. Dermatol Clin. 1995;13(4):805-15. doi: 10.1016/S0733-8635(18)30044-5, PMID 8785885.
54. Green L, Sadoff W. A clinical evaluation of tazarotene 0.1% gel, with and without a high- or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. J Cutan Med Surg. 2002;6(2):95-102. doi: 10.1007/s10227-001-0031-z, PMID 11992180.
55. Koo JY, Martin D. Investigator-masked comparison of tazarotene gel q.d. plus mometasone furoate cream q.d. versus mometasone furoate cream b.i.d. in the treatment of plaque psoria- sis. Int J Dermatol. 2001;40(3):210-2. doi: 10.1046/j.1365-4362.2001.01167.x, PMID 11422529.
56. Guenther LC, Poulin YP, Pariser DM. A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1 % cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. Clin Ther. 2000;22(10):1225-38. doi: 10.1016/s0149-2918(00)83065-9, PMID 11110233.
57. Lowe NJ. Ultraviolet B phototherapy plus topical retinoid therapy. Cutis. 1999;63:6-7.
58. Behrens S, Grundmann-Kollmann M, Schiener R, Peter RU, Kerscher M. Combination therapy of psoriasis with narrow-band UVB irradiation and topical tazarotene gel. J Am Acad Dermatol. 2000;42(3):493-5. doi: 10.1016/s0190-9622(00)90225-1, PMID 10688723.
59. Behrens S, Grundmann-Kollmann M, Peter RU, Kerscher M. Combination treatment of psoriasis with photochemotherapy and tazarotene gel, a receptor-selective topical retinoid. Br J Dermatol. 1999;141(1):177. doi: 10.1046/j.1365-2133.1999.02951.x, PMID 10417841.
60. Koo JY, Lowe NJ, Lew-Kaya DA, Vasilopoulos AI, Lue JC, Sefton J, et al. Tazarotene plus UVB phototherapy in the treatment of psoriasis. J Am Acad Dermatol. 2000;43(5 Pt 1):821-8. doi: 10.1067/mjd.2000.107940, PMID 11050587.

61. Taylor CR, Stern RS, Leyden JJ, Gilchrest BA. Photoaging/photodamage and photoprotection. J Am Acad Dermatol. 1991;22:315-7.
62. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis: photochemotherapy follow-up study. Cancer. 1994;73(11):2759-64. doi: 10.1002/1097-0142(19940601)73:11<2759::aid-cncr2820731118>3.0.co;2-c, PMID 8194017.
63. Allergan (US). Tazorac® (tazarotene topical cream): prescribing information. Irvine, (CA); 2001.
64. Allergan Ltd (UK). Zorac 0.05% Gel: Summary of Product Characteristics [online]. Available from: http://emc.medicines.org.uk.
65. Allergan Ltd (UK). Zorac 0.1% Gel: Summary of Product Characteristics [online]. Available from: http://emc.medicines.org.uk.
66. Marks R. Clinical safety of tazarotene in the treatment of plaque psoriasis. J Am Acad Dermatol. 1997 Aug;37(2 Pt 3):S25-32, PMID 9270553.
67. Shalita AR, Chalker DK, Griffith RF, Herbert AA, Hickman JG, Maloney JM, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. Cutis. 1999;63(6):349-54. PMID 10388959.
68. NDA 20-600. Approved June 13, 1997.
69. Duvic M. Tazarotene: a review of its pharmacological profile and potential for clinical use in psoriasis. Exp Opin Investig Drugs. 1997;6(10):1537-51. doi: 10.1517/13543784.6.10.1537, PMID 15989518.
70. Chandraratna RAS. Tazarotene: the first receptor-selective topical retinoid for the treatment of plaque psoriasis. J Am Acad Dermatol. 1997;37(2 Pt 3);Suppl:S12-7. doi: 10.1016/S0190-9622(97)80395-7, PMID 9270551.
71. Peris K, Fargnoli MC, Chimenti S. Preliminary observations on the use of topical tazarotene to treat basal-cell carcinoma. N Engl J Med. 1999;341(23):1767-8. doi: 10.1056/NEJM199912023412312, PMID 10610445.
72. Available from: https://go.drugbank.com/drugs/DB00799.
73. Duvic M. Tazarotene: a review of its pharmacological profile and potential for clinical use in psoriasis. Expert Opin Investig Drugs. 1997;6(10):1537-51. doi: 10.1517/13543784.6.10.1537, PMID 15989518.
74. Gaikwad J, Sharma S, Hatware KV. Review on characteristics and analytical methods of tazarotene: an update. Crit Rev Anal Chem. 2020;50(1):90-6. doi: 10.1080/10408347.2019.1586519, PMID 30942085.
75. Sherber NS, Hoch AM, Coppola CA, Carter EL, Chang HL, Barsanti FR, et al. efficacy and safety study of tazarotene cream 0.1% for the treatment of brittle nail syndrome. Cutis. 2011;87(2):96-103. PMID 21416778.
76. Available from: https://clinicaltrials.gov/ct2/show/NCT01094717.
77. Tang JY, Chiou AS, Mackay-Wiggan JM, Aszterbaum M, Chanana AM, Lee W, et al. Tazarotene: randomized, double-blind, vehicle-controlled, and open-label concurrent trials for basal cell carcinoma prevention and therapy in patients with basal cell nevus syndrome. Cancer Prev Res (Phila). 2014;7(3):292-9. doi: 10.1158/1940-6207.CAPR-13-0305, PMID 24441673.
78. Hyde MA, Hadley ML, Tristani-Firouzi P, Goldgar D, Bowen GM. A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions. Arch Dermatol. 2012;148(5):592-6. doi: 10.1001/archdermatol.2012.270, PMID 22431716.
79. Leyden J, Thiboutot DM, Shalita AR, Webster G, Washenik K, Strober BE, et al. comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. Arch Dermatol. 2006;142(5):605-12. doi: 10.1001/archderm.142.5.605, PMID 16702498.
80. Available from: https://clinicaltrials.gov/ct2/show/NCT03599193.
81. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03341910.
82. Epstein EL, Stein Gold L. Safety and efficacy of tazarotene foam for the treatment of acne vulgaris. Clin Cosmet Investig Dermatol. 2013;6:123-5. doi: 10.2147/CCID.S34054, PMID 23696711.
83. Berg JE, Bowman JP, Saenz AB. Cumulative irritation potential and contact sensitization potential of tazarotene foam 0.1% in 2 phase I patch studies. Cutis. 2012;90(4):206-11. PMID 23259209.
84. Feldman SR, Werner CP, Alió Saenz AB. The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2-multicenter, randomized, vehicle-controlled, double-blind studies. J Drugs Dermatol. 2013;12(4):438-46. PMID 23652892.
85. Dhawan SS, Gwazdauskas J. Clindamycin phosphate 1.2%-benzoyl peroxide (5% or 2.5%) plus tazarotene cream 0.1% for the treatment of acne. Cutis. 2013;91(2):99-104. PMID 23513559.
86. Available from: https://clinicaltrials.gov/ct2/show/NCT00834210.
87. Tanghetti E, Dhawan S, Green L, Del Rosso J, Draelos Z, Leyden J, et al. Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treatment of patients with at least moderate facial acne vulgaris. J Drugs Dermatol. 2010;9(5):549-58. PMID 20480800.
88. He C, Jin H, Liu X, Hu F, Zhang L, Zhang S, et al. Tazarotene/betamethasone dipropionate cream in patients with plaque psoriasis: results of a prospective, multicenter, observational study. Dermatology. 2021;237(4):603-10. doi: 10.1159/000511891, PMID 33352561.
89. Chen H, Sun J, Yang H, Sun Q, Zhang J, Gu J, et al. Fixed combination of tazarotene and betamethasone dipropionate for treatment of psoriasis vulgaris: the result of a phase 3, multicenter, randomized controlled trial. J Dermatol. 2020;47(7):728-34. doi: 10.1111/1346-8138.15349, PMID 32346959.
90. Available from: https://clinicaltrials.gov/ct2/show/NCT05314127.
91. Stein Gold L, Kircik L, Baldwin H, Callender V, Tanghetti E, Del Rosso J, et al. Tazarotene 0.045% lotion for females with acne: analysis of two adult age groups. J Drugs Dermatol. 2022;21(6):587-95. doi: 10.36849/JDD.6876, PMID 35674760.
92. Mohney LA, Singh R, Feldman SR. Tazarotene 0.045% lotion: A novel retinoid formulation. Ann Pharmacother. 2022;56(10):1174-80. doi: 10.1177/10600280211072155, PMID 35112585.
93. Available from: https://www.drugs.com/ingredient/tazarotene.html.