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CASE REPORT

# Atypical Fibroxanthoma Treated with a Topical Combination of Imiquimod, Tazarotene, and 5-Fluorouracil

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## ABSTRACT

This case report describes an 80-year-old man who presented with a growing erythematous nodule with erosion, measuring 0.6 cm × 0.6 cm, on his right temple. This lesion was later diagnosed as atypical fibroxanthoma (AFX). Instead of undergoing Mohs surgery, the gold standard treatment, the patient opted to pursue a topical treatment regimen because of financial costs associated with surgical removal and repair. This topical regimen consisted of tazarotene cream, imiquimod cream, and 5-fluorouracil solution, applied for 30 days. The patient was directed to use this combination 5 days per week for 6 weeks. The specified dosage for each medication was a fifth of a packet of imiquimod 5% cream, an equivalent amount of tazarotene 0.1% cream, and a single drop of 5-fluorouracil 2% solution. These were combined on a bandage and placed on the lesion overnight. Following the treatment, a 3-week post-application examination revealed an erosion, 1.0 cm × 0.9 cm, amidst erythema. A subsequent incisional biopsy with histopathology and stains for CD10 and CD99, 3 weeks after treatment, and three punch biopsies with histopathology and stains for CD10 and CD99, 1-year post-treatment, confirmed the absence of AFX. AFX is a superficial variant of pleomorphic dermal sarcoma (PDS), which shares histologic similarities, yet the exact relationship between AFX/PDS and undifferentiated pleomorphic sarcoma is still not well

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understood. Previous studies have indicated a genomic similarity between AFX/PDS and cutaneous squamous cell carcinoma (cSCC), which suggests the potential efficacy of cSCC-targeted treatments for AFX/PDS. This case marks the first recorded instance of successful topical medical treatment of AFX, offering an alternative for patients who may opt out of surgical intervention. Continued research to assess the broader efficacy of this approach is encouraged.

**Keywords:** Atypical fibroxanthoma; Topical therapy; Imiquimod; Tazarotene; 5-fluorouracil; Nonsurgical

| **Key Summary Points** |
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| Atypical fibroxanthoma (AFX), a rare, pleomorphic spindle cell malignancy, often manifests as a solitary erythematous papule or nodule primarily located on the head and neck. |
| Mohs surgery is currently the established treatment standard for AFX. |
| This case report introduces the first successful nonsurgical treatment of AFX using a topical regimen of tazarotene, imiquimod, and 5-fluorouracil, potentially expanding patient therapeutic options. |

## INTRODUCTION

Atypical fibroxanthoma (AFX), a rare, pleomorphic spindle cell malignancy, often manifests as a solitary erythematous papule or nodule primarily located on the head and neck. Although AFX is recognized as a superficial variant of pleomorphic dermal sarcoma (PDS), a soft tissue tumor exhibiting similar histologic characteristics to AFX, the interconnection among AFX/PDS and undifferentiated pleomorphic sarcoma remains unclear [1]. Mohs surgery is the preferred treatment method for AFX, but wide excision, radiation, and other therapies have been employed [2]. Gene mutations and expression profiles reveal similarities between AFX and cutaneous squamous cell carcinoma (cSCC), suggesting a high degree of genomic commonality between these entities [3]. Therefore, logically, treatments that target cSCC could treat AFX. Previous studies have demonstrated a high probability of tumor clearance with a nonsurgical combination of retinoids, imiquimod, and 5-fluorouracil in treating keratinocyte carcinomas (KCs), particularly cSCCs [4]. Here, we present a patient with an AFX on the right temple treated successfully with a topical combination of tazarotene cream, imiquimod cream, and 5-fluorouracil solution.

## CASE REPORT

An 80-year-old man presented with an enlarging 0.6 cm × 0.6 cm erythematous nodule with erosion on the right temple (Fig. 1). A shave biopsy demonstrated a nodule beneath an eroded epidermis composed of spindle-shaped cells that extended to the margins of the specimen. Individual cells were markedly atypical, with some cells having enlarged hyperchromatic nuclei and some having bizarre mitotic figures (Fig. 2a). Moreover, there was a background of solar elastosis. The immunostains for cytokeratin and SOX-10 were negative, and those for CD10 (Fig. 2c) and CD99 (Fig. 2e) were positive.

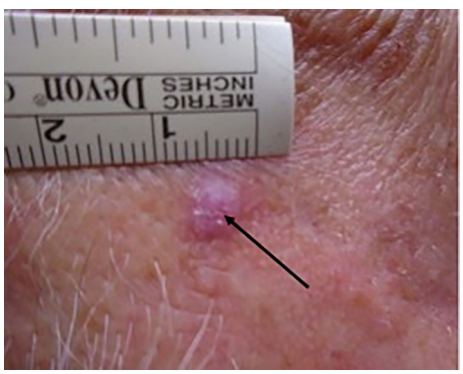


**Fig. 1** AFX on the right temple. Arrow highlights an area that is focally eroded

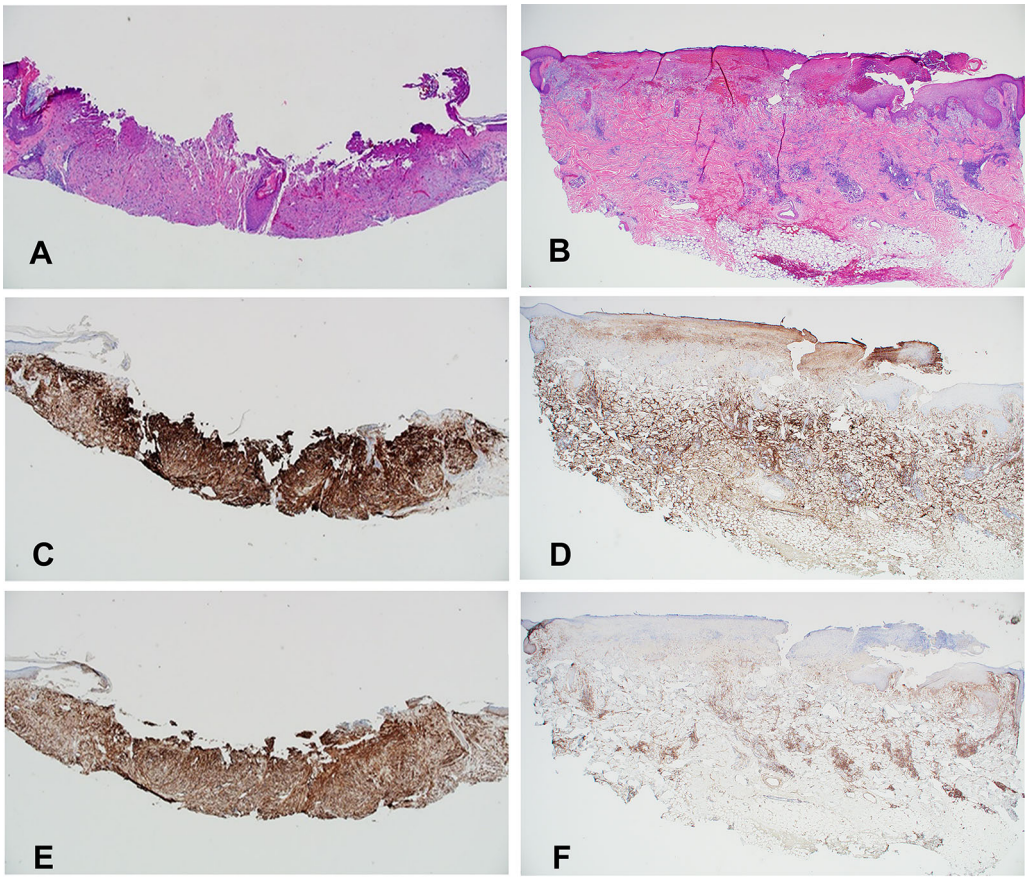


**Fig. 2** **a** Hematoxylin and eosin stain of AFX before treatment. There is a dermal neoplasm, which is composed of spindle-shaped cells beneath an eroded epidermis. **b** Hematoxylin and eosin stain of the area after topical treatment showing an inflamed but otherwise essentially normal dermis (absent for AFX). The epidermis is broadly absent, and there is an acutely inflamed crust. **c** Immunostain for CD10 of the pretreated AFX. **d** Immunostain for CD10 of the area after treatment. **e** Immunostain for CD99 of the pretreated AFX. **f** Immunostain for CD99 of the area after topical treatment. (**a**–**f**, ×40)

After options were presented to the patient, including Mohs surgery, he chose not to have a surgical procedure. The patient stated he could not afford his deductible or coinsurance amount involved with surgical removal and repair. The patient was presented with a non-surgical treatment involving tazarotene, imiquimod, and 5-fluorouracil. Per previous treatment regimens detailed for KCs, the patient applied the topical combination for 30 daily applications. The patient was instructed to use this combination 5 days a week for 6 weeks (30 applications within 42 days) but was allowed to extend the treatment phase up to 9.5 weeks (30 applications within 76 days) [4]. Specified amounts of the medications included 1/5 of a packet of imiquimod 5% cream, an equivalent amount of tazarotene 0.1% cream (1/5 of a pea), and one drop of 5-fluorouracil 2% solution. The topical medications were combined on the non-adherent part of a Band-Aid bandage or equivalent for each application and the bandage was placed over the AFX overnight. The application procedure was demonstrated to the patient with a video that detailed the amounts of each medication used.

The patient was allowed to alter his treatment application frequency on the basis of the symptoms that arose, but he applied, as recommended, the combination 5 days/week over

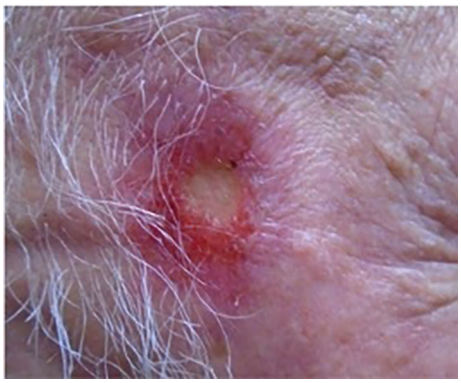

**Fig. 3** Site of previous AFX on the right temple, 3 weeks after last topical application of combination therapy. There is an ulceration in a background of erythema. After this picture was taken, a deep incisional second biopsy was performed to determine if there was complete treatment of the AFX

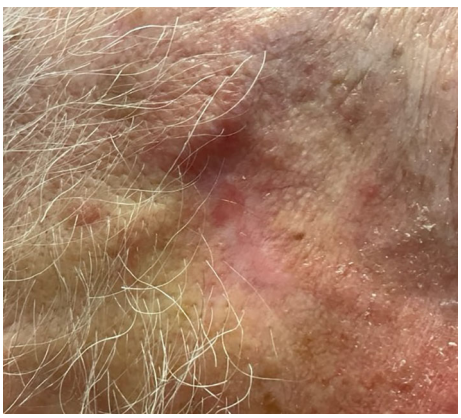

**Fig. 4** Final appearance on the right temple at 1-year follow-up that was previously treated with a combination of tazarotene, 5-fluorouracil, and imiquimod. There was acceptable cosmesis with erythema and minimal scarring

6 weeks. After 2 weeks of application, marked erythema, progressing erosion, pain, crusting, and oozing were present at the site of application on the right temple. The patient did not report any fever, chills, or body aches.

Three weeks after the final application, the patient presented with an erosion (measuring 1.0 cm × 0.9 cm) in a background of erythema over the right temple (Fig. 3). An incisional biopsy (measuring 1.0 cm × 1.0 cm × 0.5 cm) with 90° incision to the skin surface and underlying sharp dissection through the temporal fat was performed to determine if treatment was successful. No signs of an AFX were seen with hematoxylin and eosin staining (Fig. 2b). Immunostains for CD10 (Fig. 2d) and CD99 (Fig. 2f) were also negative. The biopsy site healed well after second intention (Fig. 4). The patient had follow-up evaluation in the post-treatment area every 3 months and had no clinical signs of recurrence. After 1 year from the time of post-treatment, again no clinical signs of the AFX were seen on the right temple and three punch biopsies (2 mm) with histopathology with immunostains for CD10 and CD99 also demonstrated no evidence of the AFX.

## DISCUSSION

Clinically, histopathologically, genetically, and epigenetically, contemporary perspectives propose that AFX and PDS represent a continuum of a singular pathological entity [1, 5]. Effective therapeutic outcomes can be anticipated following the comprehensive surgical removal of an AFX with Mohs surgery. Although Mohs surgery is the standard of treatment, nonsurgical procedures for treating AFX include cryotherapy, electrocautery, and primary radiation treatments in the form of brachytherapy [2, 6]. Radiation therapy is also used as an adjuvant treatment modality for patients with recurrent or metastatic AFX/PDS [7]. While the available data is not definitive, a study with a restricted patient sample has indicated a non-significant tendency towards decreased local recurrences or metastases in individuals who received adjuvant radiation therapy [8].

There is a dearth of evidence regarding the efficacy of novel medical treatment modalities, with data mainly stemming from a handful of individual case reports. Some of these therapies include chemotherapeutic agents like doxorubicin or a combination of ifosfamide and doxorubicin [3]. Electrochemotherapy has also been explored as a potential treatment avenue. However, the limited body of evidence prevents the establishment of these therapies as the standard of care. For patients presenting with AFX/PDS characterized by elevated levels of

tumor-infiltrating lymphocytes and heightened expression of programmed death-ligand 1 (PD-L1) or other immunologic checkpoint molecules, a treatment approach warranting consideration could be off-label use of checkpoint inhibitors, specifically anti-programmed death 1 (PD-1) antibodies. This therapeutic approach leverages the inherent immunological characteristics of the tumor to potentially improve clinical outcomes. A limited number of case reports have indeed suggested that the blockade of the PD-1/PD-L1 pathway may demonstrate efficacy in managing AFX/PDS [9].

AFX and PDS exhibit a significantly elevated mutational load with a UV signature, surpassing other UV-induced skin neoplasms such as cSCC. Investigations into gene mutations and expression profiles have elucidated a striking resemblance between AFX/PDS and cSCC, suggesting the highest degree of genomic commonality between these entities [3]. As such, treatments that target cSCC may have activity against AFX/PDS.

Previous studies have detailed a treatment regimen for cSCC using tretinoin, imiquimod, and 5-fluorouracil [4]. In the authors' experience with treating cSCCs, patients treated with tazarotene in a triple combination with imiquimod and 5-fluorouracil had greater success than those using tretinoin in combination. Also, in the authors' experience, when combined, tazarotene had greater treatment efficacy in patients who had recalcitrant tumors, invasive tumors, or smoked heavily. Moreover, imiquimod has extensive activity against cSCC [10, 11]. Also, 5-fluorouracil and tazarotene have activity against cSCC [12–14].

Imiquimod has the ability to modulate both innate and adaptive immunity [11]. Intrinsically, imiquimod can activate the innate immunity that may potentiate the anti-tumor activity of 5-fluorouracil and tazarotene in treating AFX. This is achieved through its direct binding to Toll-like receptors 7 and 8, found on macrophages, monocytes, and dendritic cells, which leads to the induction of apoptosis [15, 16]. Additionally, imiquimod indirectly affects immune cells by releasing cytokines [17]. The drug is also known to enhance antigen presentation by Langerhans cells and promote T cell activation in lymph nodes [17]. Imiquimod can treat skin cancers, as it triggers apoptosis via the intrinsic pathway [16]. This results in the release of pro-apoptotic factors and the activation of caspase-9 [18]. Furthermore, imiquimod is known to upregulate Bcl-2 family pro-apoptotic proteins, which promotes cancer cell death [18]. Imiquimod also elicits a cell-mediated immune response, which is beneficial in anti-tumor activity. This is achieved through the release of cytokines such as interleukin-12, tumor necrosis factor alpha, and interferon-γ [16]. These cytokines increase cytotoxic T cells and natural killer cells while inhibiting angiogenesis [16].

5-Fluorouracil's chemotherapeutic properties are based on its facilitated cellular entry, conversion to fluorodeoxyuridine monophosphate, and subsequent interaction with thymidylate synthase [19]. This interaction inhibits the production of deoxythymidine monophosphate (dTMP), which is a crucial precursor for DNA replication and repair [20]. The depletion of dTMP leads to an imbalance in intracellular nucleotides, ultimately resulting in double-stranded DNA breaks mediated by endonuclease activity [21]. Furthermore, 5-fluorouracil is a pyrimidine analogue that misincorporates into RNA and DNA, substituting for uracil or thymine [22]. This erroneous incorporation significantly damages DNA repair machinery, ultimately leading to the demise of rapidly proliferating cells [23]. Notably, the topical application of 5-fluorouracil demonstrates remarkable selectivity for actinic skin lesions while sparing normal skin. This selectivity is proposed to arise from the preferential inhibition of thymidylate synthase in actinic skin, with only partial inhibition observed in normal skin [24].

Local adverse effects commonly occur with the use of topical tazarotene. Approximately 10–30% of patients report skin peeling, dryness, redness, and a burning sensation, while a smaller proportion of users, ranging from 1% to 5%, may encounter itching, facial pain, irritation, and a stinging sensation [25–28]. These side effects are largely attributed to compromised barrier function, leading to increased transepidermal water loss, which is often

coupled with temporary heightened exfoliation, such as peeling, and mild irritation [28, 29]. This diminished skin barrier is thought to lead to enhanced cutaneous penetration of other topical medications, such as 5-fluorouracil and imiquimod [30].

Tazarotene has also been found to induce apoptosis in immortalized keratinocytes. This process is primarily facilitated through the transcriptional upregulation of *p73*, a homolog of *p53*, a well-known tumor suppressor gene that plays a significant role in the apoptotic pathway and cellular response to DNA damage [31]. This mechanism highlights the potential therapeutic applications of tazarotene in targeting abnormal proliferation, particularly relevant in skin cancer treatment and prevention [32].

Tazarotene-induced gene-3 (TIG-3) is thought to act as a tumor suppressor and is upregulated by all retinoic acid receptor-selective retinoids, including tazarotene, and is inducible in keratinocytes and HaCaT cell lines [33]. Loss of TIG-3 expression could result in epidermal malignancies. Aggressive cutaneous tumors were found to have no TIG-3 mRNA staining. TIG-3 protein, as shown by immunohistochemistry, is highest in the suprabasal epidermis of normal skin, just under the stratum corneum, and is decreased in both basal cell carcinomas and SCCs [33].

This case report is significant for several reasons. It marks the first recorded instance of successful topical treatment for AFX, offering a new option beyond surgical intervention like Mohs surgery, especially for patients unable or unwilling to undergo surgery because of factors like financial constraints or medical conditions. This case adds to the limited literature on nonsurgical approaches for AFX management, providing valuable clinical evidence that can inform future research and clinical practice in dermatology and oncology. It also highlights avenues for further exploration of molecular mechanisms and potential drug development, emphasizing the importance of personalized treatment strategies for patients with AFX.

## CONCLUSION

Here, we report on the first case involving a successful topical medical treatment for an AFX that may benefit those patients who choose not to undergo surgery. This case advances our understanding of AFX treatment by demonstrating successful nonsurgical options and underscores the need for ongoing research to refine treatment approaches and enhance outcomes for patients with an AFX.

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### *Declarations*

***Conflict of Interest.*** William J. Nahm, Evangelos V. Badiavas, Robert S. Kirsner, Carter J. Boyd, Anita A. Arthur, Sean Bae, and John Shen have nothing to disclose.

***Ethical Approval.*** As this is a case report, ethics committee approval and consent for participation were not required. The authors obtained written consent from patients for their photographs and medical information to be

published in print and online with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.



## REFERENCES

1. Soleymani T, Tyler HS. Conception and management of a poorly understood spectrum of dermatologic neoplasms: atypical fibroxanthoma, pleomorphic dermal sarcoma, and undifferentiated pleomorphic sarcoma. Curr Treat Options Oncol. 2017;18:1–11.

2. Iorizzo I, Luciano J, Brown MD. Atypical fibroxanthoma: a review of the literature. Dermatol Surg. 2011;37(2):146–57.

3. Helbig D, Klein S. Immune checkpoint inhibitors for unresectable or metastatic pleomorphic dermal sarcomas. Front Oncol. 2022;12:975342.

4. Nahm WJ, Shen J, Zito PM, et al. A non-surgical and cost-effective treatment approach employing topical imiquimod, 5-fluorouracil, and tretinoin for primary non-melanoma skin cancers. J Drugs Dermatol. 2021;20(3):260–7.

5. Griewank KG, Wiesner T, Murali R, et al. Atypical fibroxanthoma and pleomorphic dermal sarcoma harbor frequent NOTCH1/2 and FAT1 mutations and similar DNA copy number alteration profiles. Mod Pathol. 2018;31(3):418–28.

6. Doggett S, Brazil J, Limova M, et al. Electronic brachytherapy management of atypical fibroxanthoma: report of 8 lesions. J Contemp Brachytherapy. 2017;9(2):158–60.

7. Rosenfeld D, Alam M, Van Tine B, Council ML. Atypical fibroxanthoma: a malignant tumor of the skin and soft tissue. J Am Acad Dermatol. 2020;83(6):e429–30.

8. Persa O, Loquai C, Wobser M, et al. Extended surgical safety margins and ulceration are associated with an improved prognosis in pleomorphic dermal sarcomas. J Eur Acad Dermatol Venereol. 2019;33(8):1577–80.

9. Klein S, Persa O-D, Mauch C, et al. First report on two cases of pleomorphic dermal sarcoma successfully treated with immune checkpoint inhibitors. Oncoimmunology. 2019;8(12): e1665977.

10. Hengge UR, Schaller J. Successful treatment of invasive squamous cell carcinoma using topical imiquimod. Arch Dermatol. 2004;140(4):404–6.

11. Bubna AK. Imiquimod - its role in the treatment of cutaneous malignancies. Indian J Pharmacol. 2015;47(4):354–9.

12. Maxfield L, Shah M, Schwartz C, Tanner LS, Appel J. Intralesional 5-fluorouracil for the treatment of squamous cell carcinomas. J Am Acad Dermatol. 2021;84(6):1696–7.

13. Bardazzi F, Bianchi F, Parente G, Guareschi E, Landi C. A pilot study on the use of topical tazarotene to treat squamous cell carcinoma in situ. J Am Acad Dermatol. 2005;52(6):1102–4.

14. Bennardo L, Bennardo F, Giudice A, et al. Local chemotherapy as an adjuvant treatment in unresectable squamous cell carcinoma: what do we know so far? Curr Oncol. 2021;28(4):2317–25.

15. McGowan DC. Latest advances in small molecule TLR 7/8 agonist drug research. Curr Top Med Chem. 2019;19(24):2228–38.

16. Navi D, Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. Dermatol Online J. 2004. https://doi.org/10.5070/D34VW339W4.

17. Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. J Am Acad Dermatol. 2000;43(1):S6–11.

18. Leverkus M. Imiquimod: unexpected killer. J Investig Dermatol. 2004;122:xv–xvi.

19. Zhang N, Yin Y, Xu S-J, Chen W-S. 5-Fluorouracil: mechanisms of resistance and reversal strategies. Molecules. 2008;13(8):1551–69.

20. Danenberg PV. Thymidylate synthetase-a target enzyme in cancer chemotherapy. Biochim Biophys Acta. 1977;473(2):73–92.

21. Jarmuła A, Dowierciał A, Rode W. A molecular modeling study of the interaction of 2′-fluoro-substituted analogues of dUMP/FdUMP with thymidylate synthase. Bioorg Med Chem Lett. 2008;18(8):2701–8.

22. Parker JB, Stivers JT. Dynamics of uracil and 5-fluorouracil in DNA. Biochemistry. 2011;50(5):612–7.

23. Wyatt MD, Dr W. Participation of DNA repair in the response to 5-fluorouracil. Cell Mol Life Sci. 2009;66:788–99.

24. Askew D, Mickan S, Soyer P, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis - a systematic review of randomized controlled trials. Int J Dermatol. 2009;48:453–63.

25. Shalita AR, Berson DS, Thiboutot DM, et al. Effects of tazarotene 0.1% cream in the treatment of facial acnevulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. Clin Ther. 2004;26(11):1865–73.

26. Feldman SR, Werner CP. 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.

27. Kang S, Leyden JJ, Lowe NJ, 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;137(12):1597–604.

28. Sidgiddi S, Allenby K, Okumu F, Gautam A. Bioavailability, pharmacokinetics, and transepidermal water loss of short contact tazarotene lotion 0. 1% versus tazarotene (Tazorac®) cream 0.1%. J Clin Aesth Dermatol. 2019;12(9):16.

29. Chandraratna R. Tazarotene—first of a new generation of receptor-selective retinoids. Br J Dermatol. 1996;135(s49):18–25.

30. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol. 2003;49(1):S1–37.

31. Papoutsaki M, Lanza M, Marinari B, et al. The p73 gene is an anti-tumoral target of the RARβ/γ-selective retinoid tazarotene. J Investig Dermatol. 2004;123(6):1162–8.

32. Ramchatesingh B, Martínez Villarreal A, Arcuri D, et al. The use of retinoids for the prevention and treatment of skin cancers: an updated review. Int J Mol Sci. 2022;23(20):12622.

33. Duvic M, Helekar B, Schulz C, et al. Expression of a retinoid-inducible tumor suppressor, tazarotene-inducible gene-3, is decreased in psoriasis and skin cancer. Clin Cancer Res. 2000;6(8):3249–59.