

40 Years of Topical Tretinoin Use in Review

Hilary E. Baldwin MD,[a] Marge Nighland BS,[b] Clare Kendall MA,[c] David A. Mays PharmD MBA,[c] Rachel Grossman MD,[b,c] and Joan Newburger PhD[c]

[a]SUNY Downstate Medical Center, Brooklyn, NY
[b]Valeant Dermatology, a subsidiary of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ
[c]Johnson & Johnson Consumer & Personal Products Worldwide, Skillman, NJ

ABSTRACT

Topical tretinoin has been approved for use in dermatology for 40 years and is currently approved for the treatment of acne vulgaris and photodamage. During this time, topical tretinoin has accumulated significant efficacy and safety data in the treatment of acne and photodamaged skin and demonstrated clinical potential for treating a range of other dermatologic conditions. The diverse effects may be due to complex underlying mechanisms of action associated with tretinoin, including keratolytic activity, collagenesis, and other mechanisms associated with the activation of nuclear retinoic acid receptors (RARα, RARβ, and RARγ). In this article, we review the history of topical tretinoin use to date and outline emerging research suggesting that topical tretinoin may have potential clinical use for treating a multitude of other dermatological conditions when used either as monotherapy or in combination with other agents. We also describe newer formulations of topical tretinoin that have been designed to reduce irritation potential. In light of the substantial history of safety and efficacy of topical tretinoin in acne and photodamage, we speculate that it holds promise in treating many additional dermatological conditions, which may be explored in future research.

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INTRODUCTION

As early as the 1960s, topical tretinoin demonstrated clinical potential in a variety of skin disorders, including acne, actinic keratoses, other hyperkeratotic conditions, and antitumor effects in a number of basal cell cancers. Since then, other uses have been described, including the treatment of lesions of the oral mucosa and the ocular surface epithelia, hypertrophic scarring, various infections, and pigmentation disorders.[1,2]

Kligman and colleagues[3] at the University of Pennsylvania reported on the effectiveness of topical tretinoin in treating acne in 1969. In 1971, tretinoin became the first retinoid to be approved by the US Food and Drug Administration (FDA) as a topical treatment for acne vulgaris (AV).[4,5]

Soon after topical tretinoin became available to the public, elderly patients using it to treat acne reported noticing a general improvement in the condition of their skin.[6] Considering this, Kligman and colleagues began trials to study the use of topical tretinoin in treating photodamaged skin. Beneficial results were subsequently verified by large multicenter trials and clinical experience supporting the efficacy and safety of topical tretinoin to treat photodamaged skin.[6] In 1995, topical tretinoin was approved by the FDA for the palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial photodamage.[7]

The aim of this review is to provide an overview of the history and current uses of topical tretinoin, including likely mechanisms of action, approved indications and dosing, and associated safety and tolerability issues, as well as to speculate on potential therapeutic areas that may be targets for further research and future clinical applications.

Clinical Chemistry, Pharmacology, and Mechanisms of Action

Tretinoin (all-*trans* retinoic acid) is a retinoid metabolite of naturally occurring vitamin A that activates 3 nuclear retinoic acid receptors (RARα, RARβ, and RARγ). These receptors can act to modify gene expression, protein synthesis, and epithelial cell growth and differentiation.[8,9] Tretinoin may exert its clinical effects, at least in part, through activation of retinoid receptors; however, its exact mechanisms of action are unknown.[8,10] The binding profile of tretinoin differs from that of synthetic retinoids, such as adapalene, which binds preferentially to RARβ and RARγ, and tazarotene, which binds to all 3 RARs but appears to lead to an effective gene expression only via RARβ and RARγ.[11]

Topical tretinoin has the ability to modify abnormal follicular keratinization and promote comedolysis, modulate the proliferation and differentiation of epidermal cells, stimulate the formation of new collagen, reduce inflammation, stimulate fibroblasts, prevent collagen loss, and inhibit the induction of skin metalloproteinases (ie, collagenase, 92-kd gelatinase, and stromelysin, which are induced by ultraviolet [UV] irradiation and may degrade skin collagen).[8,10,12-15] In addition, tretinoin decreases epidermal melanin, as measured by Fontana Masson staining,[15,16] and may

reduce pigmentation through increasing keratinocyte turnover and diminishing tyrosinase activity.[17] Tretinoin reverses thickening of stratum corneum and abnormal desquamation of keratinocytes.[18,19] Induction of RARβ expression has also been shown to suppress carcinogenesis in a number of squamous cell tumors, including cancers of the lung, esophagus, and breast.[20-25]

The Treatment of Acne Vulgaris

Decades of research have established topical tretinoin as a first-line treatment for AV.[26] Its mechanisms of action for the treatment of acne may be mediated by its effects on reducing horny-cell adhesion, increasing epidermal-cell turnover, and increasing mitotic activity, thereby reducing comedone formation.[14,27-29] The use of topical tretinoin has been shown to reduce total acne lesion counts[26,30] and may also reduce acne-related inflammation.[10,31,32] In addition, topical tretinoin is recommended as maintenance therapy for acne, particularly because it reduces comedone formation without inducing bacterial resistance.[29,33,34]

Acne Vulgaris Clinical Studies

The following is a brief summary of key representative trials of tretinoin formulations in patients with AV.

The efficacy and safety of tretinoin gel 0.05% for adults with mild to moderate acne was studied in 2 12-week, prospective, multicenter, randomized, vehicle-controlled studies of patients aged 10 years or older with mild to moderate acne; those who applied topical tretinoin once daily showed significant improvement by week 12 in global acne severity and mean percent reductions in total lesions compared with those using vehicle (43% vs 22% and 35% vs 19%, respectively).[35,36] The most common adverse events ([AEs]; incidence ≥5%) observed were dry skin, peeling/scaling/flaking skin, burning sensation in the skin, and erythema.[35,36] A tretinoin microsphere gel (TMG) 0.04% and 0.1% formulation, developed to reduce the irritation potential associated with the use of topical tretinoin, was effective at reducing acne lesions over 12 weeks (some added benefit for tretinoin 0.1% vs 0.04% was observed at week 2) and was associated with only mild cutaneous irritation in most patients.[37] Tretinoin microsphere gel 0.04% applied nightly was also shown in 3 randomized, double-blind, vehicle-controlled studies to be well tolerated and more effective than vehicle over 12 weeks in treating adolescents and adults (aged 11-49 years) with mild to moderate facial acne.[38]

Currently, topical tretinoin is often used in combination with other therapies for acne management, in particular with clindamycin and benzoyl peroxide (BP).[32,39,40] Numerous studies of tretinoin in combination with clindamycin have been conducted. For example, in one 12-week, multicenter, randomized, blinded study of 1,649 subjects aged 12 years or older, the combination of clindamycin phosphate 1.2% and tretinoin gel 0.025% was compared with each component separately, as well as with vehicle alone. Mean total lesion-count reduction for the combination treatment, clindamycin alone, tretinoin alone, and vehicle was 55%, 49%, 51%, and 39%, respectively.[41] Combined, local AEs for subjects receiving tretinoin/clindamycin gel in this and 2 other studies of the same formulation included dryness, irritation, exfoliation, erythema, pruritus, dermatitis, and sunburn.[28,41,42]

Other research has shown that combination regimens of a TMG pump (0.04%) and BP (5% wash)[43] or fixed combinations of tretinoin gel (0.025% to 0.04%), clindamycin (1% to 1.2%), and BP (5% wash) are efficacious and tolerable for treating moderate to severe AV.[39] New regimens and formulations of topical tretinoin have been developed because it was found that BP has the potential to degrade tretinoin and that tretinoin is unstable in visible and UV light.[43] The TMG formulation has been shown to be significantly more photostable, both alone and in combination with BP and erythromycin, compared with a nonmicrosphere formulation.[44-46]

The Treatment of Photodamage and Melasma

As noted above, Kligman and colleagues[47] studied topical tretinoin for the treatment of photodamage. In this study, topical tretinoin 0.05% treatment for 3 to 12 months was shown to partially reverse both clinical and histological signs of photodamage. Among patients treated with tretinoin, histology demonstrated replacement of atrophic epidermis via hyperplasia; elimination of dysplasia, atypia, and actinic keratoses; dispersion of melanin granules; collagen formation; angiogenesis; and exfoliation of retained horn in the follicles.[47]

Other double-blind, controlled, and open-label studies in the United States and Europe have confirmed these findings in photodamaged skin. Both shorter-term (1-4 months) and longer-term (6-54 months) trials showed improvement in clinical signs of photodamage with topical tretinoin, including fine and coarse wrinkling, hyperpigmentation, roughness, and overall severity of photodamage.[48-50] Application with tretinoin prior to UVB irradiation inhibited the induction of skin metalloproteinases (including collagenase, 92-kd gelatinase, and stromelysin-1), which are induced by UV radiation and degrade skin collagen, thereby contributing to photodamage.[12]

Topical tretinoin (0.05% to 0.1%) has been shown to reduce hyperpigmentation associated with UV exposure, both alone and in combination with hydroquinone, intense pulsed light, or glycolic peels, as well as in triple-therapeutic combinations (tretinoin plus hydroquinone and triamcinolone acetonide) for hyperpigmentation conditions such as melasma.[14,51,52] Topical tretinoin is currently indicated as a part of combination therapy (with fluocinolone acetonide and hydroquinone) for treatment of melasma.[14,52,53] The mechanism of action for clinical improvement in melasma has been suggested to be inhibition of tyrosinase, and it also has been shown, when used in combination, to facilitate epidermal penetration of hydroquinone.[14,17,51,53]

Recently, findings have provided further evidence that topical tretinoin may both reverse photodamage and play a role in chemoprevention: 2 case reports using low-concentration tretinoin gel (0.05%) over 4 weeks showed both a reversal of photodamage and chemopreventive benefits.[54]

Safety and Tolerability

Historically, use of topical tretinoin has been limited in some patients due to associated AEs, including skin-irritation (dryness, tightness, and erythema) and possible heightened sunburn potential; however, the variations seen in these AEs may be based on formulation, as well as frequency and mode of application.[29,55,56] Cutaneous irritation can be mitigated by inhibiting retinoid penetration into the deep epidermis and dermis, as with slow-release tretinoin formulations (ie, TMG).[44]

One study showed an increased risk for lung cancer associated with topical tretinoin use.[57] In the Veteran's Affairs Topical Tretinoin Chemoprevention Trial, topical tretinoin was associated with an increased risk of all-cause mortality. However, post hoc analyses showed that there were other important predictors of death, including smoking, age, and comorbidities,[58] and a recent review found no other evidence of noncutaneous AEs associated with topical tretinoin.[59]

Due to the similarity of tretinoin to isotretinoin, a known human teratogen, there has been concern that the use of topical tretinoin during pregnancy may cause developmental malformations in the fetus. At least 4 case reports have been published linking congenital abnormalities with maternal use of topical tretinoin.[60-64] However, a retrospective study of 215 pregnant women exposed to topical tretinoin showed no increased incidence of retinoid embryopathy compared with 430 age-matched controls.[65] Furthermore, 2 prospective studies in 200 women who reported exposure to topical tretinoin during the first trimester of their pregnancies found that this exposure was not associated with increased risk for congenital malformations or retinoid embryopathy.[66,67] Despite the fact that the evidence is inconclusive, women are generally advised to avoid exposure to topical tretinoin during pregnancy.[66,67] Additionally, there is remarkably little percutaneous absorption of topical tretinoin (<2%) after single and repeated application (28 days and >1 year) of topical tretinoin (0.05% tretinoin emollient cream and 0.1% tretinoin gel) and its metabolites (13-*cis*-retinoic acid, all-*trans*-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid).[68,69]

Additional Uses

As noted, topical tretinoin has been studied in many other conditions outside of its approved use in acne and photodamaged skin.

To identify reports of tretinoin use outside of acne and photodamage, an electronic search was conducted in MEDLINE (via PubMed) for all studies, including case reports. Search criteria were: 1. "Tretinoin" [MeSH] AND "Administration, Topical" [MeSH] and NOT "Acne" and NOT "Photodamage"; 2. "All-trans retinoic acid" and "Administration, Topical" [MeSH] and NOT "Acne" and NOT "Photodamage." References and review articles were reviewed manually to identify other relevant studies. Following are highlights of the search results. Results are included below and in the Table.

Actinic Keratosis and Keratinocyte Carcinoma

Topical tretinoin cream may be effective in reducing actinic keratosis (compared with baseline), both alone and as an adjunct to 5-fluorouracil, possibly due to its ability to suppress epidermal proliferation and normalize differentiation (although data are based on a limited number of patients).[70-78] Topical tretinoin may also have a chemopreventive role in patients at high risk of developing keratinocyte carcinomas.[78]

Melanoma/Dysplastic Nevi

Research outcomes demonstrate the potential for topical tretinoin to be used to reverse and reduce dysplastic nevi.[79-84] Topical tretinoin has been shown to eliminate dysplastic nevi or revert them to a benign state.[81-83] Tretinoin may induce apoptosis in melanoma cells by targeting mitochondrial dysfunction.[85]

Striae/Stretch Marks/Scarring

Blinded, placebo-controlled, open-label prospective studies and case studies have demonstrated histological and clinical improvements in striae distensae with topical tretinoin, although findings are equivocal.[86-91] Collagenesis and increased epidermal proliferation induced by tretinoin may be associated with improvements in scarring and keloids.[19,86,89]

Cervical Dysplasia

Prospective observational findings indicate that tretinoin delivered via collagen sponge and cervical cap may have the potential to treat moderate to severe cervical dysplasia (CIN II/III).[92-97] However, one 12-week, placebo-controlled clinical trial failed to show a difference between patients with cervical dysplasia treated with topical tretinoin and those treated with placebo.[92] Chemopreventive effects of tretinoin might be attributed to the effect of tretinoin on cell proliferation, differentiation, and cell death.[92]

Ulcers/Wound Healing

A randomized study suggested potential for tretinoin therapy to improve foot ulcers in patients with diabetes.[98] Pretreatment with tretinoin cream was shown to reduce healing time in 2 studies (ie, healing following electroepilation and after a chemical peel).[99,100] Histological analyses also demonstrated significant healing of wounded skin with topical tretinoin treatment.[101,102] The beneficial effect in wound healing may be associated with the ability of topical tretinoin to enhance collagen production, stimulate fibroblasts, and increase angiogenesis.[99,103]

Alopecia

Results from a limited number of studies suggest that tretinoin may be used alone or in combination with minoxidil for treating alopecia.[104-107] Topical tretinoin may help promote hair growth through effects on epithelial cell proliferation and differentiation, as well as vascular proliferation.[108] In addition, topical tretinoin may enhance the absorption of minoxidil, which is known to stimulate hair regrowth.[106,107]

Warts/Nevoid Hyperkeratosis

Case studies have evaluated topical tretinoin for warts or nevoid hyperkeratosis, with equivocal findings.[109-112] Topical tretinoin may be effective in the treatment of nevoid hyperkeratosis due to its ability to modulate abnormal follicular keratinization.[10]

Hyperkeratosis Follicularis et Parafollicularis (Kyrle's Disease)/ Keratosis Follicularis (Darier's Disease)

Whereas results of a case study suggest that topical tretinoin use to treat hyperkeratosis follicularis was limited due to AEs, other studies suggest that topical tretinoin may be useful for treating Darier's disease.[113-116] The effectiveness of topical tretinoin in Kyrle's disease may be due to its effect on epidermal proliferation and keratinization.[116]

Porokeratosis

Three case studies suggest that topical tretinoin may benefit patients with porokeratosis.[117-119] The effectiveness of topical tretinoin in treating porokeratosis may be due to its ability to modulate abnormal follicular keratinization.[118]

Psoriasis

One case study showed the effectiveness of sequential application of topical tretinoin (0.3%) and a corticosteroid for treating corticosteroid-resistant plaque-type psoriasis.[120] Another study showed that adding topical tretinoin to a topical corticosteroid for treating psoriasis partially ameliorates corticosteroid-induced epidermal atrophy.[121] Effectiveness in psoriasis may be attributed to the ability of topical tretinoin to modulate many of the pathogenic factors thought to be responsible for psoriasis; tretinoin is antiproliferative, normalizes abnormal keratinocyte differentiation, and is antiinflammatory.

Acanthosis Nigricans

One report showed that a combination of 12% ammonium lactate cream and 0.05% tretinoin cream improved acanthosis nigricans associated with obesity. Case studies showed that daily topical tretinoin was effective in improving both clinical and histological measures of acanthosis nigricans.[122,123] The action of topical tretinoin in acanthosis nigricans may be attributed to its keratolytic effects.[123]

Rosacea

Randomized, double-blind data suggest that low-dose topical tretinon may be useful for treating rosacea.[124] The effects of topical tretinoin in rosacea may be due to its inhibition of skin metalloproteinases and its down-regulation of toll-like receptor 2, which is reported to be overexpressed on the epidermis of patients with rosacea.[124-126]

Nevus Comedonicus

Case studies of nevus comedonicus on the face, chest, and neck have demonstrated an extrusion of comedones and a reduction in lesion size in response to treatment with retinoic acid alone or topical tretinoin in combination with a 1450-nm diode laser.[127,128]

Keratosis Pilaris

A case report of a woman with keratosis pilaris atrophicans faciei showed that 1 month of topical tretinoin treatment was effective in decreasing erythema and follicular hyperkeratosis.[129] Effectiveness for this condition may be expected given the keratolytic effects of tretinoin.

Antilice Agent

Due to its inhibitory effects on glutathione-S-transferase, topical tretinoin has been recommended as an antilice agent to augment the effects of topical antilice agents including permethrin, pyrethrins, and dichlorodiphenyltrichloroethane (DDT).[130]

Trichoepitheliomas

Combination imiquimod and topical tretinoin may be effective as a nonscarring treatment for trichoepitheliomas.[131]

Eruptive Milia

A case study demonstrated rapid improvement of eruptive milia with topical tretinoin treatment.[132]

Lichen Planus

A case study showed that application of a tretinoin and triamcinolone combination was a successful treatment for lichen planus.[133] The effects of topical tretinoin on lichen planus may be due to increased epidermal proliferation and collagenesis.[134]

Reactive Perforating Collagenosis

One case study demonstrated the effectiveness of tretinoin cream (0.1%) for reducing the total number of reactive perforating collagenosis lesions.[135]

Keratinizing Dermatoses

Multicenter trial data showed that topical tretinoin (0.1%) was effective in treating keratinizing dermatoses, including lamellar ichthyosis and ichthyosis vulgaris.[136] It is unclear whether the keratolytic properties of tretinoin or its ability to normalize keratinocyte differentiation was responsible for the noted improvement.

Intrinsic/Chronological Aging

One clinical trial found that tretinoin cream applied once daily for 9 months in older women (aged 68-79 years) showed marked

histological improvement compared with vehicle.[137] Topical tretinoin has been shown to increase viable epidermal thickness and create a more undulating dermoepidermal junction with prominent rete ridges, as well as effecting other dermal changes such as increased glycosaminoglycan deposition and elastic fibers and the formation of new blood vessels.[137]

Multiple Miliary Osteoma Cutis

A case study suggests that topical tretinoin 0.05% may decrease the number and size of papules after 3 months of treatment.[138]

CONCLUSION

Currently, tretinoin is approved by FDA to treat AV and photodamage. However, through 40 years of research and clinical use, topical tretinoin has also been shown to be safe and effective in treating a range of other diseases and conditions, both as monotherapy and in combination with other agents. These conditions include skin and pigmentation disorders, lesions of the oral mucosa and the ocular surface epithelia, hypertrophic scarring, and various infections. Although topical tretinoin is associated with a number of application-site AEs, newer formulations and modes of application have been shown to reduce irritation potential.

The list of diseases for which the effectiveness of topical tretinoin has been evaluated is remarkably diverse. This is, in part, a testament to the complexities of retinoid biology and the protean consequences and advantages of interacting with retinoid receptors. Some clinical uses of tretinoin appear to take advantage of its keratolytic action, allowing increased penetration of medications with which it is coapplied, thus improving their efficacy.

Although it is difficult to imagine adding to the multitude of conditions listed here, additional uses of topical tretinoin will no doubt be reported in the future. In our continuing efforts to provide advice on evidence-based medicine for our patients and to provide rationale for managed care companies, we look forward to additional clinical trials to further elucidate the beneficial effects of tretinoin on the skin. Such studies will undoubtedly also help us in our efforts to better understand the complex interactions of retinoids in the human body.

TABLE 1.

Tretinoin Review: Detailed Findings			
Actinic Keratoses (AK); Keratinocyte Carcinomas (KCs)[70-76]			
Article Title	**Authors**	**Journal**	**Summary**
Prospective quality of life impact of actinic keratoses: observations from the Veterans Affairs Topical Tretinoin Chemoprevention Trial	Lee KC, Weinstock MA	*Acta Derm Venereol.* 2011;91(1):101-102	• VATTC Trial: A randomized study examining topical tretinoin 0.1% (vs placebo) for prevention of KCs in high-risk patients (≥2 KCs in previous 5 years). • The current study examined the impact of increasing AK counts over time (evaluated at 12-month intervals, up to 36 months) on QoL. • In participants with increased AK counts, QoL scores did not differ from their scores 12 months earlier, even after controlling for tretinoin usage. • Efficacy and safety data for tretinoin vs placebo are not discussed in the article (primary outcome was QoL).
Prospective quality of life impact of keratinocyte carcinomas: observations from the Veterans Affairs Topical Tretinoin Chemoprevention Trial	Lee KC, Weinstock MA; Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial Group	*J Am Acad Dermatol.* 2010;63(6):1107-1109	• VATTC Trial: A randomized study examining topical tretinoin 0.1% (vs placebo) for prevention of KCs in high-risk patients (≥2 KCs in previous 5 years). • The current study examined the impact of increasing AK counts over time (evaluated at 12-month intervals, up to 36 months) on QoL. • In participants with increased AK counts, QoL scores did not differ from their scores 12 months earlier, even after controlling for tretinoin usage. • Efficacy and safety data for tretinoin vs placebo are not discussed in the article (primary outcome was QoL).
Quality of life in the actinic neoplasia syndrome: the VA Topical Tretinoin Chemoprevention (VATTC) Trial	Weinstock MA, Lee KC, Chren MM, Marcolivio K; VATTC Trial Group	*J Am Acad Dermatol.* 2009;61(2):207-215	• VATTC Trial: This study examined QoL and associated patient characteristics in the VATTC Trial. • Participants had worse QoL compared with a reference group of patients without skin disease, and this was associated with higher AK count, past 5-fluorouracil (5-FU) use, and sun sensitivity. • Efficacy and safety data for tretinoin vs placebo are not discussed in the article (primary outcome was QoL).

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Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial	Criscione VD, Weinstock MA, Naylor MF, et al	*Cancer.* 2009;115(11):2523-2530	• VATTC Trial: Study estimated the risk of progression of AK to KCs and the risk of spontaneous regression of untreated AKs for up to 6 years in subjects from the VATTC study. • Efficacy and safety data for tretinoin vs placebo were not discussed.
Reliability of counting actinic keratoses before and after brief consensus discussion: the VA topical tretinoin chemoprevention (VATTC) trial.	Weinstock MA, Bingham SF, Cole GW, et al	*Arch Dermatol.* 2001;137(8):1055-1058	• VATTC Trial: Evaluated the reliability of dermatologist counting of AKs. • 7 dermatologists independently counted AKs on the face and ears in a sample of 9 patients from the VATTC Trial. • Significant variation was found for the dermatologists' AK counts, and joint discussion enhanced reliability. • Study concludes that AKs are common but that counts of AKs may not be reliable. • Efficacy and safety data for tretinoin vs placebo were not discussed.
Topical treatment of multiple actinic keratoses of the face with arotinoid methyl sulfone (Ro 14-9706) cream versus tretinoin cream: a double-blind, comparative study	Misiewicz J, Sendagorta E, Golebiowska A, Lorenc B, Czarnetzki BM, Jablonska S.	*J Am Acad Dermatol.* 1991;24(3):448-451	• Double-blind, randomized, comparative study that assessed the efficacy and tolerability of 0.05% Ro 14-9706 (an arotinoid methyl sulfone) vs 0.05% tretinoin in the treatment of AKs for 16 weeks (n=25 patients). • Patients applied each agent twice daily to opposite sides of the face for 16 weeks. • Mean percent decrease in the number of AKs was significant for both creams ($P<.01$ vs baseline numbers): o 37.8% for areas treated with Ro 14-9706 o 30.3% for areas treated with tretinoin
Topical chemotherapy of actinic keratoses of the upper extremity with tretinoin and 5-fluorouracil: a double-blind controlled study	Bercovitch L	*Br J Dermatol.* 1987;116(4):549-552	• Randomized, double-blind controlled study of 19 patients using 5% 5-FU cream applied to their arm, followed by nightly application of 0.05% tretinoin cream (compared with a control arm). • Daily application of 0.05% tretinoin cream significantly enhanced the efficacy of topical 5-FU in reducing AKs.

Total	Summary
7	Topical tretinoin cream may be effective in reducing AKs (compared with baseline), both alone and as an adjunct to 5-FU, although these data are based on a limited number of studies in few patients.

Melanoma/Dysplastic Nevi[79-84]

Article Title	Authors	Journal	Summary
Effects of topical tretinoin on dysplastic nevi	Halpern AC, Schuchter LM, Elder DE, et al	*J Clin Oncol.* 1994;12(5):1028-1035	• Pilot study of 5 male patients with dysplastic nevi who applied topical tretinoin to one half of the back for 6 months. Baseline and posttreatment photographs were taken and assessed for morphological changes, and nevi were also excised and histologically evaluated for dysplasia. • A reduced number of nevi met criteria for dysplasia on the tretinoin-treated side compared with the untreated side of the back. Treated lesions also showed fading and some disappearance of nevi. • All subjects developed treatment-induced irritation, and 1 patient discontinued treatment due to this irritation.
The effect of topical tretinoin on dysplastic nevi. A preliminary trial	Edwards L, Jaffe P	*Arch Dermatol.* 1990;126(4):494-499	• Randomized, double-blind study that investigated the effect of 0.05% topical tretinoin on dysplastic nevi. Subjects applied tretinoin or placebo to dysplastic nevi once daily (under tape occlusion) or twice daily (unoccluded) for 4 months. • There was marked fading and reduction of nevi and disappearance or reversion to benign status in many treated lesions. There were no changes in nevi treated with placebo.

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Role of topical tretinoin in melanoma and dysplastic nevi	Meyskens FL Jr, Edwards L, Levine NS	*J Am Acad Dermatol.* 1986;15(4 Pt 2):822-825	• Pilot study examining effect of topical tretinoin on dysplastic nevi. • Showed regression of treated lesions to benign nevi with minimal/no dysplasia.
Effect of topical tretinoin under occlusion on atypical naevi	Stam-Posthuma JJ, Vink J, le Cessie S, Bruijn JA, Bergman W, Pavel S	*Melanoma Res.* 1998;8(6):539-548	• In this randomized, double-blind study, 30 patients with atypical nevi were treated with topical tretinoin 0.1%, topical tretinoin 0.1% with hydrocortisone, or placebo. • 3 atypical nevi per subject were treated once weekly under Actiderm occlusion for 4 months. • Morphological changes were assessed from beginning of treatment, at 2 months, 1 month after treatment completion, and 6 months later. • The tretinoin-treated groups showed a reduction in the size and change in color of nevi, but all nevi still met histological criteria for atypia after treatment.
No effect of topical tretinoin on lentigo maligna	Rivers JK, McCarthy WH	*Arch Dermatol.* 1991;127(1):129	• Case studies of 4 patients treated with 0.05% topical tretinoin cream twice daily for 3 months. • There was no clinical change in any of the lesions.
Recurrent melanoma after topical tretinoin	Rivers JK, McArdle CA, Gupta G, McCarthy SW, O'Brien CJ, McCarthy WH	*Lancet.* 1989;2(8676):1393	• Case study of 1 patient with melanoma that recurred after 2-3 months of treatment with topical tretinoin 0.05%.

Total	Summary
6	Findings from 2 randomized, double-blind studies and 2 pilot studies show the potential for topical tretinoin to be used to reverse and reduce dysplastic nevi.

Stretch Marks/Abdominal Striae[86-91]

Article Title	Authors	Journal	Summary
Topical tretinoin 0.1% for pregnancy-related abdominal striae: an open-label, multicenter, prospective study	Rangel O, Arias I, García E, Lopez-Padilla S	*Adv Ther.* 2001;18(4):181-186	• This open-label, multicenter, prospective study of 20 women with pregnancy-related abdominal stretch marks showed that 0.1% tretinoin cream applied daily improved global assessments of stretch mark appearance at 12 weeks. • Common AEs were erythema and scaling, which decreased in severity after 1 month of treatment.
Striae distensae of augmented breasts after oral contraceptive therapy	Har-Shai Y, Barak A, Taran A, Weissman A	*Ann Plast Surg.* 1999;42(2):193-195	• Case study of bilateral stretch marks after breast augmentation and oral contraceptive therapy, showing prevention of additional skin marks and striae maturation with cessation of oral contraceptives and daily application of topical tretinoin cream.
Comparison of topical therapy for striae alba (20% glycolic acid/0.05% tretinoin versus 20% glycolic acid/10% L-ascorbic acid)	Ash K, Lord J, Zukowski M, McDaniel DH	*Dermatol Surg.* 1998;24(8):849-856	• This blinded study evaluated the effectiveness of daily topical 20% glycolic acid alone or with a combination of 10% L-ascorbic acid, 2% zinc sulfate, and 0.5% tyrosine to one half of the treatment area and 0.05% tretinoin emollient cream (Renova) for 12 weeks for the treatment of striae distensae on the abdomen and thighs. Both clinical and histopathological improvements were measured. • Both regimens improved the appearance of stretch marks and were accompanied by minimal skin irritation. • Elastin with the reticular and papillary dermis increased with topical glycolic acid combined with 0.05% tretinoin emollient cream. • Both regimens increased epidermal thickness and decreased papillary dermal thickness.
Topical tretinoin (retinoic acid) improves early stretch marks	Kang S, Kim KJ, Griffiths CE, et al	*Arch Dermatol.* 1996;132(5):519-526	• In this double-blind, randomized, vehicle-controlled study, 22 patients used 0.1% tretinoin or vehicle daily for 6 months to treat early stretch marks. • After 2 months, patients treated with tretinoin showed significant improvements in severity of stretch marks compared with vehicle, and after 6 months, there was marked improvement in tretinoin-treated patients compared with vehicle, including reduction in the mean length and width of marks. • There were no differences in the quality and quantity of dermal collagen and elastic fibers in tretinoin compared with vehicle.

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Low-dose tretinoin does not improve striae distensae: a double-blind, placebo-controlled study	Pribanich S, Simpson FG, Held B, Yarbrough CL, White SN	*Cutis.* 1994;54(2):121-124	• This study applied 0.025% tretinoin cream daily for 7 months for treating pregnancy-related abdominal stretch marks vs placebo. • Before and after photographs were taken and evaluated based on a standardized evaluation methodology. There were no differences found for the treatment compared with control subjects based on the evaluation methodology employed.
Treatment of striae distensae with topical tretinoin	Elson ML	*J Dermatol Surg Oncol.* 1990;16(3):267-270	• This paper describes the experience of 20 patients using topical tretinoin to treat striae distensae, with 15 of 16 subjects who completed the study experiencing significant clinical improvement.

Total	Summary
6	Both blinded, placebo-controlled, and open-label prospective studies, as well as case studies, have demonstrated histological and clinical improvements in striae distensae with topical tretinoin, although some findings were equivocal.

Cervical Dysplasia[92-97]

Article Title	Authors	Journal	Summary
Low-dose topical delivery of all-*trans* retinoic acid for cervical intraepithelial neoplasia II and III	Ruffin MT, Bailey JM, Normolle DP, et al	*Cancer Epidemiol Biomarkers Prev.* 2004;13(12):2148-2152	• 175 women with cervical intraepithelial neoplasia (CIN) II/III were given 1 of 3 doses of tretinoin (0.16%, 0.28%, and 0.36%) administered by a collagen sponge and cervical cap or placebo for 4 consecutive days. Subjects were re-evaluated by colposcopy and cervical biopsy at 12 weeks. • Tretinoin did not differ from placebo in effectiveness at 12 weeks. • There were no systemic AEs with either placebo or tretinoin treatment.
Phase II trial of β-all-*trans*-retinoic acid for cervical intraepithelial neoplasia delivered via a collagen sponge and cervical cap	Graham V, Surwit ES, Weiner S, Meyskens FL Jr	*West J Med.* 1986;145(2):192-195	• 20 patients were treated with topical tretinoin (0.372%) delivered by collagen sponge and cervical cap. • 50% of these patients showed total disease regression. • Systemic, cervical, and vaginal AEs were mild to moderate.
Cervical tissue uptake of all-*trans*-retinoic acid delivered via a collagen sponge-cervical cap delivery device in patients with cervical dysplasia	Peng YM, Alberts DS, Graham V, Surwit EA, Weiner S, Meyskens FL Jr	*Invest New Drugs.* 1986;4(3):245-249	• This study examined systemic absorption and cervical tissue uptake of topical tretinoin (0.05% and 0.372%) delivered by a collagen sponge cervical cap device in 10 patients with mild or moderate cervical dysplasia. • Cervical biopsies and blood samples 4 hours after drug administration showed that there was a rapid decrease in cervical tissue concentration 4-24 hours after exposure to topical tretinoin. • There was no systemic absorption of topical tretinoin.
A phase I trial of topically applied *trans*-retinoic acid in cervical dysplasia—clinical efficacy	Weiner SA, Surwit EA, Graham VE, Meyskens FL Jr	*Invest New Drugs.* 1986;4(3):241-244	• In this phase 1 trial, 36 evaluable women with mild to severe cervical intraepithelial neoplasia were given 4 consecutive 24-hour application of topical tretinoin (0.05% to 0.1167% or 0.1583% to 0.484%), delivered by a collagen sponge in a cervical cap. • Evaluation was at 3 months using cytology, colposcopy, and selected biopsies, for a total of 5-18 months of follow-up. • Total regression was seen in 14% of patients treated with 0.05% to 0.1167% tretinoin, and 45% of patients given 0.1583% to 0.484% tretinoin. One patient with total regression at 12 months showed a recurrence at 18 months.
Evaluation of topically applied *trans*-retinoic acid in the treatment of cervical intraepithelial lesions	Surwit EA, Graham V, Droegemueller W, et al	*Am J Obstet Gynecol.* 1982;143(7):821-823	• This was a phase 1/2 study of topical tretinoin delivered by collagen sponge/diaphragm insert device to 18 patients with CIN II/III for 4 consecutive days. • Colposcopy performed 4 weeks later showed a reduction of intraepithelial lesions in 6/18 of patients, with complete resolution of disease in 2/18 patients. • However, some vulvovaginal toxicity occurred due to leakage around the diaphragm.

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A phase I trial of β-all-*trans*-retinoic acid delivered via a collagen sponge and a cervical cap for mild or moderate intraepithelial cervical neoplasia	Meyskens FL Jr, Graham V, Chvapil M, Dorr RT, Alberts DS, Surwit EA	*J Natl Cancer Inst.* 1983;71(5):921-925	• This dose-escalation phase 1 study used a cervical sponge and cap to deliver topical tretinoin for mild to moderate intraepithelial cervical neoplasia in 35 patients. • Topical tretinoin 0.05% cream was used as the starting dose, and the dose was escalated with the use of a modified Fibonacci scale. AEs were assessed every day for 4 days and then again on days 8 and 30 by colposcopy and clinical examination. • No systemic effects were found. There was mild cervical inflammation observed at higher doses, and high vaginal toxicity was reached at a concentration of tretinoin 0.484%. • This study concludes that a concentration of tretinoin 0.372% is recommended for treating mild to moderate cervical intraepithelial neoplasia in phase 2 studies.

Total	Summary
6	Prospective observational findings indicate that tretinoin delivered via collagen sponge and cervical cap may have the potential to treat moderate to severe cervical dysplasia (CIN II/III) at concentrations between 0.05% and 0.484%. However, one 12-week, placebo-controlled clinical trial failed to show a difference between patients with cervical dysplasia treated with topical tretinoin vs those treated with placebo.

Ulcers; Wound Healing[98-102]

Article Title	Authors	Journal	Summary
The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes	Tom WL, Peng DH, Allaei A, Hsu D, Hata TR	*Arch Dermatol.* 2005;141(11):1373-1377	• Randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of short-contact administration 0.05% topical tretinoin on foot ulcers in patients with diabetes (vs placebo). • At 16 weeks, 2 (18%) of 11 ulcers in the control group vs 6 (46%) of 13 ulcers in the tretinoin group completely healed, and topical tretinoin therapy significantly decreased ulcer area and depth compared with placebo treatment. • AEs of tretinoin therapy included mostly mild pain at the ulcer site.
Topical tretinoin decreases healing times of electroepilation-induced wounds	Anthony J, Miller L, Dinehart SM	*Dermatologica.* 1991;183(2):129-131	• Pretreatment of 5 patients for 2 weeks with 0.05% tretinoin reduced healing times (mean number of days to complete healing) following electroepilation. • Subjects applied tretinoin cream to 1 groin or axilla twice daily for 2 weeks vs no pretreatment to the opposite side.
Tretinoin accelerates healing after trichloroacetic acid chemical peel	Hevia O, Nemeth AJ, Taylor JR	*Arch Dermatol.* 1991;127(5):678-682	• Double-blind, placebo-controlled, prospective, randomized study that evaluated the effect of pretreating skin with 0.1% tretinoin cream (vs placebo) before a 35% trichloroacetic acid peel in 16 male subjects. • Tretinoin or placebo creams were applied to left and right halves of the face or forearms and hands, respectively, for 14 days before the peel. • In all treatment areas, tretinoin-pretreated skin showed greater mean area healed compared with placebo, which was maximal at 5-11 days. • Authors concluded that patients pretreated with tretinoin cream showed faster healing compared with placebo.
Short-contact topical tretinoin therapy to stimulate granulation tissue in chronic wounds	Paquette D, Badia-vas E, Falanga V	*J Am Acad Dermatol.* 2001;45(3):382-386	• Histological study of 5 patients with leg ulcerations, treated with topical tretinoin solution 0.05% for 10 minutes daily. • At 1 week of treatment, an increase in granulation tissue was noted in histological analysis. • At 4 weeks, further stimulation of granulation tissue, new vascular tissue, and new collagen formation were observed.
Pretreatment of photoaged forearm skin with topical tretinoin accelerates healing of full-thickness wounds	Popp C, Kligman AM, Stoudemayer TJ	*Br J Dermatol.* 1995;132(1):46-53	• Histological study of 4 elderly men with severely actinically damaged forearms, treated with topical tretinoin (0.05% to 0.1%) daily for 16 weeks (vs vehicle). • After 16 weeks, tretinoin treatment was associated with compaction of the stratum corneum, epidermal acanthosis with correction of atypia, an increase in small vessels, and increased cellularity in the upper dermis. • Wounds on the arms were 35% to 37% smaller on days 1 and 4, and 47% to 50% reduced on days 6, 8, and 11 for the tretinoin-treated areas compared with control-treated regions.

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Total	Summary
5	A randomized study suggested potential for tretinoin therapy to improve foot ulcers in patients with diabetes. Pretreatment with tretinoin cream also reduced healing time in 2 studies (ie, healing following electroepilation and after a chemical peel). Histological analyses (2 studies) have also demonstrated significant healing of wounded skin with topical tretinoin treatment.

Alopecia[104-107]

Article Title	Authors	Journal	Summary
Alopecia in congenital hidrotic ectodermal dysplasia responding to treatment with a combination of topical minoxidil and tretinoin	Melkote S, Dhurat RS, Palav A, Jerajani HR	*Int J Dermatol.* 2009;48(2):184-185	• Case report of alopecia in Clouston's syndrome, which responded to treatment with topical minoxidil and tretinoin.
Efficacy of 5% minoxidil versus combined 5% minoxidil and 0.01% tretinoin for male pattern hair loss: a randomized, double-blind, comparative clinical trial	Shin HS, Won CH, Lee SH, Kwon OS, Kim KH, Eun HC	*Am J Clin Dermatol* 2007;8(5):285-290	• Compared the efficacy and safety of therapy using a combined solution of 5% minoxidil and 0.01% retinoin once daily with those of the conventional 5% topical minoxidil therapy applied twice daily in androgenetic alopecia. • Increases in total hair count and nonvellus hair count were similar between the 2 treatment groups. • There were no differences between treatment groups on global ratings by patients or the investigator. • AEs (pruritus or local irritation) were similar in the minoxidil group and the combined treatment group.
Topical tretinoin as an adjunctive therapy with intralesional triamcinolone acetonide for alopecia areata. Clinical experience in northern Saudi Arabia	Kubeyinje EP, C'Mathur M	*Int J Dermatol.* 1997;36(4):320	• Efficacy and safety in patients of daily 0.05% tretinoin cream in combination with monthly intralesional triamcinolone acetonide in alopecia areata was studied vs safety and efficacy in patients on treatment with monthly intralesional triamcinolone 40 mg alone for 4 months. • At 4 months, 90% regrowth was observed in 85.7% of patients receiving triamcinolone acetonide and tretinoin combination vs 66.7% of patients receiving triamcinolone acetonide alone ($P<.01$).
Comparative assessment of topical steroids, topical tretinoin (0.05%) and dithranol paste in alopecia areata	Das S, Ghorami RC, Chatterjee T, Banerjee G	*Indian J Dermatol.* 2010;55(2):148-149	• Topical steroids, topical tretinoin (0.05%), dithranol paste (0.25%), and white soft petrolatum jelly were evaluated for treatment of alopecia areata over 6 months. • 70%, 55%, 35%, and 20% of the topical steroids, topical tretinoin, dithranol paste, and control groups, respectively, showed significant regrowth of hair at 3 months. • Dermatitis and hyperpigmentation were seen only in the dithranol paste group. • Authors conclude that both topical steroids and tretinoin were each independently effective for treatment of alopecia areata.

Total	Summary
4	Results from a limited number of studies suggest that tretinoin may be used alone or in combination with minoxidil for treating alopecia. In one study, the effects of tretinoin were found to be similar to those of steroids for treating alopecia.

Warts/Nevoid Hyperkeratosis[109-112]

Article Title	Authors	Journal	Summary
Unilateral nevoid hyperkeratosis of the nipple: a report of two cases	Shastry V, Betkerur J, Kushalappa PA	*Indian J Dermatol Venereol Leprol.* 2006;72(4):303-305	• Case report of 2 females with chronic unilateral warty lesions of the nipple (this is a rare condition). Topical tretinoin cream did not improve the condition in these patients.
Nevoid hyperkeratosis of the nipple and areola: treatment with topical retinoic acid	Okan G, Baykal C	*J Eur Acad Dermatol Venereol.* 1999;13(3):218-220	• One case study of topical retinoic acid shows a favorable response for nevoid hyperkeratosis.

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Topical retinoids for warts and keratoses in transplant recipients	Euvrard S, Verschoore M, Touraine JL, et al	*Lancet.* 1992;340(8810):48-49	• Controlled, single-center, double-blind, randomized study of the safety and efficacy of 0.05% topical tretinoin for warts and keratoses in 25 organ transplantation recipients (intraindividual comparison), assessed at 3 and 6 months. • There was up to 45% reduction in the number of lesions with topical tretinoin treatment. Topical tretinoin was also generally well tolerated.
Topical tretinoin in the treatment of anogenital warts	Handley J, Dinsmore W	*Sex Transm Dis.* 1992;19(3):181	• Topical tretinoin 0.05% twice daily for 4 weeks was not effective in treating anogenital warts in 11 men studied.

Total	Summary
4	Case studies have evaluated topical tretinoin for warts or nevoid hyperkeratosis, with equivocal findings.

Hyperkeratosis Follicularis (Kyrle's Disease)/Keratosis Follicularis (Darier's Disease)[113-116]

Article Title	Authors	Journal	Summary
Kyrle disease. Treatment with topically applied tretinoin	Petrozzi JW, Warthan TL	*Arch Dermatol.* 1974;110(5):762-765	• Case study of a 43-year-old man with Kyrle's disease that was successfully treated with topical tretinoin cream 0.1% 3 times daily. • Marked flattening of papules was noted at 6-7 days. After 12 days, the treated area (right leg) was 90% clear.
Kyrle's disease	Moss HV	*Cutis.* 1979;23(4):463-466	• Case study of a 59-year-old man with hyperkeratosis follicularis that was treated with topical tretinoin that led to severe inflammatory reactions in the lesions. Topical tretinoin also did not prevent the recurrence of the disease.
Localized Darier disease. Implications for genetic studies	O'Malley MP, Haake A, Goldsmith L, Berg D	*Arch Dermatol.* 1997;133(9):1134-1138	• One study has shown some response of Darier's disease to topical tretinoin (ranging from concentrations of 0.05% to 0.2%).
Effective treatment of linear Darier's disease with topical retinoids: case report and review of the literature	Dogan S, Karaduman A, Erkin G, Gokoz O	*Acta Dermatovenerol Croat.* 2011;19(3):206-209	• Case study of 62-year-old man with linear Darier's disease on his back. Treatment with topical tretinoin 0.1% twice daily was associated with total improvement in the condition after 1 month.

Total	Summary
4	Results from 1 case study suggest that the use of topical tretinoin for treating hyperkeratosis follicularis may be limited due to AEs. Other studies suggest that topical tretinoin may be useful for treating Darier's disease.

Porokeratosis[117-119]

Article Title	Authors	Journal	Summary
A case of extensive linear porokeratosis with evaluation of topical tretinoin versus 5-fluorouracil as treatment modalities	Grover C, Goel A, Nanda S, Khurana N, Reddy BS	*J Dermatol.* 2005;32(12):1000-1004	• Case study of adult male with porokeratosis given topical tretinoin and 5-fluorouracil. • Although both were efficacious in reducing lesions, tretinoin had a better cosmetic acceptability and safety profile.
Topical tretinoin in Indian male with zosteriform porokeratosis	Agrawal SK, Gandhi V, Madan V, Bhattacharya SN	*Int J Dermatol.* 2003;42(11):919-920	• Case study of 28-year-old male showing marked improvement and resolution of zosteriform lesions with topical tretinoin 0.1% gel treatment nightly for 4 months.
Generalized linear porokeratosis	Dervis E, Demirkesen C	*Int J Dermatol.* 2006;45(9):1077-1079	• Case study of adult female with linear porokeratosis treated with topical tretinoin 0.05% once daily. • Marked improvement was seen in hyperkeratosis through the first 4 weeks of treatment, and after 10 weeks, the lesions had almost disappeared.

Total	Summary
3	Data from 3 case studies suggest that topical tretinoin may benefit patients with porokeratosis by reducing lesions.

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Acanthosis Nigricans[122,123]			
Article Title	**Authors**	**Journal**	**Summary**
Topical therapy with tretinoin and ammonium lactate for acanthosis nigricans associated with obesity	Blobstein SH	*Cutis.* 2003;71(1):33-34	• Study used a combination of 12% ammonium lactate cream and 0.05% tretinoin cream and found improvement in acanthosis nigricans associated with obesity.
Topical tretinoin in acanthosis nigricans	Lahiri K, Malakar S	*Indian J Dermatol Venereol Leprol.* 1996;62(3):159-161	• 30 cases of recalcitrant, idiopathic acanthosis nigricans were studied. Topical tretinoin applied nightly was found to be successful in treating acanthosis nigricans both histologically and clinically.
Total	**Summary**		
2	One report showed that a combination of 12% ammonium lactate cream and 0.05% tretinoin cream improved acanthosis nigricans associated with obesity. A series of case studies showed that daily topical tretinoin was effective in improving both clinical and histological measures of acanthosis nigricans.		

Psoriasis[120,121]			
Article Title	**Authors**	**Journal**	**Summary**
Concurrent application of tretinoin (retinoic acid) partially protects against corticosteroid-induced epidermal atrophy	McMichael AJ, Griffiths CE, Talwar HS, et al	*Br J Dermatol.* 1996;135(1):60-64	• In 20 patients with psoriasis, one plaque was treated once daily with betamethasone dipropionate and tretinoin 0.1% while another plaque was treated with betamethasone dipropionate and vehicle. • There was no difference in the improvement of plaques between treatments. However, there was a reduction in epidermal thickness in corticosteroid-treated skin compared with the corticosteroid/tretinoin-combination treatment.
Treatment of psoriasis with topically applied tretinoin and steroid ointment	Kaidbey KH, Petrozzi JW, Kligman AM	*Arch Dermatol.* 1975;111(8):1001-1003	• Pilot study showing that the treatment of psoriasis with tretinoin 0.3% cream plus corticosteroid ointment was more effective than either treatment alone. This effect was particularly evident in steroid-resistant psoriasis. • Tretinoin-related irritation was an AE.
Total	**Summary**		
2	One case study showed the effectiveness of sequential application of topical tretinoin (0.3%) and a corticosteroid for treating plaque-type psoriasis. This combination was particularly effective for corticosteroid-resistant psoriasis. Another study showed that the addition of topical tretinoin to a topical corticosteroid for treating psoriasis partially ameliorates corticosteroid-induced epidermal atrophy.		

Nevus Comedonicus[127,128]			
Article Title	**Authors**	**Journal**	**Summary**
Nevus comedonicus: a novel approach to treatment	Givan J, Hurley MY, Glaser DA	*Dermatol Surg.* 2010;36(5):721-725	• Case study of nevus comedonicus of the neck showing clinical improvement with topical tretinoin in combination with a 1450-nm diode laser.
Naevus comedonicus—treatment with retinoic acid	Decherd JW, Mills O, Leyden JJ	*Br J Dermatol.* 1972;86(5):528-529	• 2 case reports of patients with nevus comedonicus on the face or chest, treated daily with 0.1% retinoic acid in equal parts with 95% ethanol and propylene glycol. • There was a marked resolution and extrusion of comedones in each patient at 3 and 4 weeks, respectively. • Treatment of nevus comedonicus in these 2 patients was associated with no irritation.
Total	**Summary**		
2	Case studies of nevus comedonicus on the face, neck, and chest show a response to treatment with retinoic acid (with equal parts 95% ethanol and propylene glycol) or with tretinoin in combination with a 1450-nm diode laser.		

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Rosacea[124]			
Article Title	**Authors**	**Journal**	**Summary**
A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea	Ertl GA, Levine N, Kligman AM	*Arch Dermatol.* 1994;130(3):319-324	• Randomized, double-blind trial of severe or recalcitrant rosacea treatment with isotretinoin 10 mg/day, topically applied tretinoin 0.025% cream, or the combined use of both isotretinoin and tretinoin over 32 weeks (the first 16 weeks, subjects received one of these 3 trial regimens, and for the next 16 weeks, treatment continued with only tretinoin cream or a placebo cream). • There were no differences between the groups after 16 weeks; each treatment produced therapeutic benefit for the number of papules and pustules and erythema. • There was no additive benefit. • All treatments were well tolerated, and there were few AEs.
Total	**Summary**		
1	Randomized, double-blind study suggests that low-dose topical tretinoin may be useful for treating rosacea.		
Keratosis Pilaris[129]			
Article Title	**Authors**	**Journal**	**Summary**
Atrophic pilar keratosis of the face: case report. [Article in Croatian]	Golusin Z, Jovanović M, Poljacki M	*Med Pregl.* 2001;54(9-10):486-489	• A case study of a 24-year-old woman with keratotic follicular papules, surrounded by erythema, on the cheeks, forehead, and chin. • Topical tretinoin was found to visibly reduce erythema and follicular hyperkeratosis after 1 month of treatment.
Total	**Summary**		
1	A case study supports the efficacy of topical tretinoin in the treatment of erythema and follicular hyperkeratosis associated with keratosis pilaris.		
Antilice Agent[130]			
Article Title	**Authors**	**Journal**	**Summary**
The addition of tretinoin to permethrin, pyrethrins, and DDT for production of powerful anti-lice agents	Namazi MR	*Med Hypotheses.* 2005;65(5):992	• An editorial that discusses a recommendation for topical tretinoin to be used in combination with DDT, permethrin, and pyrethrins as an antilice agent.
Total	**Summary**		
1	It is recommended that topical tretinoin be used in combination with DDT, permethrin, and pyrethrins as an antilice agent.		
Trichoepitheliomas[131]			
Article Title	**Authors**	**Journal**	**Summary**
Treatment of multiple trichoepitheliomas with topical imiquimod and tretinoin	Urquhart JL, Weston WL	*Pediatr Dermatol.* 2005;22(1):67-70	• Case study of a pediatric female (aged 11 years) with trichoepitheliomas treated with topical imiquimod and tretinoin gel. • There was approximately 80% clearing of lesions without scarring after 3 years of treatment.
Total	**Summary**		
1	Case study showed potential for combination of tretinoin and imiquimod for treating trichoepitheliomas.		
Eruptive Milia[132]			
Article Title	**Authors**	**Journal**	**Summary**
Eruptive milia and rapid response to topical tretinoin	ConnellyT	*Arch Dermatol.* 2008;144(6):816-817	• Case study of an 18-year-old woman with eruptive milia that responded quickly to treatment with topical tretinoin.
Total	**Summary**		
1	Case study demonstrated rapid efficacy of treatment with topical tretinoin for eruptive milia treatment.		

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Lichen Planus[133]			
Article Title	**Authors**	**Journal**	**Summary**
Lichen planus with bullous manifestation on the lip	van Tuyll van Serooskerken AM, van Marion AM, de Zwart-Storm E, Frank J, Poblete-Gutiérrez P	*Int J Dermatol.* 2007;46(Suppl 3):S25-S26	• Case study of an older adult female with a previous history of cutaneous lichen planus who developed vesiculae and blisters on the lip and was successfully treated with a topical combination of tretinoin 0.025% and triamcinolone 0.1%.

Total	Summary
1	Case study showed that application of tretinoin and triamcinolone combination was a successful treatment for lichen planus.

Reactive Perforating Collagenosis[135]			
Article Title	**Authors**	**Journal**	**Summary**
Successful treatment of reactive perforating collagenosis with tretinoin	Cullen SI	*Cutis.* 1979;23(2):187-191, 193	• Tretinoin cream 0.1% reduced the total number of lesions present in a case of a 25-year-old woman with lifelong reactive perforating collagenosis.

Total	Summary
1	One case study demonstrated the effectiveness of tretinoin cream 0.1% for reducing the total number of reactive perforating collagenosis lesions.

Keratinizing Dermatoses[136]			
Article Title	**Authors**	**Journal**	**Summary**
Keratinizing dermatoses. Combined data from four centers on short-term topical treatment with tretinoin	Muller SA, Belcher RW, Esterly NB, et al	*Arch Dermatol.* 1977;113(8):1052-1054	• Double-blind, short-term study from 4 medical centers with 40 patients evaluating the effectiveness of tretinoin cream 0.1% and salicylic acid 2% cream. • Tretinoin was more effective vs salicylic acid in treating several keratinizing dermatoses (except palmar-plantar hyperkeratosis). • Tretinoin was particularly effective in lamellar ichthyosis and ichthyosis vulgaris. • AEs included pruritus, erythema, burning, excoriation, and irritation, which were not severe and were controlled through modifying the treatment regimen.

Total	Summary
1	Data from a multicenter trial showed that topical tretinoin 0.1% was effective in treating several keratinizing dermatoses, including lamellar ichthyosis and ichthyosis vulgaris.

Intrinsic/Chronological Aging[137]			
Article Title	**Authors**	**Journal**	**Summary**
Effects of topical tretinoin on the non-sun-exposed protected skin of the elderly	Kligman AM, Dogadkina D, Lavker RM	*J Am Acad Dermatol.* 1993;29(1):25-33	• 6 women, aged 68-79 years, used 0.025% tretinoin cream on one thigh and vehicle cream on the other once daily for 9 months. • Tretinoin cream increased viable epidermal thickness, resulted in more undulating dermoepidermal junction with prominent rete ridges, and resulted in other dermal changes such as increased glycosaminoglycan deposition, elastic fibers, and new blood vessel formation.

Total	Summary
1	One clinical trial found that tretinoin cream applied once daily for 9 months in older women (aged 68-79 years) showed marked histological improvement compared with vehicle.

Multiple Miliary Osteoma Cutis[138]

Table continued on next page

Article Title	Authors	Journal	Summary
Treatment of multiple miliary osteoma cutis of the face with local application of tretinoin (all-*trans*-retinoic acid): a case report and review of the literature	Cohen AD, Chetov T, Cagnano E, et al	*J Dermatolog Treat.* 2001;12(3):171-173	• Case study of a 60-year-old woman with multiple miliary osteoma cutis on her face, which was treated with topical tretinoin 0.05% nightly. • At 3 months of treatment, a decrease in lesion size and a reduction in the number of papules were observed.

Total	Summary
1	A case study suggests that topical tretinoin 0.05% may decrease the number and size of papules after 3 months of treatment.

QoL, quality of life; AE, adverse event.

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AUTHOR CORRESPONDENCE

Hilary E. Baldwin MD
E-mail:.....Hilary.Baldwin@downstate.edu