

## B. TRETİNOİN

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### ÖZET

A vitamininin doğal metaboliti olan tretinoin, aynı zamanda sentezlenen ilk retinoiddir. Birinci jenerasyon sentetik non-aromatik retinoidler grubunda yer alır. Tretinoin topikal olarak çeşitli dermatolojik hastalıkların tedavisinde, sistemik olarak ise akut promiyelositik lösemi tedavisinde kullanılmaktadır. Topikal tretinoinin akne vulgaris ve fotoyaşlanmaya bağlı deri değişikliklerinin tedavisinde kullanımı onaylanmıştır. Bu iki endikasyon dışında topikal tretinoin pek çok dermatolojik hastalığın (melazma, aktinik keratoz, displastik nevus, stria, skar, alopesi, siğiller, keratozis pilaris, nevus komedonikus, perforan hastalıklar, porokeratoz, vb) tedavisinde kullanılmaktadır.

### Giriş

A vitamininin doğal metaboliti ve biyolojik aktif ligandı olan tretinoin, aynı zamanda sentezlenen ilk retinoid olup izotretinoin ve alitretinoin ile birlikte birinci jenerasyon sentetik non-aromatik retinoidler grubunda yer alırlar. (1-4)

Tretinoin (all-trans retinoik asit, ATRA), bir altıgen halka, bir yan zincir (hepsi trans konfigürasyonda olan 4 tane çift bağlı) ve bir karboksil uç içeren 20 karbonlu bir moleküldür (Şekil 6). 9-cis- retinoik asit (alitretinoin) ve 13-cis-retinoik asit (izotretinoin) tretinoinin stereo-izomerleridir. (1-3)

Tretinoin vücutta doğal olarak sentezlenir. A vitamini (retinol) önce reversibl olarak retinaldehide okside olur, daha sonra irreveribl olarak retinoik aside (tretinoin) dönüşür. Hüresel retinol bağlayıcı protein I (Cellular Retinol Binding Protein I, CRBP-I) bu enzimatik reaksiyonların gerçekleşmesine yardımcı olur. (1-4)

Topikal tretinoin 1960'ların başından itibaren kullanılmaktadır, Amerikan Gıda ve İlaç Dairesi (FDA) tarafından 1971 yılında akne vulgarisin, 1995 yılında fotoyaşlanmaya bağlı deri değişikliklerinin tedavisinde kullanımını onaylanmıştır. Bu iki endikasyon dışında topikal tretinoin pek çok dermatolojik hastalığın

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**Tablo 4: Topikal tretinoinin klinik özellikleri**

<b>Topikal Tretinoin</b>	
Sınıfı	Birinci jenerasyon sentetik non-aromatik retinoid
Etki Mekanizması	Hücre nükleusundaki retinoik asit reseptörlerine (RAR) bağlanarak etkisini gösterir. Retinoik asit-RAR kompleksleri DNA üzerindeki retinoik asit yanıt elemanlarına (RARE) bağlanarak gen transkripsiyonunu etkiler. Komedolitik etki gösterir, keratinositlerin proliferasyonunu ve farklılaşmasını düzenler, inflamasyonu azaltır, yeni kolajen yapımını uyarır, matris metalloproteinazları inhibe eder. Epidermal döngüyü hızlandırır, keratinositlere melanozom transferini önler.
Endikasyon	FDA onaylı Akne vulgaris, fotoyaşlanma <b>Diğerleri</b> Melazma, aktinik keratoz, displastik nevus, stria, skar, alopesi, siğiller, keratozis pilaris, nevus komedonikus, perforan hastalıklar, porokeratoz
Doz	%0.02 ile %0,1 arasında değişen konsantrasyonlarda, günde 1 defa, geceleri, az miktarda, ince bir tabaka şeklinde sürülmesi önerilir
Yan etki / Kontrendikasyon	Uygulama bölgesinde ortaya çıkan kuruluk, kaşıntı-yanma hissi, eritem ve deskuamasyon Gebelikte özellikle ilk trimesterde kullanılmamalıdır
Gebelik kategorisi	C
Laktasyon	Anne sütüne geçip geçmediği bilinmemektedir; bu nedenle emziren annelerde kullanılmamalıdır
Çocuklarda kullanım	12 yaş altında etkinlik ve güvenlik verileri bilinmemektedir

## Kaynaklar

1. Saurat JL, and Sorg O. Retinoids. In: Bologna JL, Schaffer JV, Cerroni L, editors. Dermatology. 4<sup>th</sup> ed. China: Elsevier; Chapter 126. Available from: <https://www.elsevier.com/books/dermatology-2-volume-set/bologna/978-0-7020-6275-9>.
2. Orfanos CE, Zouboulis CC, Almond-Roesler B, Geilen CC. Current use and future potential role of retinoids in dermatology. Drugs. 1997;53(3):358-88.
3. Baldwin HE, Nighland M, Kendall C, Mays DA, Grossman R, Newburger J. 40 years of topical tretinoin use in review. J Drugs Dermatol. 2013;12(6):638-42.

4. Beckenbach L, Baron JM, Merk HF, Löffler H, Amann PM. Retinoid treatment of skin diseases. *Eur J Dermatol*. 2015;25(5):384-91.
5. Hubbard BA, Unger JG, Rohrich RJ. Reversal of skin aging with topical retinoids. *Plast Reconstr Surg*. 2014;133(4):481e-90e.
6. Buchanan PJ, Gilman RH. Retinoids: Literature Review and Suggested Algorithm for Use Prior to Facial Resurfacing Procedures. *J Cutan Aesthet Surg*. 2016;9(3):139-44.
7. di Masi A, Leboffe L, De Marinis E, Pagano F, Cicconi L, Rochette-Egly C, et al. Retinoic acid receptors: from molecular mechanisms to cancer therapy. *Mol Aspects Med*. 2015; 41:1-115.
8. Noble S, Wagstaff AJ. Tretinoin. A review of its pharmacological properties and clinical efficacy in the topical treatment of photodamaged skin. *Drugs Aging*. 1995; 6(6):479-96.
9. See JA, Goh CL, Hayashi N, Suh DH, Casintahan FA. Optimizing the use of topical retinoids in Asian acne patients. *J Dermatol*. 2018; 45(5):522-8.
10. Veraldi S, Barbareschi M, Benardon S, Schianchi R. Short contact therapy of acne with tretinoin. *J Dermatolog Treat*. 2013; 24(5):374-6.
11. Kligman DE. Regarding tretinoin peeling. *Dermatol Surg*. 2001; 27(6):608.
12. Cucé LC, Bertino MC, Scattone L, Birkenhauer MC. Tretinoin peeling. *Dermatol Surg*. 2001; 27(1):12-4.
13. Kligman DE, Draeol ZD. High- strength tretinoin for rapid retinization of photoaged facial skin. *Dermatol Surg*. 2004;30(6):864-6.
14. Ghersetich I, Troiano M, Brazzini B, Arunachalam M, Lotti T. Melasma: Treatment with 10% tretinoin peeling mask. *J Cosmet Dermatol*. 2010; 9:117-21.
15. Sumita JM, Leonardi GR, Bagatin E. Tretinoin peel: a critical view. *Ann Bras Dermatol*. 2017; 92(3):363-366.
16. Thiboutot DM, Dréno B, Abanmi A, Alexis AF, Araviiskaia E, Barona Cabal MI, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2018;78(2 Suppl 1): S1-S23.e1.
17. Conforti C, Chello C, Giuffrida R, di Meo N, Zalaudek I, Dianzani C. An overview of treatment options for mild-to-moderate acne based on American Academy of Dermatology, European Academy of Dermatology and Venereology, and Italian Society of Dermatology and Venereology guidelines. *Dermatol Ther*. 2020; 33(4): e13548.
18. Kang HY, Valerio L, Bahadoran P, Ortonne JP. The role of topical retinoids in the treatment of pigmentary disorders: an evidence-based review. *Am J Clin Dermatol*. 2009;10(4):251-60.
19. Akhavan A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. *Am J Clin Dermatol*. 2003;4(7):473-92.
20. McKesey J, Tovar-Garza A, Pandya AG. Melasma Treatment: An Evidence-Based Review. *Am J Clin Dermatol*. 2020;21(2):173-225.
21. Adigun CG, Pandya AG. Improvement of idiopathic acanthosis nigricans with a triple combination depigmenting cream. *J Eur Acad Dermatol Venereol*. 2009;23(4):486-7.
22. Treeririchod A, Chaithirayanon S, Wongjitrat N. Comparison of the efficacy and safety of 0.1% adapalene gel and 0.025% tretinoin cream in the treatment of childhood acanthosis nigricans. *Pediatr Dermatol*. 2019;36(3):330-4.
23. Freeman SA, Moon SD, Spencer JM. Clindamycin phosphate 1.2% and tretinoin

- 0.025% gel for rosacea: summary of a placebo-controlled, double-blind trial. *J Drugs Dermatol*. 2012;11(12):1410-4.
25. Patterson JW, Graff GE, Eubanks SW. Perforating folliculitis and psoriasis. *J Am Acad Dermatol*. 1982;7(3):369-76.
  26. Kovich O. Acquired perforating disorder. *Dermatol Online J*. 2004;10(3):16.
  27. Virgili A, Corazza M, Bianchi A, Mollica G, Califano A. Open study of topical 0.025% tretinoin in the treatment of vulvar lichen sclerosus. One year of therapy. *J Reprod Med*. 1995;40(9):614-8.
  28. Borghi A, Corazza M, Minghetti S, Virgili A. Topical tretinoin in the treatment of vulvar lichen sclerosus: an advisable option? *Eur J Dermatol*. 2015;25(5):404-9.
  29. Sloberg K, Hersle K, Mobacken H, Thilander H. Topical tretinoin therapy and oral lichen planus. *Arch Dermatol*. 1979;115(6):716-8.
  30. Kar HK, Parsad D, Gautam RK, Jain RK, Sharma PK. Comparison of topical tretinoin and betamethasone in oral lichen planus. *Indian J Dermatol Venereol Leprol*. 1996;62(5):304-5.
  31. Alpsoy E, Yilmaz E, Aykol A. Hyperkeratosis of the nipple: report of two cases. *J Dermatol*. 1997;24(1):43-5.
  32. Okan G, Baykal C. Nevroid hyperkeratosis of the nipple and areola: treatment with topical retinoic acid. *J Eur Acad Dermatol Venereol*. 1999;13(3):218-20.
  33. Handley J, Dinsmore W. Topical tretinoin in the treatment of anogenital warts. *Sex Transm Dis*. 1992;19(3):181.
  34. al Aboosi M. Treatment of plane warts by tretinoin-induced irritant reaction. *Int J Dermatol*. 1994;33(11):826-7.
  35. Polat M, Altunay Tuman B, Sahin A, Dogan U, Boran C. Bilateral nevus comedonicus of the eyelids associated with bladder cancer and successful treatment with topical tretinoin. *Dermatol Ther*. 2016;29(6):479-481.
  36. Capusan TM, Chicharro P, Rodriguez-Jimenez P, Martinez-Mera C, Urquía A, Aragués M, et al. Successful treatment to a tretinoin/clindamycin gel in a late onset of nevus comedonicus. *Dermatol Ther*. 2017;30(4).
  37. Rangel O, Arias I, García E, Lopez-Padilla S. Topical tretinoin 0.1% for pregnancy-related abdominal striae: an open-label, multicenter, prospective study. *Adv Ther*. 2001;18(4):181-6.
  38. Gamil HD, Ibrahim SA, Ebrahim HM, Albalat W. Platelet-Rich Plasma Versus Tretinoin in Treatment of Striae Distensae: A Comparative Study. *Dermatol Surg*. 2018;44(5):697-704.
  39. Dematte MF, Gemperli R, Salles AG, Dolhnikoff M, Lanças T, Saldiva PH, et al. Mechanical evaluation of the resistance and elastance of post-burn scars after topical treatment with tretinoin. *Clinics (Sao Paulo)*. 2011;66(11):1949-54.
  40. Kwon SY, Park SD, Park K. Comparative effect of topical silicone gel and topical tretinoin cream for the prevention of hypertrophic scar and keloid formation and the improvement of scars. *J Eur Acad Dermatol Venereol*. 2014;28(8):1025-33.
  41. Rados J, Marinović Kulisić S, Lipozencić J, Budimčić D, Lončarić D. Macular amyloidosis: a case report. *Acta Dermatovenerol Croat*. 2008;16(3):138-41.
  42. Saki N, Ahramiyangpour N, Heiran A, Alipour S, Parvizi MM. Efficacy of topical dimethyl sulfoxide (DMSO) 50% solution vs tretinoin 0.5% cream in treatment of patients with primary macular amyloidosis: A split-side single-blinded randomized

- clinical trial. *Dermatol Ther.* 2020;33(3): e13305.
43. Femiano F, Gombos F, Scully C, Battista C, Belnome G, Esposito V. Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg.* 2001;30(5):402-6.
  44. Starzyńska A, Pawłowska A, Renkielska D, Michajłowski I, Sobjanek M, Błażewicz I, et al. Estimation of oral leukoplakia treatment records in the research of the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk. *Postepy Dermatol Alergol.* 2015;32(2):114-22.
  45. Sumita JM, Miot HA, Soares JLM, Raminelli ACP, Pereira SM, Ogawa MM, et al. Tretinoin (0.05% cream vs. 5% peel) for photoaging and field cancerization of the forearms: randomized, evaluator-blinded, clinical trial. *J Eur Acad Dermatol Venereol.* 2018;32(10):1819-26.
  46. Ianhez M, Pinto SA, Miot HA, Bagatin E. A randomized, open, controlled trial of tretinoin 0.05% cream vs. low-dose oral Ízotretinoin for the treatment of field cancerization. *Int J Dermatol.* 2019;58(3):365-73.
  47. Meyskens FL Jr, Edwards L, Levine NS. Role of topical tretinoin in melanoma and dysplastic nevi. *J Am Acad Dermatol.* 1986;15(4 Pt 2):822-5.
  48. Halpern AC, Schuchter LM, Elder DE, Guerry D 4th, Elenitsas R, Trock B, et al. Effects of topical tretinoin on dysplastic nevi. *J Clin Oncol.* 1994;12(5):1028-35.
  49. O'Hern K, Chambers M, Ryan C, Chapman MS. In lieu of penectomy: complete resolution of penile melanoma in situ with topical imiquimod and tretinoin. *Int J Dermatol.* 2020 Dec 5:1-2
  50. Wang EA, Kao J, Ma C, Cheng MY, Barton VR, Petukhova TA, et al. Non-surgical management of primary invasive melanoma. *J Dermatolog Treat.* 2019; 20:1-4.
  51. Leventhal JS, Odell ID, Imaeda S, Maverakis E, King BA. Treatment of melanoma in-transit metastases with combination intralesional interleukin-2, topical imiquimod, and tretinoin 0.1% cream. *JAAD Case Rep.* 2016;2(2):114-6.
  52. Strange PR, Lang PG Jr. Long-term management of basal cell nevus syndrome with topical tretinoin and 5-fluorouracil. *J Am Acad Dermatol.* 1992;27(5 Pt 2):842-5.
  53. Brenner S, Wolf R, Dascalu DI. Topical tretinoin treatment in basal cell carcinoma. *J Dermatol Surg Oncol.* 1993;19(3):264-6.
  54. Fayne R, Nanda S, Nichols A, Shen J. Combination Topical Chemotherapy for the Treatment of an Invasive Cutaneous Squamous Cell Carcinoma. *J Drugs Dermatol.* 2020;19(2):202-4.
  55. Ferry JJ, Forbes KK, VanderLugt JT, Szpunar GJ. Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. *Clin Pharmacol Ther.* 1990;47(4):439-46.
  56. 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):285-90.
  57. Arantes VT, Faraco AAG, Ferreira FB, Oliveira CA, Martins-Santos E, Cassini-Vieira P, et al. Retinoic acid-loaded solid lipid nanoparticles surrounded by chitosan film support diabetic wound healing in in vivo study. *Colloids Surf B Biointerfaces.* 2020; 188:110749.
  58. Griffiths CE, Finkel LJ, Tranfaglia MG, Hamilton TA, Voorhees JJ. An in vivo ex-

- perimental model for effects of topical retinoic acid in human skin. *Br J Dermatol.* 1993;129(4):389-94.
59. Lavker RM, Leyden JJ, Thorne EG. An ultrastructural study of the effects of topical tretinoin on microcomedones. *Clin Ther.* 1992;14(6):773-80.
  60. Berger R, Rizer R, Barba A, Wilson D, Stewart D, Grossman R, et al. Tretinoin gel microspheres 0.04% versus 0.1% in adolescents and adults with mild to moderate acne vulgaris: a 12-week, multicenter, randomized, double-blind, parallel-group, phase IV trial. *Clin Ther.* 2007;29(6):1086-97.
  61. Harper JC, Baldwin H, Stein Gold L, Guenin E. Efficacy and Tolerability of a Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate or Severe Acne Vulgaris in Adult Females. *J Drugs Dermatol.* 2019;18(11):1147-54.
  62. Dogra S, Sumathy TK, Nayak C, Ravichandran G, Vaidya PP, Mehta S, et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *J Dermatolog Treat.* 2020 Feb 5:1-9.
  63. Kligman AM, Grove GL, Hirose R, Leyden JJ. Topical tretinoin for photoaged skin. *J Am Acad Dermatol.* 1986;15(4 Pt 2):836-59.
  64. Lowe PM, Woods J, Lewis A, Davies A, Cooper AJ. Topical tretinoin improves the appearance of photo damaged skin. *Australas J Dermatol.* 1994;35(1):1-9.
  65. Griffiths CE, Kang S, Ellis CN, Kim KJ, Finkel LJ, Ortiz-Ferrer LC, et al. Two concentrations of topical tretinoin (retinoic acid) cause similar improvement of photoaging but different degrees of irritation. A double-blind, vehicle-controlled comparison of 0.1% and 0.025% tretinoin creams. *Arch Dermatol.* 1995;131(9):1037-44.
  66. Bercovitch L. Topical chemotherapy of actinic keratoses of the upper extremity with tretinoin and 5-fluorouracil: a double-blind controlled study. *Br J Dermatol.* 1987;116(4):549-52.
  67. Taylor SC, Torok H, Jones T, Lowe N, Rich P, Tschen E, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis.* 2003;72(1):67-72.
  68. Schäfer-Korting M, Korting HC, Ponce-Pöschl E. Liposomal tretinoin for uncomplicated acne vulgaris. *Clin Investig.* 1994;72(12):1086-91.
  69. Embil K, Nacht S. The Microsponge Delivery System (MDS): a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *J Microencapsul.* 1996;13(5):575-88.
  70. Teknetzis A, Ioannides D, Vakali G, Lefaki I, Minas A. Pyogenic granulomas following topical application of tretinoin. *J Eur Acad Dermatol Venereol.* 2004;18(3):337-9.
  71. Hogan DJ. Scarring following inappropriate use of 0.05% tretinoin gel. *J Am Acad Dermatol.* 1987;17(6):1056-7.
  72. Tosti A, Guerra L, Morelli R, Piraccini BM. Contact dermatitis due to topical retinoic acid. *Contact Dermatitis.* 1992;26(4):276-7.
  73. Vestita M, Giudice G, Bonamonte D, Apruzzi D, Filoni A. Beard hair density increase. A possible role of topical tretinoin application? *Dermatol Ther.* 2017;30(3): e12450