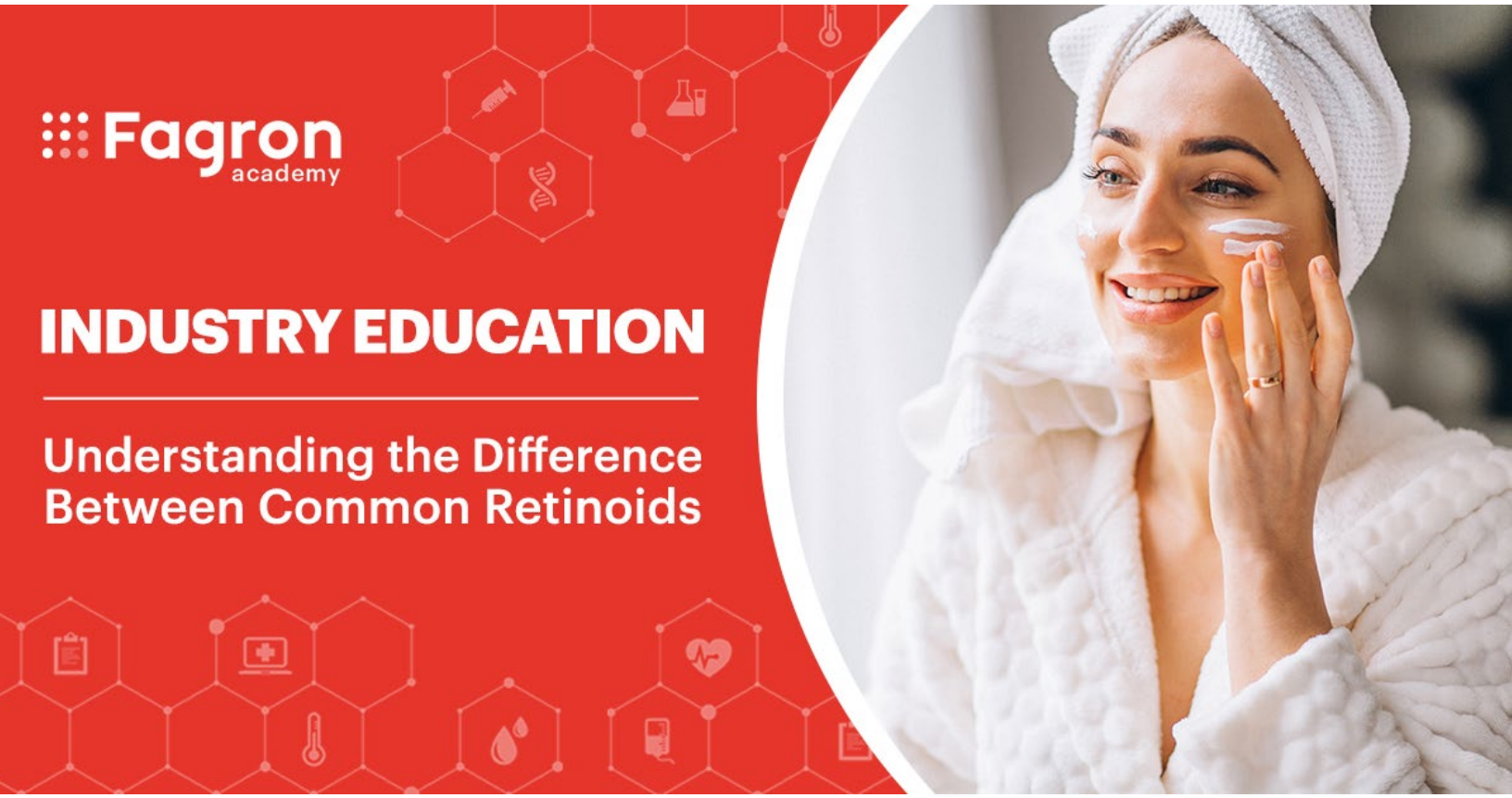


May 23, 2023

Sarah Taylor, PharmD
Academy Director

What are retinoids?

Retinoids are vitamin A (retinol) derivatives either synthetic or natural. Natural retinoid derivatives include retinoic acid (tretinoin), and retinyl esters. Synthetic retinoid derivatives include newer retinoids like tazarotene or adapalene. Retinoids play a role in a wide variety of processes within the body including reproduction, vision, inflammation, and cell differentiation and proliferation among others.[1] Common retinoids such as tretinoin and adapalene are FDA approved for the management of acne vulgaris, tazarotene is approved for use for acne as well as plaque psoriasis.[2,3,4] Currently, retinoids are approved for a relatively limited number of conditions, but studies have been evaluating their use for other purposes for many years. Some of these conditions include management of scars/keloids or stretch marks, aging skin, hyperpigmentation, rosacea, alopecia, and oral lichen planus. In this blog post, we'll talk about information to support the use of various retinoids for off label indications and available information on comparative efficacy and tolerability.

Scars and Stretch Marks

Fibroblasts play an important role in wound healing, but scarring can develop as a result of fibroblast activation resulting in excessive extracellular matrix deposition.[5] Application of retinoids has been shown to decrease fibroblast proliferation and studies of topical tretinoin 0.05% have found that application results in marked scar size reduction and even a decrease in pruritis associated with scarring.[6] One study of both adapalene 0.3% and tazarotene 0.1% for management of acne found significant improvement in macular acne scars in the tazarotene group.[7,8] Another study on adapalene compared to placebo did note that adapalene 0.3% gel

improved the appearance of skin texture and atrophic scars by 50% and 80% respectively.[9] In addition to general scaring and acne scars, some studies have noted the benefit of retinoids for striae distensea (stretch marks) as well. One study of tretinoin 0.1% noted reduction of length and width of stretch marks over the 6-month study period.[10]

Photoaging

The proposed mechanism of action for retinoids in aging skin is multifaceted, but in summary it is thought that topical retinoids improve photoaging by increasing epidermal proliferation, compacting the stratum corneum, preventing collagen degradation, and by increasing synthesis of glycosaminoglycans by binding to certain areas of DNA known as retinoic acid response elements.[11] Tretinoin is commonly used in concentrations ranging from 0.05 to 0.1% for this condition. Placebo controlled trials lasting 3 to 12 months evaluating tretinoin 0.05% have demonstrated tretinoin to be superior to placebo. Another placebo-controlled, double-blind study of tretinoin 0.1% over a period of 16 weeks found significantly improved signs of photoaging in almost all patients treated.[12,13] Another randomized vehicle controlled parallel comparison trial of tazarotene cream at various strengths compared to tretinoin 0.05% cream and found tazarotene at higher concentrations (0.1%) was associated with improved mottled hyperpigmentation and fine wrinkles compared to the tretinoin 0.05% group.[14] Another double-blind randomized study comparing tazarotene 0.1% to tretinoin 0.05% over a 24 week period also found tazarotene to be more efficacious than tretinoin for fine and coarse wrinkling, overall photodamage, and mottled hyperpigmentation. The study did note increased irritation associated with tazarotene in the first week as compared to tretinoin, but this difference was not noted beyond the first week.[15]

Hyperpigmentation

Retinoids such as tretinoin suppress UVB induced pigmentation and promote increased epidermal turnover to limit contact time between keratinocytes and melanocytes. Tretinoin is also sometimes used in combination with hydroquinone to enhance penetration. Skin lightening benefits may take longer to become apparent as comparted with hydroquinone if used as a single agent.[6] Tretinoin used in combination with other agents, usually between 0.01-0.05%, or used as a single agent, up to 0.1%, has been shown in placebo-controlled studies to decrease pigmentation.[16,17] Adapalene 0.1% has also been studied for hyperpigmentation. One study of adapalene 0.1% gel in black patients found a significant reduction in acne-associated hyperpigmentation.[18] Another randomized double-blind placebo-controlled trial of tazarotene 0.1% for post inflammatory hyperpigmentation in patients with darker skin found significant improvement in area and intensity of hyperpigmentation over the course of the 18-week study.[19]

Alopecia

In addition to their many cosmetic indications, some retinoids have been studied for potential benefit for alopecia. Tretinoin is thought to enhance minoxidil response in patients with androgenetic alopecia. One study positing that tretinoin enhances percutaneous delivery of minoxidil, compared minoxidil 5% applied twice daily versus minoxidil 5% combined with 0.01% tretinoin applied once daily found that once daily combination therapy was as effective as twice daily application of minoxidil alone for patients with androgenetic alopecia.[20,21] Information on the use of other retinoids, including adapalene and tazarotene, for alopecia is limited. One study evaluating mometasone furoate 0.1% vs mometasone furoate 0.1% in conjunction with adapalene 0.1% for alopecia areata found statistically significant more hair growth with the combination product than with mometasone alone over the 12-week study.[22] At this time studies evaluating tazarotene for alopecia are not available.

Acne

Tretinoin, adapalene, and tazarotene are all FDA approved for acne. The mechanism of action of retinoids for acne involves their effect on reducing keratinocyte proliferation as well as their ability to block inflammatory pathways commonly associated with the development of acne. Though retinoids share a mechanism of action,

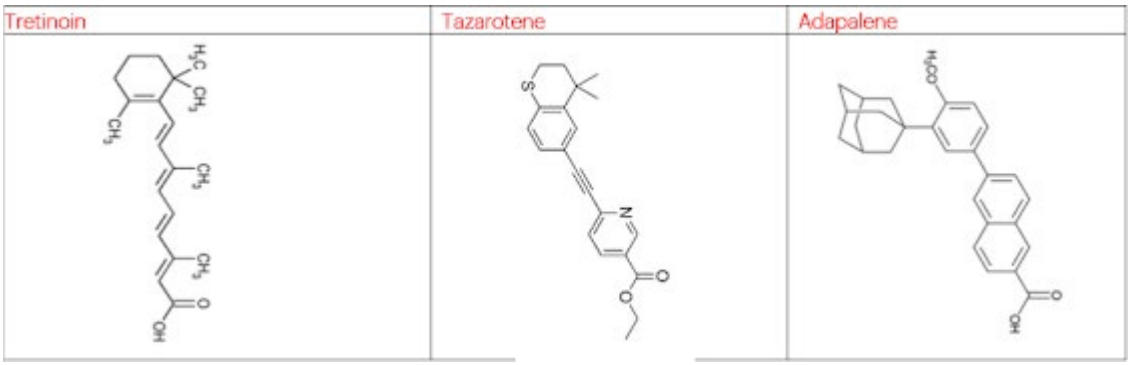
studies have compared and contrasted them for acne and found differences between them. Tazarotene 0.1% has been noted to be more effective than tretinoin 0.025% or 0.1%, whereas adapalene 0.1% has been found to be equally effective to tretinoin 0.025-0.1%, but significantly better tolerated than tazarotene 0.1% gel and tretinoin 0.025-0.1% topical preparations.[24] Another review of topical retinoids for acne found that patients on tretinoin 0.05% had a higher incidence of adverse effects than adapalene at 0.1 and 0.3% strengths.[25] Studies have also suggested adapalene to be better tolerated topically than tazarotene when both used at the same 0.1% strength.[26]

Psoriasis

Currently, between adapalene, tretinoin, and tazarotene, only tazarotene is FDA approved for psoriasis.[4] One study evaluating the safety and efficacy of tazarotene 0.1% compared to clobetasol propionate for palmoplantar psoriasis found a similar success rate with both treatments with onset of efficacy being faster for clobetasol up to 8 weeks, but at 12 weeks, both treatments were equally efficacious.[26] Other studies looking at combination therapy noted that combination tazarotene 0.1% and mometasone 0.1% cream was better tolerated and more efficacious than mometasone monotherapy for patients with moderate to severe plaque psoriasis. The study posited that there may be a benefit to the use of combination therapy to induce remission and then ongoing treatment with tazarotene alone.[27] Tazarotene has even been used at 0.05-0.1% topically to manage psoriasis of the nail.[28,29]

Stability

Tretinoin is known to be prone to oxidation. One study evaluating tretinoin compatibility with benzoyl peroxide noted significant degradation in just two hours when the combination was exposed to light, whereas when protected from light degradation didn't occur over a 7-hour test period.[30] Tretinoin alone, even without benzoyl peroxide, can degrade 60-80% when exposed to normal daylight over a period of 24 hours. Another study that looked at adapalene and tretinoin under similar conditions combined with 10% benzoyl peroxide found significant degradation of the tretinoin product, but noted good stability of adapalene with benzoyl peroxide even in the presence of light over the 72 hour exposure period.[31] This increased stability is in part attributable to structural changes in which the double bonds of the tretinoin molecule are replaced by a more robust naphthoic acid aromatic ring.[32] Though still prone to photodegradation, tazarotene has also been noted to have superior photostability to tretinoin with adapalene being considered the least prone to photodegradation of the three.[33,34] FDA approved topical tretinoin products tend to contain stabilizers and antioxidants such as butylated hydroxytoluene and/or butylated hydroxyanisole for stability as do tazarotene preparations, whereas aqueous adapalene products do not.



Sources:

1. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging. 2006;1(4):327-348. doi:10.2147/ciia.2006.1.4.327
2. Tretinoin [package insert]. Actavis Pharma Inc. Parsippany, NJ. 2019.
3. Adapaelene [package insert]. Perrigo New York Inc. Allegan, MI. 2017.
4. Tazorac (Tazarotene) [package insert]. Allergan Inc. Irvine, CA. 2018.
5. Viera MH, Amini S, Valins W, Berman B. Innovative therapies in the treatment of keloids and hypertrophic scars. J Clin Aesthet Dermatol. 2010;3(5):20-26.
6. Panabiere-Castaings MH. Retinoic acid in the treatment of keloids. J Dermatol Surg Oncol. 1988;14:1275–1276.
7. Bikash C, Sarkar R. Topical management of acne scars: The uncharted terrain. Journal of Cosmetic Dermatology. 2023: https://doi.org/10.1111/jocd.15584
8. Tanghetti E, Dhawan S, Green L, 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):549-558.
9. Loss MJ, Leung S, Chien A, Kerrouche N, Fischer AH, Kang S. Adapalene 0.3% Gel Shows Efficacy for the Treatment of Atrophic Acne Scars. Dermatol Ther (Heidelb). 2018;8(2):245-257. doi:10.1007/s13555-018-0231-8
10. Ud-Din S, McGeorge D, Bayat A. Topical management of striae distensae (stretch marks): prevention and therapy of striae rubrae and albae. J Eur Acad Dermatol Venereol. 2016;30(2):211-222. doi:10.1111/jdv.13223
11. Mukherjee S, Date A, Patravale V, Korting H, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging. 2006; 1(4): 327-348.
12. Klingman A, Grove G, Hirose R, Leyden J. Topical tretinoin for photoaged skin. J Am Acad Dermatol. 1986; 836-59.
13. Weiss JS, Ellis CN, Headington JT, et al. Topical tretinoin improves photoaged skin: a double-blind vehicle-controlled study. JAMA. 1988;259:527–32.
14. 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):1597–1604. doi:10.1001/archderm.137.12.1597
15. Nicholas J Lowe, Michael Gifford, Emil Tanghetti, Yves P Poulin, Mitchel Goldman, Yardy Tse, Paul Yamauchi, Helene Rosenzweig & Sewon Kang (2004) Tazarotene 0.1% cream versus tretinoin 0.05% emollient cream in the treatment of photodamaged facial skin: a multicenter, double-blind, randomized, parallel-group study, Journal of Cosmetic and Laser Therapy, 6:2, 79-85, DOI: 10.1080/14764170410032406
16. Bandyopadhyay D. Topical treatment of melasma. Indian J Dermatol. 2009; 54(4): 303-309.
17. Griffiths C, Finkel L, Ditre C, Hamilton T, Ellis C, Voorhees J. Topical tretinoin (retinoic acid)
18. Jacyk WK. Adapalene in the treatment of African patients. J Eur Acad Dermatol Venereol. 2001;15 Suppl 3:37-42. doi:10.1046/j.0926-9959.2001.00011.x
19. Grimes P, Callender V. Tazarotene cream for postinflammatory hyperpigmentation and acne vulgaris in darker skin: a double-blind randomized, vehicle-controlled study. Therapeutics for the Clinician. 2006: 77; 45-50.
20. Sharma A, Goren A, Dhurat R, et al. Tretinoin enhances minoxidil response in androgenetic alopecia patients by upregulating follicular sulfotransferase enzymes. Dermatol Ther. 2019;32(3):e12915. Doi:10.1111/dth.12915
21. Shin HS, Won CH, Lee SH, Kwon OS, Kim KH, Eun HC. Efficacy of 5% minoxidil versus combined 5% minoxidil and 0.01% tretinoin for male pattern hair loss: a randomized, double-blind, comparative clinical trial. Am J Clin Dermatol. 2007;8(5):285-290. doi:10.2165/00128071-200708050-00003

22. Unal M. Use of adapalene in alopecia areata: Efficacy and safety of mometasone furoate 0.1% cream versus combination of mometasone furoate 0.1% cream and adapalene 0.1% gel in alopecia areata. Dermatol Ther. 2018;31(1):10.1111/dth.12574. doi:10.1111/dth.12574
23. Leyden J, Stein-Gold L, Weiss J. Why Topical Retinoids Are Mainstay of Therapy for Acne. *Dermatol Ther (Heidelb)*. 2017;7(3):293-304. doi:10.1007/s13555-017-0185-2
24. Thielitz A, Abdel-Naser MB, Fluhr JW, Zouboulis CC, Gollnick H. Topical retinoids in acne--an evidence-based overview. *J Dtsch Dermatol Ges*. 2008;6(12):1023-1031. doi:10.1111/j.1610-0387.2008.06741.x
25. Kolli, S.S., Pecone, D., Pona, A. et al. Topical Retinoids in Acne Vulgaris: A Systematic Review. Am J Clin Dermatol 20, 345–365 (2019). https://doi.org/10.1007/s40257-019-00423-z
26. Mehta BH, Amladi ST. Evaluation of topical 0.1% tazarotene cream in the treatment of palmoplantar psoriasis: an observer-blinded randomized controlled study. Indian J Dermatol. 2011;56(1):40-43. doi:10.4103/0019-5154.77550
27. Lebwohl M. Strategies to optimize efficacy, duration of remission, and safety in the treatment of plaque psoriasis by using tazarotene in combination with a corticosteroid. J Am Acad Dermatol. 2000;43:S43–6.
28. Diluvio L, Campione E, Paternò EJ, Mordenti C, El Hachem M, Chimenti S. Childhood nail psoriasis: a useful treatment with tazarotene 0.05%. Pediatr Dermatol. 2007;24(3):332-333. doi:10.1111/j.1525-1470.2007.00421.x
29. Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: a double-blind study. Acta Derm Venereol. 2007;87(2):167-168. doi:10.2340/00015555-0195
30. Del Rosso JQ, Pillai R, Moore R. Absence of Degradation of Tretinoin When Benzoyl Peroxide is Combined with an Optimized Formulation of Tretinoin Gel (0.05%). J Clin Aesthet Dermatol. 2010;3(10):26-28.
31. Martin B, Meunier C, Montels D, Watts O. Chemical stability of adapalene and tretinoin when combined with benzoyl peroxide in presence and in absence of visible light and ultraviolet radiation. Br J Dermatol. 1998;139 Suppl 52:8-11. doi:10.1046/j.1365-2133.1998.1390s2008.x
32. Czernielewski J, Michel S, Bouclier M, Baker M, Hensby C. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. 2001: 15(s3): 5-12.
33. Kryczyk-Poprawa A, Zupkó I, Bérdi P, Żmudzki P, Popiół J, Muszyńska B, Opoka W. Photostability Testing of a Third-Generation Retinoid—Tazarotene in the Presence of UV Absorbers. Pharmaceutics. 2020; 12(9):899. https://doi.org/10.3390/pharmaceutics12090899
34. Motamedi M, Chehade A, Sanghera R, Grewal P. A Clinician's Guide to Topical Retinoids. Journal of Cutaneous Medicine and Surgery. 2022;26(1):71-78. doi:10.1177/12034754211035091

For further information or questions, please feel free to reach out to us by heading to www.fagronacademy.us!