REVIEW

The Evolution of Topical Retinoids in Dermatology: A Cornerstone of Acne Management (1971–2025)

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OBJECTIVE: Topical retinoids have been a cornerstone in the management of acne vulgaris for over 5 decades, and they remain important even as treatment paradigms evolve. There is an ongoing need to understand the history and context of current retinoid use to support future innovations and improvements in the care of patients with acne. **METHODS:** Peer-reviewed literature was searched to identify articles related to topical retinoids, including their development, receptor selectivity, mechanisms of action, efficacy, tolerability, and role in the treatment of acne and management of acne sequelae. **RESULTS:** Molecular design for stability and receptor-specific activity distinguishes the retinoid generations. Increased selectivity for retinoic acid receptor γ (RARγ) has changed the profile of modulated genes, with many of the altered genes having known roles with implications in the pathogenesis of acne and acne sequelae. Finally, the potential of retinoids to manage acne sequelae, such as atrophic scarring and acne-induced hyperpigmentation, has been demonstrated in clinical trials. **LIMITATIONS:** Most available studies are heterogeneous in design, with few large-scale trials directly comparing newer selective RARγ agonists with older agents. Moreover, long-term safety data beyond 1 year are limited, and real-world adherence metrics are underreported. Finally, formulation variability across studies complicates direct efficacy and tolerability comparisons. **CONCLUSION:** Advancements in the selectivity of retinoids, adjunctive skincare, and patient education have reduced adverse effects of topical retinoids and improved adherence. A thorough understanding of retinoid biology and pharmacology is essential for dermatologists to optimize patient outcomes and maximize the therapeutic potential of this important drug class. **KEYWORDS:** Tretinoin, tazarotene, adapalene, trifarotene, acne, acne-induced scarring, acne-induced hyperpigmentation

Since the approval of topical tretinoin by the United States (US) Food and Drug Administration (FDA) in 1971, retinoids have been the cornerstone of acne treatment.[1] Topical retinoids address the pathophysiology of acne in a number of ways; they modulate inflammation in a dose-dependent manner, alter epithelial proliferation and differentiation to normalize follicular keratinization, resolve existing comedones and prevent the formation of new ones, and reduce the risk of long-term acne sequelae such as atrophic scarring.[2–4] Retinoids are effective in addressing both comedonal acne and precursor lesions as well as inflammatory papules and pustules, making them a foundational component of most acne treatment regimens.[5,6]

Beyond the primary acne lesion, studies have increasingly demonstrated that retinoids have significant implications for overall long-term skin health. Studies of tretinoin, adapalene, and tazarotene have reported the ability of first- and third-generation retinoids to mitigate acne sequelae and improve skin quality.[7–10] Although comparative data are limited, recent phase 4 outcomes (NCT04856904) have demonstrated that the fourth-generation retinoid trifarotene may be particularly well suited to mitigate acne sequelae such as acne-induced scarring and hyperpigmentation.[11,12]

The therapeutic efficacy of topical retinoids is fundamentally linked to their role as signaling molecules that regulate gene expression.[13] This

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TABLE 1. Retinoid classification: 4 generations of retinoids

GENERATION	STRUCTURAL FEATURES[14,15]	RECEPTOR SELECTIVITY[2,3,15]	KEY EXAMPLES[1,14]	CLINICAL APPLICATIONS[14]
First	Natural vitamin A derivatives or isomers	Nonselective RAR/RXR binding	Tretinoin, isotretinoin, retinol	Acne, photoaging, psoriasis
Second	Synthetic monoaromatic compounds (oral use)	Nonselective RAR/RXR binding	Acitretin, etretinate	Psoriasis, ichthyosis
Third	Synthetic polyaromatic compounds	Selective RARβ/RARγ binding	Adapalene, tazarotene	Acne, photoaging
Fourth	Pyranone derivatives (topical)	Exclusive RARγ agonism	Trifarotene	Acne vulgaris

RA: retinoic acid receptor; RARβ: retinoic acid receptor β; RARγ: retinoic acid receptor γ; RXR: retinoid X receptor

regulation occurs through their interaction with nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), leading to transcriptional modulation of numerous genes involved in cell proliferation, differentiation, organization of the extracellular matrix, and inflammation.[16] The evolution of retinoid therapy has led to the development of molecules with distinct structures and pharmacologic profiles.[14,17] Moreover, each retinoid exhibits a unique transcriptomic signature, which is shaped by its binding affinity and selectivity for specific RAR isoforms (α, β, and γ).[17,18] Ultimately, these molecular distinctions, along with their formulations, underpin their varied clinical profiles.[2]

While retinoids are highly effective acne therapies, skin irritation associated with retinoids can be challenging for patients and reduce adherence to treatment.[19,20] Termed "retinoid phobia," patient misperceptions around retinoids—including beliefs that retinoids are limited to comedonal acne, are uniformly irritating, markedly increase sun sensitivity, or cannot be combined with other skincare products—reduce use of the therapies by patients who would otherwise benefit.[21] Nonclinical sources (eg, social media) may amplify these concerns with unverified claims (eg, "skin thinning" and pronounced exacerbation of acne known as "retinoid purging") without providing appropriate context.[16,21] In a US claims analysis, topical retinoids were prescribed in 32.4% of acne encounters in which a topical agent was indicated, suggesting underuse relative to guideline recommendations.[4]

While the initial retinization period does include transient erythema, dryness, and peeling,[4,22] adjunctive skincare can mitigate local skin reaction (LSR) burden during treatment. In a 28-day open-label study of a standardized cleanser plus moisturizer regimen in addition to acne treatment (N=91), transepidermal water loss decreased −7.83% at Day 28 (P=0.036) and epidermal hydration increased (+6.02% at Day 14; +5.71% at Day 28, not statistically significant); ≥94% of patients rated products as nonirritating, and there were no discontinuations for adverse events (AEs).[23] Research to understand the mechanisms of retinization is ongoing. One proposed mediator is the transient receptor potential vanilloid 1 protein, which can transmit pain and itch signals and is activated by topical retinoids, including tretinoin, adapalene, and tazarotene.[24] Other factors that may contribute to the symptoms patients experience during retinization include the chosen retinoid, retinoid concentration, and drug formulation.[1,4,25–27] Another aspect of retinization that is challenging for some patients is retinoid purging, a consequence of increased keratinocyte turnover, which can temporarily accelerate microcomedone maturation. Although an on-target effect of retinoids, a paradoxical increase in acne lesions can be discouraging. Management of patients' expectations and education around the typical severity and duration of skin irritation and temporary purging are important for maintaining consistent therapy during the early period of treatment.[1,4,28,29]

Educating patients on realistic timelines for improvement is also key for treatment adherence. Patient frustration with a perceived lack of improvement may contribute to premature treatment discontinuation. Baseline photographs may help patients perceive early improvements as well as selecting therapies that have demonstrated early onset of effect in clinical trials.[30–32] Additionally, it is important to address the individual patient's concerns. For instance, management of acne-induced hyperpigmentation (AIH) is frequently the motivating factor driving affected patients to seek a dermatologist.[9] Likewise, about half of patients with facial acne also have acne on their torso or back and expect therapy to address both.[33,34] Other patients may be concerned about scarring or tolerability.

The therapeutic potential of retinoids continues to expand, as the evolution across 4 distinct generations has culminated in highly targeted molecules, with fourth-generation retinoids exhibiting selective binding to RARγ, the predominant RAR in the skin.[18] This specificity leads to a more focused transcriptomic activity and narrower targeting of the skin for both facial and truncal acne,[14] ultimately translating into better clinical outcomes for patients.[35,36] The need to optimize efficacy and tolerability and understand how to manage acne sequelae and preserve or restore skin health is ongoing.

DEFINING RETINOIDS: WHAT ARE THEY?

Definition and classification. Retinoids constitute a large, diverse class of chemical compounds that are structurally related to or functionally mimic vitamin A (retinol). This broad family includes both natural forms found in the body and synthetic analogues developed to optimize therapeutic effects and minimize adverse effects.[1,14,15,36,37] The primary mechanism of action (MOA) of retinoids in the skin involves binding to nuclear receptors to modulate gene expression, thereby influencing a wide range of cellular processes, including proliferation, differentiation, and inflammation.[1,14,15,36,37]

The retinoid family can be broadly categorized into natural and synthetic compounds. Natural vitamin A derivatives include retinol, retinal (retinaldehyde), retinoic acid, and retinyl esters. In contrast, synthetic retinoids, which include molecules such as tretinoin, adapalene, tazarotene, and trifarotene, were engineered to provide more targeted receptor activity and improved stability. This structural diversity is the basis for the classification of retinoids into 4 distinct generations, each defined by its molecular structure and resulting receptor selectivity profile (**Table 1**). **Figure 1** illustrates a clear evolutionary trend from the broad activity of the first generation to the highly targeted, selective action of the fourth generation.[1,14,15,36,37]

First-generation retinoids are natural, nonselective, monoaromatic retinoids obtained by modifying polar groups at the end side

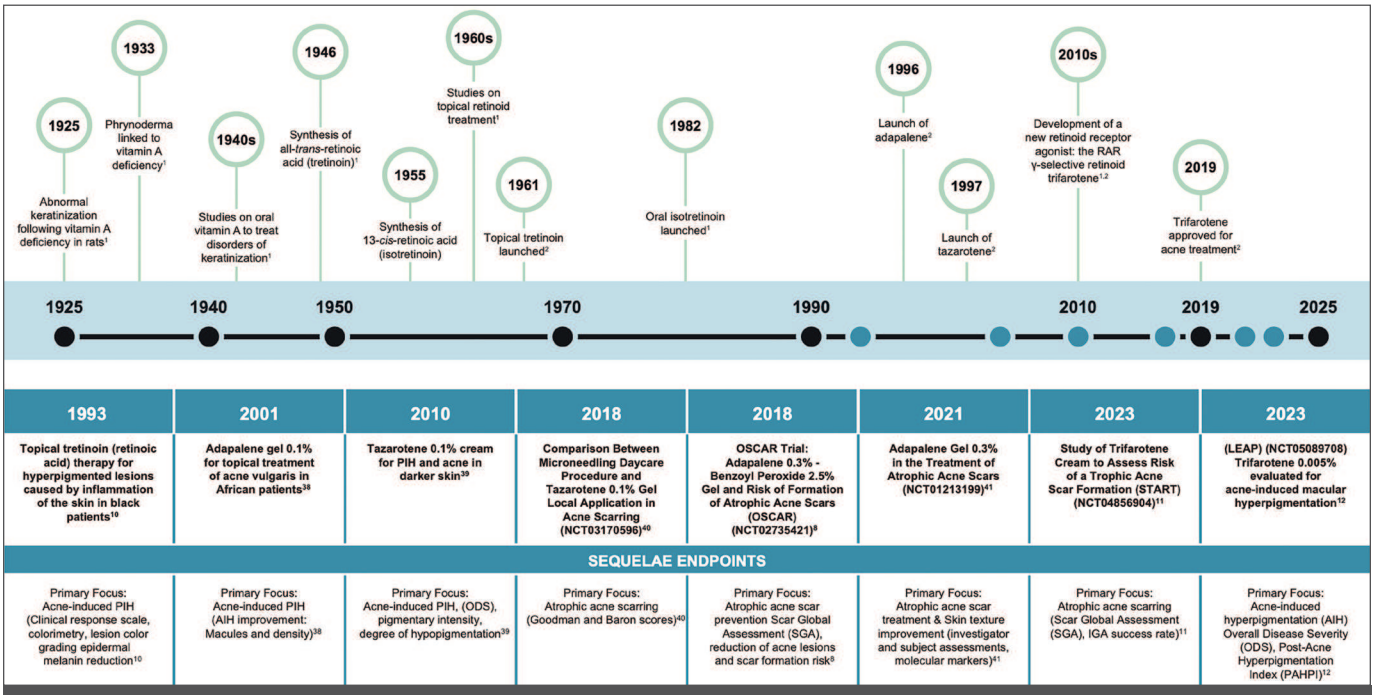

FIGURE 1. Historical timeline of the clinical development of retinoids as acne treatment. (Top) The foundational history of retinoids, beginning with early discoveries in the 1920s linking vitamin A deficiency to keratinization disorders, through the synthesis of tretinoin and isotretinoin in the mid-20th century, and culminating in the launch of the second-, third-, and fourth-generation agents.[1,42] (Bottom) A focused look at the modern era of clinical research, from 1993 to 2023, specifically highlighting the evolution toward pivotal trials on acne sequelae.
AIH: acne-induced hyperpigmentation; IGA: investigator global assessment; ODS: overall disease severity; PAHPI: Post-Acne Hyperpigmentation Index; PIH: postinflammatory hyperpigmentation; RAR: retinoic acid receptor; SGA: subjective global assessment

chain of the polyene vitamin, vitamin A. This generation includes the natural metabolites tretinoin (all-trans-retinoic acid) and isotretinoin, as well as retinol itself. These agents exhibit nonselective binding to RAR and RXR subtypes and are broadly active against acne lesions.[2] However, first-generation retinoids are susceptible to damage by oxidation and UV exposure and are associated with localized skin irritation.[43,44]

Second-generation retinoids are synthetic, monoaromatic retinoids, also known as etretinate derivatives. In these compounds, the cyclohexenyl ring of the natural retinoid structure is replaced by a benzene ring. Key examples include etretinate and its active metabolite, acitretin.[2] Due to heightened teratogenicity, use of acitretin is limited to patients with psoriasis.[45]

Third-generation retinoids consist of polyaromatic retinoids, which are synthetic compounds characterized by the cyclization of the polyene side chain. This structural modification confers receptor selectivity. Adapalene and tazarotene are the prominent members of this generation used in acne therapy. Adapalene is a derivative of 1-napthalenecarboxylic acid and exhibits selectivity for RARβ and RARγ, while tazarotene is a synthetic retinoid prodrug that binds across all RAR subtypes with a greater selectivity for RARβ and RARγ. In general, third-generation retinoids have greater lipophilicity and are more photostable than first-generation compounds but are still associated with skin irritation, particularly tazarotene.[3,26]

The fourth and most recent generation of retinoids is defined by its use of receptor-based modern molecular design to generate extremely high receptor specificity. Trifarotene is the first-in-class, pure RARγ-selective agonist. Its novel triaryl chemical structure, featuring a pyranone core, was specifically engineered to optimize selective binding to RARγ—the most prevalent RAR subtype in the epidermis—while minimizing off-target effects on RARα and RARβ.[15,35,36,46] This targeted mechanism was designed to maximize therapeutic activity in the skin while improving the overall benefit-risk profile. The unique structure of trifarotene makes it preferentially stable in keratinocytes, with a short systemic half-life, and its high level of RARγ selectivity imparts a unique retinoid signaling profile that will be described later in this manuscript. These features make trifarotene uniquely suited for use on broad body surface areas and when there is a heightened concern for acne sequelae.[11,12,18,35]

OVERVIEW OF TOPICAL RETINOID CLINICAL STUDIES IN ACNE

Evolution of efficacy and tolerability of topical retinoids. Advances in understanding acne pathogenesis have progressed in tandem with the improved management of acne with topical retinoids. Clinical trials of first- and third-generation retinoids established the efficacy of monotherapy treatment for patients with mild-to-moderate acne. For example, in a double-blind, vehicle-controlled trial, mean percent reductions in lesion counts at Week 12 were 35.5% (total), 38.2% (inflammatory), and 33.6% (noninflammatory) with tretinoin vs 20.9%, 19.2%, and 20.4% with vehicle ($P<0.05$).[47] For patients with mild-to-severe

acne, lesion resolution ranged from 46% to 71% with 12 weeks of tretinoin treatment, depending on the formulation.[48] The efficacy of adapalene was compared to topical retinoids in a series of early clinical trials. A meta-analysis of 5 studies demonstrated comparable lesion resolution at 12 weeks (difference of −1.5% [95% CI: −8% to +5%] for inflammatory lesions and −6.0% [95% CI: −12% to +1%] for noninflammatory lesions).[49] In a 12-week evaluator-blinded, randomized controlled trial (N=172), adapalene gel, 0.3%, achieved 61% median total-lesion reduction vs 57% with tazarotene gel, 0.1% (noninferior; 95% CI: −5.2% to 9.6%).[50] In a separate 12-week trial (N=202), adapalene gel, 0.1%, was noninferior to tazarotene cream, 0.1%, for lesion reduction (median difference: −1.18%; lower confidence limit: −9.26%).[51] Finally, a retrospective photograph-based study of tretinoin (0.1% microsponge and 0.025% gel), adapalene (0.1% gel), tazarotene (0.1% gel and 0.1% cream), and vehicle reported that all 3 agents were clinically effective at reducing inflammatory acne (the incidences of clinically significant improvements in the tretinoin microsponge, adapalene, and tazarotene groups were 21%, 17%, and 24%, respectively, vs vehicle 7%).[52]

While lesion resolution is generally equivalent between first- and third-generation retinoids, there are more substantial differences in tolerability. Irritation with topical tretinoin was an early observation but may have been accentuated by the use of a hydroalcoholic vehicle, which was later replaced.[1] Nonetheless, adapalene (0.1% gel) was found to have superior tolerability compared to tretinoin (0.025% gel).[49] The tolerability of third-generation retinoids has also been studied. In the randomized controlled trial of adapalene vs tazarotene by Thiboutot et al,[53] adapalene had lower mean tolerability scores across erythema/dryness/scaling/stinging-burning ($P<0.014$) and a lower rate of treatment-related AEs (3.5% vs 14.0%). In the adapalene vs tazarotene noninferiority trial reported by Pariser et al,[51] adapalene gel, 0.1%, showed fewer treatment-related AEs than tazarotene (36% vs 58%) and fewer "definitely related" AEs (20% vs 45%); early (Week 2) erythema/scaling were also higher with tazarotene.

Taken together, the clinical picture of early-generation retinoids is that monotherapy efficacy was found across all agents and could be improved with different formulations. Moreover, it was tempting to speculate that greater retinoid specificity to RARγ and RARα could be the basis for improved tolerability with third-generation retinoids, particularly adapalene compared to first-generation tretinoin.

Clinical data of fourth-generation trifarotene. In the two phase 3 studies of trifarotene (0.005% cream) or vehicle treatment of 2,420 patients aged 9 years and older with moderate facial and truncal acne, 12-week response rates for facial acne (clear/almost clear with ≥2-grade improvement) were 29.4% vs 19.5% and 42.3% vs 25.7% in Study 1 and Study 2, respectively.[54] For truncal acne, 35.7% responded to trifarotene vs 25.0% to vehicle in Study 1. In Study 2, 42.6% responded to trifarotene vs 29.9 % to vehicle. Notably, these trials were the first (and still only) large-scale, well-controlled clinical trials to include prespecified endpoints of truncal acne lesion counts and treatment success on defined areas of the chest and back. In the stand-alone, single-arm, 52-week safety study (NCT02189629), investigator global assessment success rates of 65.1% and physician global assessment success rates of 66.9% were seen by Week 52.[55] LSRs were mostly mild-moderate and peaked early; maximum scores for facial events were reached at Week 1 and at Weeks 2 to 4 for truncal events. AEs were generally limited to application-site irritation (7.5% with trifarotene vs 0.3% with vehicle) and application-site pruritis (2.4% vs 0.8%).[55] Similar rates of treatment-emergent AEs were reported in a phase 4 trial (5.8% vs 2.5%).[11] These data show that, like earlier generations of retinoids, trifarotene is clinically efficacious at improving acne lesions. Despite RARγ selectivity, there were still some LSRs in the first 4 weeks of treatment; however, the researchers concluded that trifarotene was well tolerated and only 1 patient discontinued the study due to treatment-emergent AEs. Although it is the newest agent, the long-term safety and efficacy of trifarotene are supported by clinical trial data and 5 years of postmarket surveillance with no unexpected safety concerns; real-world evidence will continue to refine our understanding.

Clinical data of retinoids on acne sequalae. In addition to the resolution and prevention of acne lesions, there is a growing awareness of the importance of selecting treatments that can improve long-term skin health. Advances in our understanding of acne pathophysiology have also shed light on the mechanisms that lead to long-term sequalae, including scar formation and AIH.

A single-arm study of adapalene (0.3% gel) for 24 weeks found that 55.6% of patients showed an improvement of 1 or 2 grades from baseline on the full-face global scarring grade. The subject global assessment (SGA) for skin texture and acne scars improved for 83% and 89% of patients, respectively. Patients also reported an increase in quality of life (QOL), and 88% were satisfied with the effectiveness of the treatment.[41]

A randomized controlled trial (NCT03170596) reported by Afra et al[40] used a split-face approach to compare tazarotene (0.1% gel) to microneedling at a depth of 1.5 mm. Both treatments resulted in improvements to scarring; 29.4% of patients had more improvement on the microneedling side, 17.6% reported more improvement on the tazarotene side, and 52.9% had similar improvement on both sides of the face.[40]

In a 24-week split-face, vehicle-controlled study, total atrophic scar counts decreased by 55.2% on trifarotene-treated sides of the face vs 29.9% with vehicle; the mean absolute change from baseline was -6.2 ± 5.6 with trifarotene vs -2.8 ± 3.9 with vehicle. The between-side difference was evident by Week 2 and maintained through Week 24. The SGA was improved for 53.5% of patients on the trifarotene-treated side compared to 32.3% on the vehicle-treated side.[11]

A summary of key clinical trials investigating the effects of topical retinoids on acne sequelae is presented in **Table 2**. This table highlights primary studies for adapalene, tazarotene, tretinoin, and trifarotene, providing essential clinical study information, efficacy and safety data, and any available QOL or patient-reported outcome (PRO) data. A key focus of the table is endpoints directly related to sequelae (**Figure 1**), including quantitative and qualitative assessments of atrophic scarring, postinflammatory hyperpigmentation, and postinflammatory erythema. Where available, LSR frequencies/severity and AE-related discontinuations are included to aid interpretation. Together, these studies report reductions in active-acne endpoints and, in select designs, quantified changes in sequelae

TABLE 2. Key clinical trials investigating the effects of topical retinoids on acne sequelae

STUDY TITLE	CLINICAL STUDY DETAILS	EFFICACY/SAFETY	QoL/PRO DATA	SEQUELAE ENDPOINTS (SCARRING, PIH, PIE)	TOLERABILITY AND LOCAL SKIN REACTIONS
Study of trifarotene cream to assess risk of atrophic acne scar formation (START; NCT04856904)[11,56]	**Design:** Phase 4, multicenter, randomized, double-blind, vehicle-controlled, split-face study **Duration:** 24 weeks N=121 patients (aged 17–35 years) with moderate-to-severe facial acne and existing atrophic scars ≥2 mm (≥10 total)	**Primary endpoint met:** Absolute change from baseline in total atrophic acne scar count at Week 24 **Results:** −5.9 (trifarotene) vs −2.7 (vehicle), $P<0.0001$ **Scar reduction:** 55.2% vs 29.9% at Week 24 **Early efficacy:** Significant difference as early as Week 2 ($P=0.001$)	Patient education and compliance maintained throughout study, with an 81.8% completion rate[56]	**Primary focus:** Atrophic acne scarring **SGA success rate:** 31.3% vs 8.1% at Week 24 **IGA success rate:** 63.6% vs 31.3% at Week 24 **Post hoc analysis:** Greatest improvement in patients >27 years of age[56]	**TEAE incidence:** 5.8% (trifarotene) vs 2.5% (vehicle) **Most common:** Skin tightness (1.7% vs 0.8%) **Severity:** All events mild to moderate **Well tolerated:** Consistent with previous trifarotene studies
Efficacy and safety of trifarotene cream 50 µg/g for the treatment of acne-induced postinflammatory hyperpigmentation in subjects with Fitzpatrick Skin Types I–VI (LEAP; NCT05089708)[56,57]	**Design:** Phase 4, multicenter, randomized, double-blind, vehicle-controlled study **Duration:** 24 weeks N=123 patients (aged 13–35 years) with AIH	**Primary endpoint not met:** AIH ODS scores comparable at Week 24: −2.1 vs −2.1 ($P=0.8879$) **Week 12 significance:** −1.6 vs −1.1 ($P=0.03$) **Key secondary endpoint met:** PAHPI score reduction −18.9% vs −11.3% at Week 24	Comprehensive skincare routine provided, including SPF 30, likely contributed to outcomes[56]	**Primary focus:** AIH ODS, 9-point scale (0=clear, 8=severe) **PAHPI:** Composite score with early improvement at Week 12 (−8.4% vs −4.5%) **Post hoc analysis:** Greatest improvement in patients aged 21–28 years	**Safety profile:** All AEs mild or moderate in severity **Local tolerability:** Good in both trifarotene and vehicle groups **Consistent tolerability:** Aligned with previous trifarotene studies
OSCAR trial: adapalene 0.3% - benzoyl peroxide 2.5% gel and risk of formation of atrophic acne scars (OSCAR; NCT02735421)[8,58]	**Design:** Phase 4, 2-part study **Part 1:** Split-face design, 24 weeks (N=54) **Part 2:** Open-label extension, 24 weeks (N=45) **Total duration:** 48 weeks	**Part 2 primary endpoint:** Total atrophic acne scar count per half-face at Week 24 **Results:** 21.7% decrease at Week 24, 26.9% decrease at Week 48 **Rapid acne lesion reduction:** As early as Week 1 **IGA clear/almost clear:** 64.2% vs 19.4% ($P<0.0001$)	**Patient satisfaction:** 90.1% satisfied to very satisfied with treatment vs 59.0% with vehicle	**Primary focus:** Atrophic acne scar prevention **SGA:** 32.9% clear/almost clear with treatment vs 16.4% with vehicle at Week 24 ($P<0.01$) **Prevention approach:** Effective reduction of acne lesions reduced scar formation risk	**Tolerability data:** Not extensively detailed in available sources, but treatment was well completed through 48 weeks
Adapalene gel 0.3% in the treatment of atrophic acne scars (NCT01213199)[41]	**Design:** Phase 2, single-center, open-label, exploratory study **Duration:** 24 weeks + follow-up to 48 to 72 weeks N=20 patients (aged 18–50 years) with moderate-to-severe facial atrophic acne scars	**Investigator assessment:** 50% improvement in skin texture/scars at Week 24 **Patient assessment:** >80% reported improvement **Dosing:** Once daily (4 weeks), then twice daily (20 weeks)	**QoL:** Patients reported satisfaction with treatment and improvements in QoL **PRO:** Positive across multiple domains	**Primary focus:** Atrophic acne scar treatment **Skin texture improvement:** Measured by both investigator and subject assessments **Molecular markers:** Skin biopsy analysis in subgroup showed collagen synthesis changes	**Tolerability profile:** Favorable throughout study **Long-term follow-up:** Effects maintained through 48 to 72 weeks **Dosing tolerance:** Patients tolerated escalation from once to twice daily
Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in Black patients[9,10,56]	**Design:** Double-blind, vehicle-controlled study **Duration:** 40 weeks 68 Black individuals with moderate-to-severe PIH enrolled; 54 individuals completed 40 weeks of treatment	**Clinical response:** 92% of tretinoin vs 57% control achieved "lighter" or "much lighter" response ($P<0.001$) **Colorimetry:** Significant lightning; mean increase in L* value 2.7 vs 1.2 units ($P=0.05$)	**PROs:** High satisfaction with PIH improvement in tretinoin group	**Primary focus:** PIH **Assessment methods:** Clinical response scale (−2=much darker to 2=much lighter), colorimetry, lesion color grading **Epidermal melanin reduction:** 23% vs 3% with vehicle[10]	**AEs:** 50% of patients experienced moderate-to-severe erythema and desquamation **Retinoid dermatitis:** Documented as expected with tretinoin therapy

TABLE 2 CONTINUED. Key clinical trials investigating the effects of topical retinoids on acne sequelae

STUDY TITLE	CLINICAL STUDY DETAILS	EFFICACY/SAFETY	QoL/PRO DATA	SEQUELAE ENDPOINTS (SCARRING, PIH, PIE)	TOLERABILITY AND LOCAL SKIN REACTIONS
Tazarotene 0.1% cream for PIH and acne in darker skin[56,59]	**Design:** Double-blind, randomized, vehicle-controlled study **Duration:** 18 weeks N=74 patients with Fitzpatrick skin type of III to VI	**ODS:** 1.2 vs 0.2 reduction (P=0.010) **Pigmentary intensity:** 1.1- vs 0.5-grade reduction (P=0.044) **Area of hyperpigmentation:** 0.9- vs 0.4-grade reduction (P=0.026)	Treatment satisfaction and adherence maintained throughout study period	**Primary focus:** PIH **ODS scale:** Assessed pigmentary intensity, area, and degree of hypopigmentation **Significant improvements:** In both intensity and area of PIH lesions	**Irritation levels:** Average irritation, no more than trace **Dryness:** No more than mild in both groups **Superior tolerability:** Compared to other retinoids in PIH treatment
Comparison between microneedling daycare procedure and tazarotene 0.1% gel local application in acne scarring (NCT03170596)[40]	**Design:** Prospective, randomized, active-controlled, observer-blinded pilot study **Duration:** 6 months N=36 (34 completed) participants with facial acne scars	**Quantitative scores:** Significant improvement from baseline (median: 8.0–5.0) vs microneedling (7.0–4.5) **Comparable efficacy:** Both treatments showed similar improvement (P=0.42)	**Patient global assessment:** Scored on a 0 to 10 scale for patient satisfaction with improvement	**Primary focus:** Atrophic acne scarring **Goodman and Baron scores:** Both quantitative and qualitative assessments **Independent dermatologist scoring:** 0 to 10 scale for improvement assessment **6-month follow-up:** Sustained improvement demonstrated	**Comparable tolerability** to microneedling procedure **Nightly application:** Well tolerated over 6-month period **AEs:** Not extensively detailed but treatment completion was high
Adapalene gel 0.1% for topical treatment of acne vulgaris in African patients[59,60]	**Design:** Open-label study **Duration:** 12 weeks N=65 African patients with acne and hyperpigmentation	**AIH improvement:** Macules and density decreased in 66% of patients **Dual benefit:** Both acne lesions and hyperpigmentation improved	Patient satisfaction with dual acne and PIH improvement reported	**Primary focus:** AIH **Assessment:** Reduction in both number and density of hyperpigmented macules **Dark skin efficacy:** Demonstrated in African patient population	**Tolerability:** Well tolerated in dark-skinned patients **AEs:** Minimal irritation reported **Ethnic skin compatibility:** Good safety profile in African population

AE: adverse event; AIH: acne-induced hyperpigmentation; IGA: investigator global assessment; ODS: overall disease severity; PAHPI: Post-Acne Hyperpigmentation Index; PIE: postinflammatory erythema; PIH: postinflammatory hyperpigmentation; PRO: patient-reported outcome; QoL: quality of life; SGA: scar global assessment; TEAE: treatment-emergent adverse event

measures over defined durations; extrapolation should consider study design, duration, and population.[8,11,56]

Knowledge gaps, challenges, and future directions. Despite decades of use, several knowledge gaps and challenges remain in topical retinoid therapy. Evaluations of formulations, delivery systems, and combinations to further enhance stability, release, and tolerability are ongoing. In addition, ongoing trials seek to fill gaps in knowledge around key mechanistic questions and chronic use, particularly in individuals with richly pigmented skin. These gaps, coupled with the expanding number of agents and therapeutic options, support a highly individualized treatment approach.

Encapsulation technologies, such as solid lipid nanoparticles and nanostructured lipid carriers, have been investigated for effects on retinoid stability, irritation, and controlled release; clinical impact should be reported using prespecified outcomes.[61,62] Additional efforts involve dual-drug nanocarriers (eg, retinoic acid + minocycline) and next-generation vehicles that are under investigation for enhanced efficacy and tolerability.[1,4,14,63–65]

Combination therapy is also commonly used for acne, and fixed-dose combinations can simplify regimens. Building on early studies that showed the combination of benzoyl peroxide (BPO) and tretinoin was more effective than either agent alone, combination approaches have been an area of great interest. The first FDA-approved fixed-dose triple-combination therapy—topical clindamycin 1.2%, BPO 3.1%, and adapalene 0.15%—was approved in 2023.[66,67] Older tretinoin formulations were susceptible to BPO-mediated degradation, whereas optimized/microencapsulated tretinoin formulations have shown no measurable degradation with BPO and have been evaluated in randomized studies.[43,68,69] The staggered application of individual agents, such as BPO in the morning and a retinoid at night, has been investigated to improve efficacy and tolerability outcomes.[70–72]

Despite extensive completed and ongoing clinical research (summarized in **Table 2**), key mechanistic questions remain, including how individual retinoids modulate inflammatory pathways and cellular processes in vivo.[18,73] Moreover, while many head-to-head comparative studies exist, there is no consensus

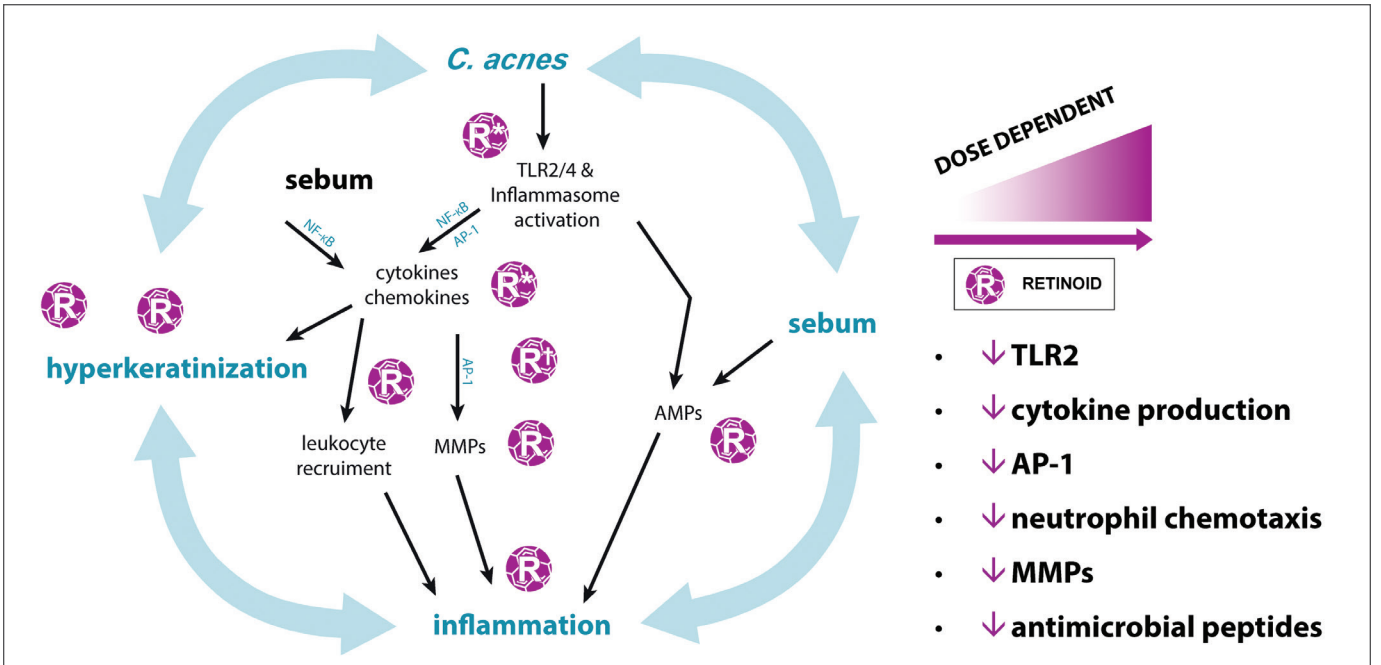

FIGURE 2. Retinoids and modulation of the innate immune system. Retinoids can decrease the activity of TLRs, reduce the production of key cytokines, inhibit the transcription factor AP-1, reduce neutrophil chemotaxis, and decrease the expression of AMPs.[18,74]
*Dose-dependent effect of retinoid has been shown.
†Demonstrated potent AP-1 inhibition by AMPs.
AMP: antimicrobial peptide; AP-1: activator protein-1; MMP: matrix metalloproteinase; NF-κB: nuclear factor–κB; TLR: toll-like receptor

on the superiority of one retinoid over another. Finally, more data are needed on long-term use in diverse populations (eg, age, gender, skin type, and geography).[14,75,76]

Given these challenges as well as the availability of newer agents such as trifarotene, the therapeutic landscape for acne is evolving toward highly personalized and targeted strategies.[14,62,65,77,78] Advances in pharmacogenomics, skin microbiome profiling, and digital dermatology may inform individualized retinoid selection based on genetic and phenotypic markers.[14,79,80]

RETINOID MOA BASICS: HOW RETINOIDS WORK ON ACNE AND IMPROVE SKIN QUALITY

The mechanisms by which retinoids exert their therapeutic effects are complex, involving a cascade of events that begins with metabolic activation and culminates in the modulation of gene expression, cellular behavior, and inflammatory pathways. Formulation-specific differences in efficacy and tolerability support selecting an agent aligned with the patient's presentation and expected tolerance.[47,51,81,82]

MOA

Activation of retinoids via a 2-step oxidative conversion pathway. Therapeutic activity of naturally occurring retinoids begins with activation of the retinoids via a 2-step oxidation process. Retinol is first converted to retinal by retinol dehydrogenase or alcohol dehydrogenase; retinal is then oxidized to retinoic acid by retinaldehyde dehydrogenase.[2,83] This metabolic conversion is crucial, because retinoic acid serves as the active ligand for nuclear receptors, while retinol itself has minimal biological activity.[2,84]

The lipophilic nature of retinoids necessitates specialized cellular binding proteins that facilitate intracellular transport.[84] Cellular retinol-binding proteins and cellular retinoic acid-binding proteins serve as essential chaperones that solubilize retinoids and retinoic acid in the aqueous cellular environment and direct them to appropriate metabolic enzymes.[14,22,85–87]

Cellular retinoic acid-binding protein (CRABP) 1 primarily facilitates retinoid catabolism by delivering all-trans retinoic acid to cytochrome P450 26A1 (CYP26) enzymes for degradation, thereby limiting retinoid bioavailability.[2,84] In contrast, CRABP2 promotes retinoid signaling by transporting retinoic acid directly to nuclear receptors through protein-protein interactions, markedly enhancing transcriptional efficiency compared to free retinoic acid.[84]

Retinoid interaction with nuclear hormone receptors. Retinoids exert their biological effects primarily through binding to nuclear hormone receptors that function as ligand-dependent transcription factors.[88] The retinoid signaling system comprises 2 distinct but functionally interconnected receptor families, RARs and RXRs, each existing in 3 distinct subtypes (α, β, and γ). These receptors form obligate heterodimers that bind to specific DNA sequences, called retinoic acid response elements (RAREs), located within the promoter regions of target genes. In the absence of ligand, RAR/RXR heterodimers repress transcription at RAREs. When retinoic acid binds a subtype of RAR, the heterodimer complex recruits transcriptional cofactors and initiates gene transcription.[14,22,85–87]

RARγ is the main RAR subtype in the skin, accounting for approximately 87% to 90%

of total RAR protein expression.[88] It plays an important role in epidermal maturation, keratinocyte differentiation, and maintaining skin barrier integrity. In addition to its structural functions, RARγ contributes to the anti-inflammatory properties of retinoids by modulating toll-like receptor 2 (TLR2) signaling and attenuating *Cutibacterium acnes*–induced inflammation (**Figure 2**).[5,18,74] This predominance of specific receptor subtypes in cutaneous tissue and the role of RARγ in restoring skin barrier integrity and reducing inflammation underlies the rationale for developing skin-selective retinoids with enhanced therapeutic indices.

RARα is widely expressed in many tissues, where it plays a crucial role in development and differentiation. In the skin, RARα is involved in multiple important roles in dermal biology but is present at much lower levels than RARγ (about 11%–13% of total RAR protein).[88] In some cellular contexts, RARα may act in opposing ways to RARγ, exerting antagonistic effects on gene expression, highlighting the complexity of retinoid signaling.[89,90] Unlike RARγ and RARα, RARβ is not typically detected in whole human skin, and its role remains largely unclear.[88]

Unraveling deeper mechanisms: non-nuclear and noncanonical pathways. While the nuclear receptor–mediated actions of retinoids are well characterized, our understanding of noncanonical and non-nuclear pathways is still emerging.[85,91–93] Recent evidence suggests retinoids can activate transcription through pathways that do not involve classical RAR-RXR heterodimer binding to RAREs.[93] Furthermore, retinoids may have cytoplasmic pro-apoptotic effects in sebocytes and keratinocytes that are not mediated by nuclear receptors. However, the composition, regulation, and functional impact of co-activator and corepressor complexes in acne-affected skin under retinoid treatment are not well characterized.[91] Likewise, the efficiency and selectivity of CRABP1 and CRABP2 in transporting retinoids to the nucleus—and their influence on noncanonical signaling—are not well understood.[92,94] Noncanonical retinoid signaling through CRABP1-mediated activation of kinase cascades, including ERK2 and CaMKII, may contribute to rapid cellular responses.[95] Moreover, the SUMOylation-dependent nuclear translocation of CRABP2 represents a regulatory mechanism, but factors controlling this process in different skin cell types remain unclear.[94] Exploring these less-understood mechanisms represents an area in retinoid research that may reveal potential targets for future therapeutic development.

Clinical evidence supporting different retinoid generation-specific MOAs. The molecular mechanisms of different retinoids can influence pharmacologic effects, as different retinoids can produce distinct transcriptomic signatures based on their receptor selectivity and binding affinities.[36,85]

Some first-generation compounds act without prior metabolic conversion, with transcriptional effects observed after application.[96] Moreover, first- and second-generation retinoids bind nonselectively to all RAR subtypes with varying affinities.[2] Tretinoin exhibits a high affinity for RARα, RARβ, and RARγ, resulting in broad transcriptional activity that includes therapeutic effects and known AEs. Local skin reactions and "retinization" may be a result of this nonselective binding.[4] Third-generation retinoids such as adapalene and tazarotene demonstrate selectivity for specific RAR subtypes in preclinical and clinical characterizations.[2] Adapalene exhibits preferential binding to RARβ and RARγ, while in vitro studies show that tazarotene can bind all 3 RAR subtypes but only activates gene transcription via RARβ and RARγ.[97]

Fourth-generation retinoids were developed through structure-activity relationship studies to increase receptor selectivity. The selectivity of trifarotene is attributed to its triaryl chemical scaffold, which binds the RARγ ligand-binding domain.[35,98] In vitro, trifarotene exhibited >16-fold and 65-fold selectivity for RARγ over RARα and RARβ, respectively.[35] Genetic analysis suggests that this selectivity facilitates skin-specific pathways and may minimize off-target effects mediated by other receptor subtypes.[35,99] Trifarotene has been shown to influence the gene networks involved in skin hydration (eg, *AQP3*), cell adhesion, and inflammatory responses (eg, *MMP13*, *CXCL13*). These genes would be expected to support restoration of skin homeostasis.[18,35]

Clinical efficacy of retinoids across generations is mechanistically linked to their interaction with RARγ, the common receptor that all retinoids bind. It is less clear, however, which pathways mediate skin irritation associated with retinoids.

SHIFTING PARADIGMS OF RETINOIDS AND THE IMMUNE SYSTEM

Our understanding of acne pathogenesis has undergone a significant paradigm shift, moving away from a simple infectious model centered on *C. acnes* to a more complex view of acne as a primary inflammatory disease originating in the pilosebaceous unit.[5,74] This framework highlights the multifaceted role of retinoids and their involvement across several pathways; a deeper understanding of this model may identify new opportunities to decrease irritation, improve long-term acne sequalae, and preserve skin health.

Direct action of retinoids on the inflammatory cascade. Emerging insights into the temporal dynamics of the immune response reveal a strong initial adaptive immune response that may dictate whether a lesion resolves cleanly or results in a scar. For example, patients who tend to form scars have been shown to have increased T helper cells (Th) in perilesional infiltrates relative to those less likely to form scars.[18,100–104] As **Figure 2** illustrates, *C. acnes*, a commensal bacterium, can activate TLR2 on the surface of keratinocytes. This triggers a downstream inflammatory signaling cascade involving nuclear factor–κB (NF-κB) and activator protein-1 (AP-1) transcription factor complexes, leading to the release of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α). In addition, matrix metalloproteinases (MMPs) from resident and invading immune cells are upregulated, leading to the breakdown of collagen and increased procollagen. Finally, sebum alterations, including changes in lipid composition, may also contribute to this inflammatory response, as dysregulation of Wnt/β-catenin signaling in sebaceous stem cells has been shown to promote comedogenesis.[4,20,22,92,100,105]

Retinoids can downregulate TLR2, NF-κB, and AP-1 signaling, thereby interrupting the cascade that leads to tissue destruction and scarring. Moreover, retinoids promote sebocyte differentiation and reduce progenitor-like activity (**Figure 3**).[106] In addition, recent transcriptomic studies have revealed that topical retinoids modulate gene expression patterns that reduce inflammation and promote healing of lesions. Retinoids stimulate dermal fibroblast procollagen production and downregulate profibrotic macrophages and expression of MMPs (MMP12, MMP13).[11,18,107]

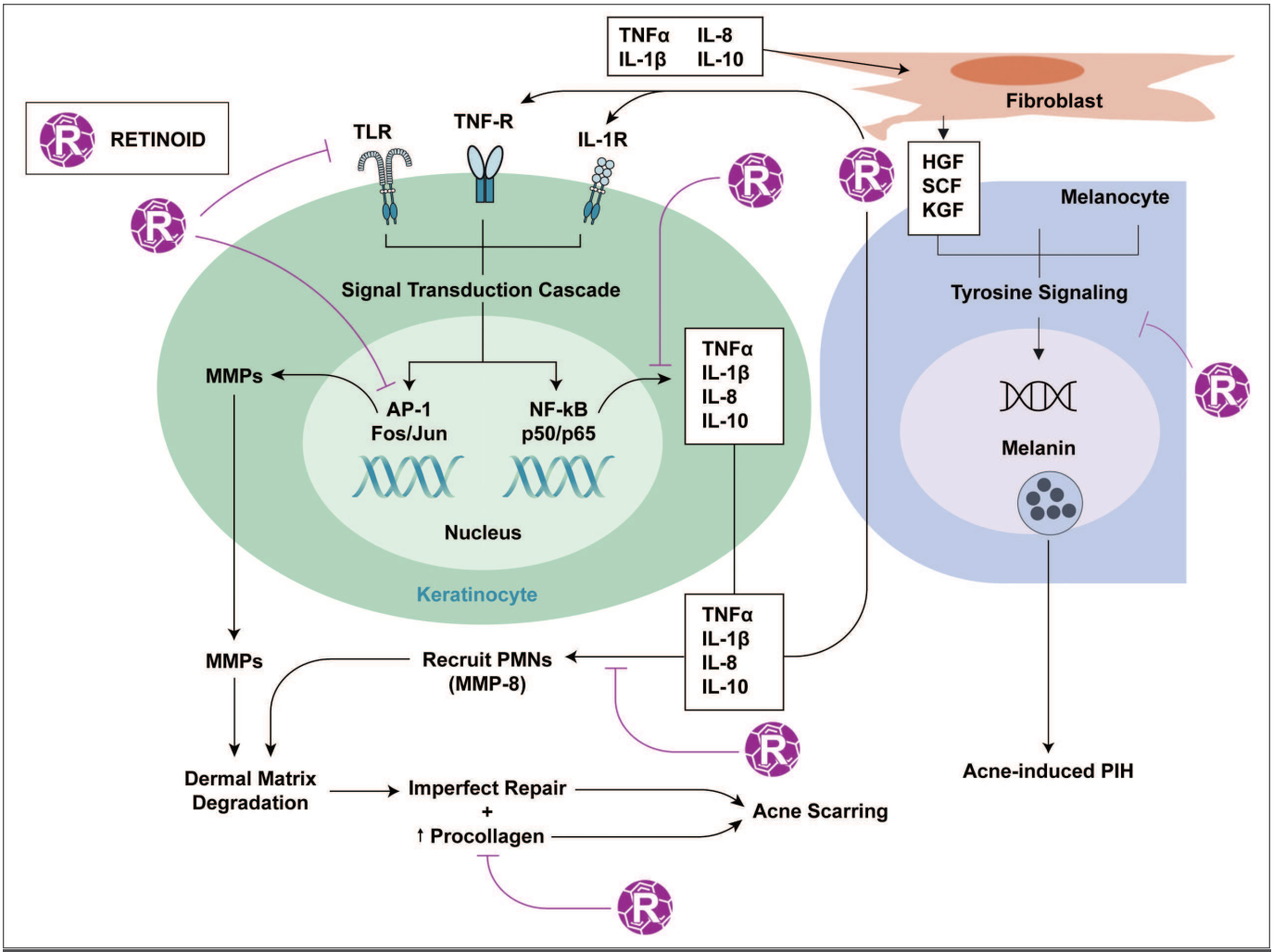

FIGURE 3. Acne pathogenesis and the role of retinoids. Key intervention points for retinoids, which can downregulate TLR2, MMPs, and pro-inflammatory cytokines, thereby interrupting the cascade that leads to tissue destruction, scarring, and AIH. Adapted from established models of acne pathogenesis.[5,18,74]
AIH: acne-induced hyperpigmentation; AP-1: activator protein-1; HGF: hepatocyte growth factor; IL: interleukin; KGF: keratinocyte growth factor; MMP: matrix metalloproteinase; NF-κB: nuclear factor–κB; PIH: postinflammatory hyperpigmentation; PMN: polymorphonuclear leukocyte; SCF: stem cell factor; TLR: toll-like receptor; TNFα: tumor necrosis factor α; TNF-R: tumor necrosis factor receptor

Indirect effects of retinoids on inflammation via modulation of keratinocytes. This inflammatory environment contributes to abnormal keratinocyte proliferation and differentiation and follicular hyperkeratinization, a process that contributes to the formation of microcomedones, the earliest subclinical acne lesion.[14] Retinoids may help counteract this process through comedolytic and anticomedogenic effects. Retinoids normalize desquamation and promote corneocyte shedding, reducing the likelihood of follicular occlusion and further recruitment of inflammatory cells.[4] Retinoids help prevent formation of new comedones by helping repair the skin barrier. Signaling and structural changes associated with follicular remodeling have been reported.[3,85,92,109]

KNOWLEDGE GAPS, CHALLENGES, AND FUTURE OPPORTUNITIES

Receptor-specific actions. The majority of discourse in acne on the activity of retinoids has focused on RAR binding; however, it is worth remembering that functional RAR requires an RXR heterodimeric partner. Recent studies have shown that receptor competition mechanisms exist between RAR and RXR, wherein RAR can "silence" RXR activity in heterodimers unless both receptors are ligand bound.[91] However, the precise molecular mechanisms underlying these competitive interactions in acne-affected skin remain poorly understood. While RARγ is the predominant RAR expressed in skin, the functional differences between RAR subtypes in mediating canonical vs noncanonical signaling pathways in acne pathogenesis are not fully elucidated.[85,91] Finally, RXR can form heterodimers with multiple nuclear receptors beyond RAR, for complex signaling crosstalk.[91] However, these interactions are understudied in the context of acne treatment.

Gene expression and retinoid function. While transcriptomic analyses have identified retinoid-regulated genes in keratinocytes, the relationship between specific DNA sequence elements and tissue-specific gene expression patterns remains incompletely characterized.[92]

Genetic variations in RAR genes have been shown to influence clinical outcomes in systemic retinoid therapy. Alzoubi and colleagues[110] reported that a cluster of single-nucleotide polymorphisms in the RARα gene was more common in patients who experienced AEs such as elevated liver enzymes during isotretinoin therapy. Equivalent pharmacogenomic investigations focusing on topical retinoids in acne, including those involving RXRα, are currently lacking. There is a need for studies comparing the efficacy of different retinoids in acne treatment. Current systematic reviews suggest minor differences in efficacy between topical retinoids, but head-to-head comparative studies with standardized endpoints remain scarce.[20]

Clinical response variability. There is limited understanding of the factors that predict individual patient efficacy and tolerability responses to different acne therapies. Genetic factors affecting retinoid metabolism and receptor sensitivity may contribute to individual variability, but predictive biomarkers for treatment response have not been established. Topical retinoids are used in long-term maintenance therapy; however, most studies of topical retinoids are 12 weeks or shorter, with few longer-term studies and fewer still long-term controlled studies. Thus, personalized therapy, long-term, and maintenance studies remain areas in need of further investigation.

Biomarkers before and after retinoid studies. While CRABP2 expression confirms RAR activation in the sebaceous gland, it does not correlate with clinical outcomes.[111] In contrast, the suppression of MMP2 strongly correlates with wrinkle improvement in photoaging (r=0.54; P=0.01), though its utility as an acne biomarker is unconfirmed.[111] The effects of different generations of topical retinoids on acne-related inflammatory cytokines, such as IL-17, IL-8, and TNF-α, are also not well understood. A biopsy study published in 2021 analyzed gene expression following the use of topical trifarotene for 27 days. A unique set of 67 genes involved in cell migration, inflammation, and extracellular matrix were modulated with trifarotene, including genes linked to secreted phosphoprotein 1 (SPP1) macrophages. Of interest, the authors reported that the gene profile associated with trifarotene was highly similar to that of naturally healing comedones, suggesting that the genes regulated by trifarotene could be associated with acne resolution.[85] An earlier gene study also reported that SPP1 was part of a gene cluster involved in extracellular matrix-receptor interactions that was upregulated in samples of inflammatory acne.[112] Despite these informative studies, the temporal relationship between retinoid application, biomarker modulation, and clinical improvement is still poorly understood, and the predictive value of early biomarker changes for long-term outcomes requires further investigation.[20,111]

Immune cell responses. Our understanding of the specific effects of topical retinoids on cutaneous dendritic cell maturation, neutrophil function, macrophage polarization (M1 vs M2), and the Th17/Treg balance in acne lesions is in an early stage.[9,113–118] Elucidating the role of RAR subtype selectivity in these pathways is an important area of investigation. Likewise, cell-specific responses within the pilosebaceous unit are not well defined, obscuring how the interplay between keratinocytes, sebocytes, and immune cells drives therapeutic effects following retinoid application.[119–121]

EDUCATIONAL INITIATIVES: A DUAL PERSPECTIVE

Optimizing retinoid therapy requires a concerted educational effort directed at both physicians and patients.

From the physician perspective. There is a clear need for ongoing education for dermatologists.[5] There may be a perception that there is "nothing new," as topical retinoids have been used to treat patients with acne since the 1970s. Moreover, prescribing habits can be ingrained, leading to slow adoption of new therapies as they become available. To ensure that patients receive the best option, retinoid education should include basic prescribing information to cover the key pharmacologic and pharmacokinetic distinctions between retinoids, the clinical relevance of receptor selectivity (eg, the advantages of RARγ specificity), the evolving clinical data supporting their use for both facial and truncal acne, and the data supporting their use in the management of acne sequelae.[5,11,54] A deeper understanding of the tolerability profiles, formulation science, and effective use of adjunctive strategies, such as barrier-repairing moisturizers, can help providers personalize regimens, proactively manage irritation, and improve patient adherence.[4,23] Educational programs, including workshops, seminars, and online courses focused on the latest research, are important for keeping clinicians abreast of this evolving field.

An area of discussion for clinicians involves personalizing acne therapy decisions to patient concerns. AIH is one example. Dark marks are frequently a patient's primary concern, and they may seek treatment outside of the window of active acne; therapeutic regimens that do not take that into account are likely to have poor adherence.[59,122] Adult acne is increasingly common, and patients may have additional concerns or conditions that need to be considered alongside acne management.[123] Existing tools, such as skin quality scales, discussion guides, and PRO tools, can be used to facilitate discussion.[124,125] Similarly, practical questions about layering retinoids with moisturizers or other products are common and have been studied with certain retinoids.[23] Finally, data on the stability of various retinoid formulations when used with ingredients such as hyaluronic acid or glycerin may be valuable for guiding patient recommendations.

From the patient perspective. For patients, successful therapy hinges on clear, accessible education. Clinicians must actively work to dispel persistent myths surrounding retinoids, such as unsupported fears of skin thinning, extreme sun sensitivity, or incompatibility with moisturizers.[4,16,23,61] Helping patients develop realistic expectations plays an important role in fostering adherence and long-term engagement with therapy. This includes counseling on the initial retinization phase and providing a timeline for improvement rooted in clinical data.[104] Emphasizing the long-term skin health benefits, including acne scar prevention and other improvements in skin quality, may improve treatment satisfaction and adherence by framing the therapy as part of a long-term skin care plan.[11,16,126] There is a need for patient-centered educational materials that address these concerns in an accessible manner.

CONCLUSION

Topical retinoids have been used in acne treatment for decades and have evolved over 4 generations of therapeutic agents. Full understanding of these nuclear receptor agonists, their clinical data, and their MOA in acne will help healthcare practitioners use them effectively and choose between the

available retinoids and retinoid formulations. To realize the full clinical application of topical retinoids, alignment is needed between mechanistic insights, practical application, and patient education. Counseling that sets expectations for the initial adjustment period and outlines practical mitigation strategies can support adherence and outcomes and counter misinformation. Ongoing attention to patient education and emerging clinical findings can help align treatment choices with individual goals and improve care for people with acne vulgaris.

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