



# 50 Years of Topical Retinoids for Acne: Evolution of Treatment

Hilary Baldwin<sup>1,2</sup> · Guy Webster<sup>3</sup> · Linda Stein Gold<sup>4</sup> · Valerie Callender<sup>5,6</sup> · Fran E. Cook-Bolden<sup>7</sup> · Eric Guenin<sup>8</sup>

Published online: 19 April 2021

© The Author(s), under exclusive licence to Springer Nature Switzerland AG part of Springer Nature 2021

## Abstract

Since the US Food and Drug Administration (FDA) approved tretinoin in 1971, retinoids alone or combined with other agents have become the mainstay of acne treatment. Retinoids act through binding to retinoic acid receptors, altering expression levels of hundreds of cellular proteins affecting multiple pathways involved in acne pathogenesis. Retinoids have evolved from first-generation agents, such as tretinoin, through chemical modifications resulting in a second generation (etretinate and acitretin for psoriasis), a third generation (adapalene and tazarotene) and, most recently, a fourth (trifarotene). For all topical retinoids, local irritation has been associated with poor tolerability and suboptimal adherence. Efforts to improve tolerability have utilized novel delivery systems and/or novel agents. This qualitative literature review summarizes the evolution of the four topical single-agent retinoids available for the treatment of acne in the US today and their various formulations, presenting the rationale behind their development and data from key studies.

## 1 Introduction

In 1971, the US Food and Drug Administration (FDA) granted approval of the first topical retinoid, tretinoin 0.05% solution (also: all-trans retinoic acid [ATRA]; vitamin A acid), for use in acne vulgaris [1]. In the years that followed, novel retinoids, formulations, and combinations were introduced to improve efficacy and tolerability. Today, topical retinoids, either alone or in combination with benzoyl peroxide or topical antibiotics, are the mainstay of acne therapy

### Key Points

Topical retinoids—alone or in combination with other agents—have become the mainstay of acne treatment in the 50 years since the initial approval of tretinoin.

The local irritation associated with topical retinoids, which is most prominent in the first few weeks of therapy, has been associated with poor treatment adherence.

Further research has resulted in new generations and formulations of retinoids with improved stability and greater tolerability, which offer today's clinical dermatologists better options for ensuring patient adherence and consequently treatment success.

✉ Hilary Baldwin  
HBaldwin@acnetrc.com

<sup>1</sup> The Acne Treatment and Research Center, Brooklyn, NY, USA

<sup>2</sup> Robert Wood Johnson University Hospital, New Brunswick, NJ, USA

<sup>3</sup> Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

<sup>4</sup> Henry Ford Hospital, Detroit, MI, USA

<sup>5</sup> Callender Dermatology and Cosmetic Center, Glenn Dale, MD, USA

<sup>6</sup> Howard University College of Medicine, Washington D.C., USA

<sup>7</sup> PLLC and Department of Dermatology, Mount Sinai Hospital Center, New York, NY, USA

<sup>8</sup> Ortho Dermatologics, a Division of Bausch Health US, LLC, Bridgewater, NJ, USA

[2–6]. They are strongly recommended for acne management and treatment by the American Academy of Dermatology based on consistent, good-quality, patient-oriented evidence [5]. In addition, topical retinoids have provided treatment options in other dermatological conditions including atrophic scarring [7], postinflammatory hyperpigmentation [8], photodamaged skin [9], and melasma [10]. In this qualitative literature review, we focus on key aspects of the 50-year evolution of single-agent topical retinoids specifically for the treatment of acne vulgaris.

Acne pathology and the mechanisms of action of retinoids are complex and multifactorial. Major factors in acne pathogenesis include epithelial hyperproliferation, increased sebum production with concurrent alterations in its composition, increased *Cutibacterium acnes* population, and follicular and perifollicular inflammation [11]. These can impair normal functioning of the pilosebaceous unit, leading to the formation of microcomedones, comedones, inflammatory lesions, or nodules.

Retinoids, analogs of vitamin A, have pleiotropic effects including comedolysis and reduction of microcomedonal formation. They have been shown to benefit both comedonal and inflammatory acne [12, 13]. The mechanisms through which these effects occur are believed to involve binding to retinoic acid receptors (RARs). Three subtypes, RAR- $\alpha$ , RAR- $\beta$ , and RAR- $\gamma$ , are known, of which RAR- $\gamma$  expression is highest in human skin [14, 15]. Different retinoids vary in their receptor subtype affinity and may be more selective for one receptor versus another. The hypothesis that receptor subtype selectivity might improve topical retinoid efficacy and/or tolerability fueled the search for, and eventual discovery of, subtype-selective retinoids. However, no evidence exists to suggest that retinoid receptor subtypes influence efficacy or tolerability. Indeed, some retinoids have the same receptor binding yet differ in potency and tolerability.

Tretinoin, the principle active metabolite of vitamin A, binds with similar affinity to all three subtypes, but binding to RAR- $\gamma$  is key to its effects. This binding activates the RAR- $\gamma$  complex with the retinoid X receptor (RXR)- $\alpha$  [16, 17]. The activated complex in turn binds to specific DNA promoter sequences known as retinoic acid response elements (RAREs), stimulating gene transcription through transactivation and resulting in activation of more than 300 genes that alter expression levels of hundreds of proteins [16, 18].

Tretinoin also exerts indirect effects on DNA lacking RAREs through downregulation of pro-inflammatory nuclear transcription factors such as AP-1, which normally upregulates the matrix metalloproteases responsible for acne scar formation [19]. The direct and indirect effects of retinoids result in inhibition of leukocyte migration, cytokine production, and arachidonic acid metabolism, as well as downregulation of toll-like receptor (TLR) activation. Collectively, these effects reduce inflammation, which is now increasingly recognized as a common feature of all acne lesions, whether clinically inflamed or not [11, 19].

## 2 Evolution of Topical Retinoids for Acne

### 2.1 First- and Second-Generation Retinoids

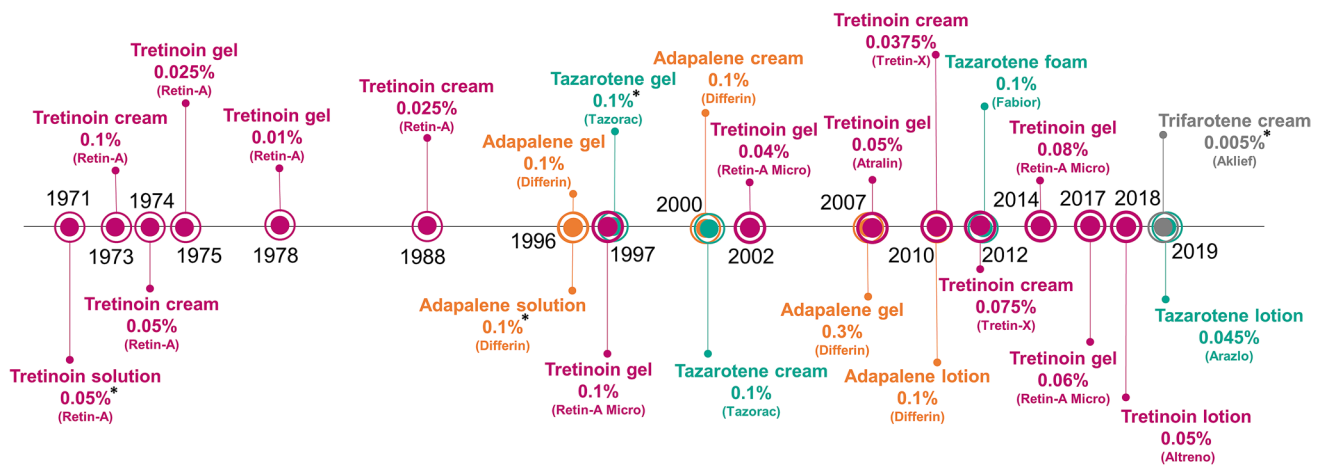
The effects of tretinoin on acne were first described in 1969 [20]. Two years later, it became the first retinoid to be

approved for use in treating acne by the US FDA (Fig. 1) [1]. Tretinoin, along with its 13-*cis*-retinoic acid isomer isotretinoin (FDA approved only for oral use in acne) and its 9-*cis*-retinoic acid isomer alitretinoin (used in treating Kaposi's sarcoma)—all metabolites of vitamin A—constitute the first generation of clinically useful retinoids [21].

Tretinoin, as originally approved, had room for improvement. Irritation at the application site—now believed to be due in large part to the hydroalcoholic vehicle used in the original formulation—was pronounced [22] and led to speculation that retinoid efficacy went hand-in-hand with irritation [23]. In addition, tretinoin in the original formulation was unstable when exposed to light and oxygen [18], which led to limitation of daytime use. Chemically, the long polyene sidechain of tretinoin provides the flexibility to adopt multiple configurations, some of which can bind to receptors other than its target [24]. It could also isomerize to 9-*cis*-retinoic acid, a ligand for RXRs. Replacing the flexible polyene sidechain with more rigid ones could therefore benefit both stability and selectivity, the latter of which might be expected to translate into better tolerability and/or efficacy [24]. After a second generation of retinoids was produced by modification of the cyclic end group, resulting in the systemic drugs etretinate and acitretin for the treatment of psoriasis [24–26], a third generation of retinoids was produced by replacing the polyene sidechain with rigid, aromatic structures.

### 2.2 Third-Generation Retinoids

In 1996, topical adapalene 0.1% became the first of these conformationally rigid, third-generation compounds to be approved for the treatment of acne (Fig. 1) [27]. Although adapalene acts primarily via RAR- $\gamma$ , similar to tretinoin, the structural and biochemical properties of these drugs vary considerably. While tretinoin binds to RAR- $\alpha$ , RAR- $\beta$ , and RAR- $\gamma$  as well as to cytosolic retinoic acid binding proteins (CRABPs), adapalene binds selectively to RAR- $\beta$  and RAR- $\gamma$  only and is stable in the presence of light and benzoyl peroxide [18, 28]. Furthermore, the percutaneous absorption of topical adapalene appeared to be considerably less than that of tretinoin [29, 30], which could be beneficial if irritation were caused by excess absorption [31]. Adapalene was specifically engineered to a particle size of 3–10 microns to allow preferential delivery into hair follicles [18]. As comparative studies of adapalene and tretinoin demonstrated varying results, a meta-analysis of five clinical studies with 900 patients with mild-to-moderate acne was conducted to compare adapalene 0.1% gel with tretinoin 0.025% gel [32]. There were no significant differences between these agents at week 12 in reduction of inflammatory, noninflammatory, or total lesion counts. However, adapalene demonstrated superior local tolerability over tretinoin (overall mean side



**Fig 1** Timeline of FDA approval dates for single-agent topical retinoid formulations for the treatment of acne (Source: [www.accessdata.fda.gov/scripts/cder/daf](http://www.accessdata.fda.gov/scripts/cder/daf)). \*First approval for the active ingredient. All other dates shown are for the first approval of new formulation (e.g.,

gel, cream, lotion) or new concentration. Colors indicate type of retinoid. Note: Some formulations shown may be discontinued or may be sold as generics or under different brand names

effect score  $p < 0.001$ ). Although the basis for this superior tolerability was never elucidated, at the time many attributed it to the RAR- $\beta/\gamma$  subtype selectivity of adapalene, further fueling the search for other selective retinoids.

Shortly after the approval of adapalene, another conformationally rigid, third-generation retinoid, tazarotene gel (0.1%), was approved for use in mild-to-moderate acne in 1997 (Fig. 1) [33]. Tazarotene is an ethyl ester prodrug that is converted to the active component, tazarotenic acid. Molecular features were introduced to avoid accumulation of the compound or its metabolites in fatty tissue and ensure rapid systemic elimination [24]. Like adapalene [28], tazarotene is stable to UV light [34] and its metabolite, tazarotenic acid, binds RAR- $\beta$  and RAR- $\gamma$ , but not RAR- $\alpha$  or RXRs [24]. A multicenter, double-blind, randomized trial comparing once-daily tazarotene 0.1% gel to once-daily tretinoin 0.025% gel in 143 patients with mild-to-moderate facial acne found that tazarotene was significantly more effective in reducing noninflammatory lesion counts ( $p \leq 0.05$ ) and numerically more effective in reducing the total inflammatory lesion count [35]. At week 4, however, tazarotene was associated with more peeling, dryness, and burning than tretinoin ( $p < 0.05$ ). Another multicenter randomized trial over 12 weeks compared once-daily tazarotene 0.1% gel and once-daily adapalene 0.1% gel in patients with mild-to-moderate facial acne [36]. Tazarotene was associated with significantly greater treatment success (78% vs 52%;  $p < 0.05$ ) and reductions in severity, noninflammatory lesion count, and inflammatory lesion count than adapalene ( $p < 0.05$ , all). Tazarotene, however, was significantly associated with transiently greater levels of burning, pruritis, and erythema than adapalene at week 4 ( $p < 0.01$ ) and greater levels of peeling at weeks 4 and 8 ( $p < 0.05$ ). Interestingly, another

12-week study comparing once-daily tazarotene 0.1% cream with once-daily adapalene 0.1% cream found that tazarotene provided a significantly greater treatment success rate (77% vs 55%;  $p \leq 0.01$ ) and a significantly greater reduction in comedone count ( $p \leq 0.001$ ), with peeling and burning scores that were significantly higher than those for adapalene at weeks 4 and 8, but not significantly different at week 12 [37]. When considered in light of the previously described tazarotene studies, the tolerability results cast doubt on the hypothesis that receptor subtype specificity alone could explain retinoid tolerability.

Although few studies have compared these three agents, one retrospective study used clinician evaluations of patient photographs from seven phase IV, randomized, double-blind, parallel-group studies of tazarotene (0.1% gel and 0.01% cream), adapalene 0.1% gel, or tretinoin (0.1% micro-sponge and 0.025% gel) [13]. Photographs were assessed for clinically meaningful (1-grade improvement on a 7-point severity scale) and clinically significant ( $\geq 2$ -grade improvement) changes in inflammatory acne severity after 12 or 15 weeks of treatment [13]. Overall, a higher proportion of retinoid-treated participants showed clinically meaningful and clinically significant improvements versus vehicle-treated participants ( $p \leq 0.001$ , both). When comparing active treatments, tazarotene 0.1% gel showed greater clinically significant improvements compared with adapalene 0.1% gel ( $p \leq 0.001$ ) and tretinoin 0.025% gel ( $p \leq 0.01$ ), but not tretinoin 0.01% micro-sponge. Caution must be taken, however, when interpreting these results due to the retrospective nature of the study.

Recently, a systematic review also compared these three agents and concluded that tretinoin (0.05% cream and 0.04% and 0.1% microsphere) worked more rapidly than tazarotene

(0.1% foam and 0.1% cream) in reducing inflammatory lesions and that adapalene (0.1% lotion and 0.1% and 0.3% gel) was better tolerated than tazarotene and tretinoin [38]. A major caveat to this interpretation, however, is that a wide variety of concentrations and formulations of all three agents (some in trials designed to establish non-inferiority) were included, leaving the relevance to any particular comparison open to question. Adapalene has often been considered the best tolerated but also the least effective of these three retinoids, while tazarotene has been considered the most efficacious but least well tolerated [22, 39]. However, factors such as retinoid concentration and vehicle formulation (discussed subsequently) can also affect tolerability and efficacy [2, 40].

### 2.3 Fourth-Generation Retinoids

The most recently approved topical retinoid for acne treatment is the fourth-generation, first-in-class, purely RAR- $\gamma$  selective agent trifarotene 0.005% cream [41]. Approved in 2019 for acne treatment (Fig. 1), it was designed to be stable in keratinocytes but rapidly metabolized if systemically absorbed. In the 12-week, double-blind, phase III PERFECT 1 and PERFECT 2 studies, a total of 2420 patients with moderate facial and truncal acne received either once-daily trifarotene 0.005% cream or vehicle for 12 weeks [42]. Rates of success (clear or almost clear skin at week 12) and reductions in inflammatory and noninflammatory lesion counts were significantly higher with trifarotene than vehicle in both studies ( $p < 0.05$ , all). The most common adverse events (AEs) were application-site irritation (trifarotene vs vehicle: 7.5% vs 0.3%) and application-site pruritis (2.4% vs 0.8%) [43]. Potent and selective binding to the RAR- $\gamma$  receptor was thus efficacious but failed to completely abrogate the skin irritation frequently observed with retinoid treatments.

## 3 Topical Retinoid Tolerability and Adherence

Several skin reactions are commonly associated with irritation from topical retinoids, including dryness, erythema, and peeling [44]. In 2015, Culp et al. examined the tolerability of topical retinoids in acne treatment by analyzing data from 34 clinical studies that provided safety data for tretinoin, adapalene, or tazarotene [44]. Table 1 summarizes the incidence rates of AEs reported in those trials. Rates of burning, irritation, erythema, and dry skin were remarkably varied for the same retinoid in different study reports. For example, incidence of erythema was reported to be 4.0% for tazarotene foam 0.1% in one study and 95.0% for tazarotene gel 0.1% in another [45, 46]. These data, however, are from various concentrations and vehicle formulations for each retinoid, and tolerability had been reported using different

scales. Nonetheless, as has been observed across multiple studies, AEs increase in severity with increasing retinoid concentration regardless of vehicle or retinoid [38, 44]. Further, increases in mean scores for irritation, dryness, and erythema were most frequent during the first few weeks of treatment regardless of retinoid concentration and vehicle formulation [42, 47]. This is believed to result from the process of normalizing desquamation in the epidermis, during which corneocyte arrangement is disrupted and cohesion is lost, leading to symptoms of irritation. After 1–2 weeks of continued treatment, the rearrangement is complete and irritation generally resolves [2].

A split-face study of retinoid tolerability in 253 healthy volunteers, each using one of several topical retinoids (tazarotene, tretinoin, or adapalene) in various dosages/formulations, identified four factors influencing tolerability: retinoid concentration, vehicle formulation, skin sensitivity, and the specific retinoid [47]. Of these, skin sensitivity had the greatest influence. Other factors that may influence tolerability include frequency of use, length of exposure, mode of application, sun exposure, and the use of moisturizers [48]. Additionally, a study of topical tretinoin identified the concurrent use of other topical medications as a predictor of increased AEs (odds ratio 1.88;  $p < 0.05$ ) [49].

Tolerability is important for topical retinoids as the occurrence of side effects correlates with poor adherence, which reduces response to treatment [50]. In 34 topical retinoid clinical studies, only a small percentage of patients dropped out [44], although it is possible that some who did not formally discontinue therapy may have reduced their medication usage. Furthermore, clinical study populations do not represent real-world patient populations. In trials, carefully standardized instructions are provided, frequent follow-up visits encourage adherence, patients may be told they are being monitored, and they are being paid to use medications (which are provided at no cost) [44, 51]. These conditions do not apply in clinical practice.

Medication adherence can refer to new prescriptions dispensed within a defined number of days after being ordered or to having a prescription refilled within a defined number of days [52], the latter of which could be affected by tolerability [53, 54]. Adherence (new prescription dispensed) to topical and systemic acne medications was examined for 109 acne medications prescribed at a university dermatology clinic; patients were queried by telephone [55]. The non-adherence rate for any topical medication was 13% and the rate for topical retinoids was 30%. Cost and forgetfulness were common, unprompted reasons given for nonadherence. Adherence (medication consumed as estimated by prescription refills) to acne medications was also explored in a retrospective study of mostly young acne patients enrolled in Medicaid [56]. This study assessed Medication Possession Ratio (MPR), a metric calculated by dividing ‘the number

**Table 1** Incidence of adverse events for any single-agent topical retinoid formulation approved for acne

Retinoid	No. studies	<i>N</i>	Skin burning (%)	Cutaneous irritation (%)	Erythema (%)	Dry skin (%)
Tretinoin microsphere 0.1% gel [44]	2	78; 161	7.7; 11	3.8; 23	5.1; 5.0	2.6; 32
Tretinoin microsphere 0.04% gel [44]	3	78; 55; 20	2.6; 2.1; 23.5	6.4; 23.6; NR	1.3; 8.5; NR	2.6; 29.7; NR
Tretinoin 0.05% gel [44]	1	161	8	5	5.0	14
Tretinoin 0.05% cream [44]	1	35	23/11 <sup>b</sup>	NR	65.7/45.7 <sup>b</sup>	11/23 <sup>b</sup>
Tretinoin 0.025% gel [44]	3	464; 635; 846	1; 6; NR	3; <1; NR	1.0; 5.0; NR	3; 8; <1
Tretinoin 0.05% lotion [69]	2 <sup>a</sup>	767	< 1.0 [73]	< 1.0 [73]	1.4 <sup>c</sup>	3.7 <sup>c</sup>
Adapalene 0.1% gel [44]	3	258; 85; 24	5; NR; NR	NR; 5; NR	NR; 6; 35.0	7; 5; NR
Adapalene 0.3% gel [44]	2	90; 261	30; 6	NR	0; NR	0; 14
Adapalene 0.1% cream [44]	2	130; 87	NR; 5	NR; 2	NR; 2	3; 8
Adapalene 0.1% lotion [44]	2	130; 533	NR	NR	NR	4; 9
Tazarotene 0.1% gel [44]	1	24	NR	NR	95.0	NR
Tazarotene 0.1% foam [44]	1	373; 371	0; 2.0	11.0; 18.0	4.0; 9.0	8.0; 6.0
Tazarotene 0.1% cream [44]	2	86; 90	1; 51	2; NR	6; 6	7; 7
Tazarotene 0.045% lotion [72]	2 <sup>a</sup>	779	0 [74]	< 1.0 [74]	1.8 <sup>c</sup>	3.6 <sup>c</sup>
Trifarotene 0.005% cream [43]	2 <sup>a</sup>	1220	NR	7.5	NR	NR

Note: tolerability was reported using different terms and scales in different studies

Table adapted from the Culp et al. 2015 systematic review [44]; for three drugs approved after publication of the manuscript, results from pivotal studies of those formulations have been added above

NR not reported

<sup>a</sup>Two pooled studies

<sup>b</sup>Split-face study where second value indicates tretinoin in conjunction with facial moisturizer

<sup>c</sup>Treatment-related adverse events

of days of medication supplied within the refill interval' by 'the number of days in the refill interval' [57]; an MPR of 1.0 indicates all medication was consumed. In patients aged 0–64 years ( $N = 24,438$ ), of whom 89% were < 18 years of age, the average MPR was 0.34 for all acne drugs and 0.31 for topical retinoids. For all acne drugs, only 11.7% of patients were adherent ( $MPR \geq 0.80$ ) [56]. Reasons for non-adherence were not examined, but medication type (e.g., topical retinoids, oral antibiotics) affected adherence. Finally, another study of 250 patients with acne (96% mild or moderate) who were prescribed topical medications found 54.4% adherence (treatment not discontinued before the scheduled time) [58]. Side effects were reported by 41.3% of the 75 patients treated with topical single-agent retinoids. Of the patients on retinoid monotherapy who discontinued ( $n = 30$ ), 50% discontinued due to side effects.

## 4 Improving Retinoid Tolerability

Several different approaches have been taken to improve topical retinoid tolerability, including short contact therapy and new vehicle formulations, which allow for lower-dose formulations.

### 4.1 Short Contact Therapy

Short contact therapy minimizes the length rather than frequency of exposure through rinsing off the product after an appropriate amount of time. In a multicenter, single-arm study, tretinoin 0.05% cream applied once daily for 30 minutes for up to 32 weeks (mean treatment duration: 12 weeks) was associated with efficacy similar to that of its standard once-daily administration regimen, with better tolerability (17.6% mild skin irritation, 5.4% discontinuation due to skin irritation) [59]. Since skin irritation is greatest during the first few weeks of therapy, short contact application of retinoids (30–60 min) has been recommended for the first 2–4 weeks to improve tolerability [2].

### 4.2 Non-Daily Application

Topical retinoids for acne treatment are indicated for once-daily use. In order to reduce the frequency of exposure, however, retinoids could be applied every other day. In a double-blind, randomized, parallel-group study, alternate-day tazarotene 0.1% gel use was compared with once-daily adapalene 0.1% gel in patients with mild-to-moderate acne [60]. Both treatment regimens showed similar efficacy and tolerability, indicating that alternate day use of tazarotene

0.1% gel is as effective and may provide better tolerability than once-daily use.

### 4.3 Role of Vehicle Formulation

Most research on improving the efficacy and tolerability of topical retinoids has focused on the vehicle formulation [61]. The vehicle largely determines the absorption characteristics of the topical agent and may itself modify cutaneous properties to allow penetration of the active ingredient. Furthermore, vehicles can be formulated to increase skin hydration and decrease transepidermal water loss [62]. Vehicle optimization generally aims to ensure slow delivery of appropriate amounts of retinoids specifically to their site of action, the pilosebaceous unit, while reducing uneven drug distribution and penetration into the deep epidermis and dermis [21]. Much of the evolution of topical retinoids has involved improvements in vehicle, as can be seen in Table 2, which summarizes efficacy data for currently approved topical retinoid formulations for acne. Given that cross-trial comparisons are problematic due to factors such as differences in study design and baseline patient populations, perhaps the most notable trends are those towards larger trials with stricter success criteria over time.

As indicated in Table 1, reported AE rates for a given topical retinoid vary markedly, part of which undoubtedly reflects dosage and formulation differences. Further, in addition to the caveats involved in cross-trial comparisons, the wide variety of terms used to describe AEs and scales to assess them over the 50-year history of retinoids confounds attempts to dissect out formulation effects on tolerability for a given retinoid except in head-to-head trials, few of which have been reported.

### 4.4 Microsponge Delivery System

A number of novel retinoid formulations have been developed. One such formulation is the microsponge delivery system (MDS), where polymeric microspheres (5–300 microns in diameter) with numerous interconnecting voids entrap the active component and release it onto the surface of skin in a controlled manner in response to rubbing, elevated temperature, or changes in pH (Fig. 2a) [62, 63]. MDS offers potential advantages in improved stability, reduction in skin oiliness through sebum absorption, and reduced irritation by preventing uneven, locally high retinoid concentrations ('dumping'). A 12-week study of 360 patients with acne who were treated with either MDS tretinoin gel 0.1% or vehicle found significantly greater lesion reductions with the MDS tretinoin formulation and transient mild to moderate irritation [64]. A split-face tolerance study of 25 patients comparing the MDS tretinoin gel 0.1% to tretinoin gel 0.1% reported 92% of patients preferred the MDS formulation for

its mildness [64]. A meta-analysis of three randomized, double-blind, vehicle-controlled studies of MDS tretinoin 0.04% in 629 patients with acne demonstrated significant superiority to vehicle in lesion reduction at 12 weeks, but erythema, peeling, and dryness, albeit mostly mild, still occurred in 60–63% and 27–51% of patients in the MDS tretinoin and vehicle arms, respectively [65]. Additionally, reductions in oiliness and facial shine with MDS tretinoin gel have also been documented in several studies [66]. The MDS formulations (tretinoin gel 0.04% and 0.1%) were approved for acne treatment by the FDA in February 1997 (Table 2; Fig. 1).

### 4.5 Polyolprepolymer-2

A gel formulation of polyolprepolymer-2 (PP-2) was designed to allow the controlled, selective delivery of tretinoin to the skin, preventing too-rapid retinoid release. A randomized, controlled trial compared the novel tretinoin gel 0.025% containing PP-2 with commercially available tretinoin gel 0.025% and vehicle in 215 patients with mild-to-moderate acne [67]. Both tretinoin formulations had similar efficacy and were significantly better than vehicle on days 7, 56, and 84. However, the PP-2 formulation demonstrated significantly less peeling than the commercial tretinoin gel on days 28, 56, and 84; significantly less dryness by day 84; and significantly less itching on day 14. Burning and erythema occurred less frequently with the PP-2 formulation than the commercial tretinoin gel at all assessment time points, but the differences were not significant. The PP-2 formulation (tretinoin gel 0.025%) was FDA approved for acne treatment in January 1998 (Table 2; Fig. 1).

### 4.6 Micronization and Polymeric Emulsion Technology

As previously discussed, a sufficiently small particle size allows better access to the pilosebaceous unit, the site of action for topical retinoids. Micronization of tretinoin 0.05%—into particles predominately < 10 microns in diameter—resulted in better cutaneous tolerability and stability in the presence of benzoyl peroxide and similar efficacy to a microsphere formulation containing twice the concentration of tretinoin (0.1%) [68]. These tretinoin particles, as well as moisturizers and hydrating ingredients, are dispersed within a polymeric honeycomb matrix that provides a more uniform distribution of all ingredients (Fig. 2b) [62]. This formulation allows for the controlled and even release of tretinoin into hair follicles with improved skin hydration. Two 12-week, multinational, double-blind, phase III studies randomized a total of 1640 patients with moderate-to-severe acne to tretinoin lotion 0.05% or vehicle [69]. At week 12, tretinoin lotion 0.05% proved superior to vehicle in reducing inflammatory lesions (52% vs 41%;  $p < 0.001$ )

**Table 2** Efficacy data at week 12 for topical retinoid monotherapies approved by the US FDA for the treatment of acne as of April 21, 2020 for which prescribing information efficacy data in facial acne are available

Retinoid	Approval date	N	Success (%)		Inflammatory lesion, mean % reduction from BL		Noninflammatory lesion, mean % reduction from BL	
			Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
Adapalene gel (Differin) 0.1% <sup>a</sup>	May 31, 1996							
Agent		261		NR	–49.7	NR	–35.2	NR
Vehicle		134		NR	–40.7	NR	–27.2	NR
Tretinoin gel (Retin-A Micro) 0.1%	February 7, 1997							
Agent		72		71	–37	–29	–49	–32
Vehicle		72		67	–18	–24	–22	–3
Tazarotene gel (Tazorac) 0.1% <sup>a</sup>	June 13, 1997							
Agent		150 <sup>d</sup>		149 <sup>d</sup>	–42	–47	–55	–43
Vehicle		148 <sup>d</sup>		149 <sup>d</sup>	–30	–28	–35	–27
Tretinoin gel (Avita) 0.025% <sup>a</sup>	January 29, 1998							
Agent		198		58	–35	–38	–36	–42
Vehicle		204		58	–25	–23	–27	–26
Adapalene cream (Differin) 0.1% <sup>a</sup>	May 26, 2000							
Agent		119		175	–32	–14	–34	–35
Vehicle		118		175	–17	–6	–18	–15
Tazarotene cream (Tazorac) 0.1%	September 29, 2000							
Agent		218		206	–41 <sup>g</sup>	–44 <sup>g</sup>	–46 <sup>g</sup>	–41 <sup>g</sup>
Vehicle		218		205	–27 <sup>g</sup>	–25 <sup>g</sup>	–27 <sup>g</sup>	–21 <sup>g</sup>
Tretinoin gel (Retin-A Micro) 0.04%	May 10, 2002							
Agent		108		111	–44	–41	–37	–29
Vehicle		110		103	–13	–30	2	–14
Adapalene gel (Differin) 0.3% <sup>a</sup>	June 19, 2007							

Table 2 (continued)

Retinoid	Approval date	N	Success (%)		Inflammatory lesion, mean % reduction from BL		Noninflammatory lesion, mean % reduction from BL	
			Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
Agent	July 26, 2007	258		NR		NR	–39.7	NR
Vehicle		134		NR		NR	–27.2	NR
Tretinoin gel (Atralin) 0.05% <sup>a</sup>		375	21 <sup>b</sup>		–51.6	NR		
Agent				299	–41	–30	–43	–37
Vehicle	March 17, 2010	185	12 <sup>h</sup>	302	–26	–17	–21	–20
Adapalene lotion (Differin) 0.1%								
Agent		533	26.3 <sup>j</sup>	535	–54.9	–46.0	–49.6	–43.1
Vehicle		542	17.3 <sup>j</sup>	531	–40.3	–36.9	–35.7	–30.2
Tazarotene foam (Fabior) 0.1% <sup>l</sup>	May 11, 2012							
Agent		371	29 <sup>k</sup>	373	–58	–55	–55	–57
Vehicle	August 23, 2018	372	16 <sup>k</sup>	369	–45	–45	–33	–41
Tretinoin lotion (Altreno) 0.05% <sup>l</sup>								
Agent		406	16.5 <sup>i</sup>	413	–50.9	–53.4	–47.5	–45.6
Vehicle		414	6.9 <sup>i</sup>	407	–40.4	–41.5	–27.3	–31.9
Trifarotene cream (Aklief) 0.005% <sup>m</sup>	October 4, 2019							
Agent		612	29.4 <sup>k</sup>	602	–54.4	–66.2	–49.7	–57.7
Vehicle	December 18, 2019	596	19.5 <sup>k</sup>	610	–44.8	–51.2	–35.7	–43.9
Tazarotene lotion (Arazlo) 0.045% <sup>l</sup>								
Agent		402	25.5 <sup>i</sup>	397	–55.5	–59.5	–51.4	–60
Vehicle		411	13 <sup>i</sup>	404	–45.7	–49	–41.5	–41.6

**Table 2** (continued)

Retin-A (tretinoin) creams (0.1%, 0.05%, 0.025%) and gels (0.025%, 0.01%) have no original labels with data on the US FDA site and are therefore not included here; the 0.025% gel formulation was later produced under the brand name Avita and data for that product are listed above

Acne severity is noted if details were provided in the label. Discontinued formulations are not listed (Source: [www.accessdata.fda.gov/scripts/cder/daf/](http://www.accessdata.fda.gov/scripts/cder/daf/))

BL baseline, EGSS Evaluator's Global Severity Score, FDA US Food and Drug Administration, IGA Investigator's Global Assessment, NR not reported

<sup>a</sup>Patients had mild-to-moderate acne

<sup>b</sup>Defined as 'clear' or 'almost clear' by IGA

<sup>c</sup>Defined as achieving 'an excellent result'

<sup>d</sup>N values are for lesion count data. For 12-week global improvement, in Trial 1 agent and vehicle N values are 105 and 117, respectively; in Trial 2 they are 117 and 110, respectively

<sup>e</sup>Defined as improvement of  $\geq 75\%$

<sup>f</sup>Defined as no or minimal acne/no, minimal, or mild acne

<sup>g</sup>Median values

<sup>h</sup>Defined as 0 (clear) or 1 (very mild) by EGSS

<sup>i</sup>Defined as 0 (clear) or 1 (almost clear/very mild) with  $\geq 2$  grade reduction from baseline by EGSS

<sup>j</sup>Defined as  $\geq 2$ -point reduction from baseline on a 5-point IGA scale (definition from Eichenfield et al. 2010) [75]

<sup>k</sup>Defined as 0 (clear) or 1 (almost clear) with a  $\geq 2$  grade reduction from baseline by IGA

<sup>l</sup>Studies were in patients with moderate-to-severe acne

<sup>m</sup>Studies were in patients with moderate facial and truncal acne; data shown are for facial acne

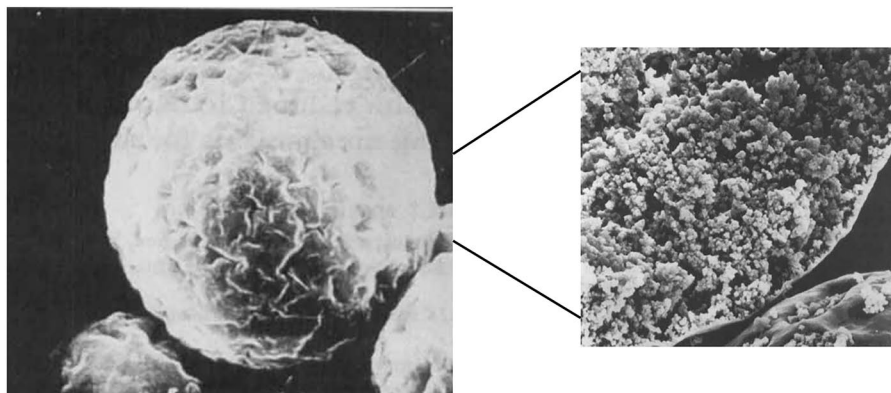
and noninflammatory lesions (46% vs 30%;  $p < 0.001$ ), in treatment success (18% vs 9%;  $p < 0.001$ ), and in patient satisfaction (53% vs 43%;  $p < 0.001$ ). Application-site pain, dryness, and erythema, all mostly mild or moderate, were reported in 3.1%, 3.7%, and 1.4% of tretinoin 0.05% lotion patients, respectively. This tretinoin 0.05% lotion formulation received FDA approval for acne in August 2018 (Table 2; Fig. 1).

Polymeric emulsion technology has also been applied to tazarotene to improve its tolerability. It provides for the simultaneous release of the retinoid along with emollients and humectants from a 3-D mesh matrix (Fig. 2c, parts 1 and 2), potentially allowing the use of lower drug concentrations while maintaining efficacy [70]. This theory was put to the test in a phase II, multicenter, double-blind, vehicle-controlled study of a novel tazarotene 0.045% polymeric lotion and commercially available tazarotene 0.1% cream [71]. Among the 210 patients with moderate-to-severe acne randomized to the three arms, the tazarotene 0.045% lotion proved superior to vehicle in reducing lesion counts and improving clinical success. At less than half the concentration of the tazarotene 0.1% cream, the novel formulation proved numerically more effective in reducing inflammatory (63.8% vs 60.0%) and noninflammatory (56.9% vs 54.1%) lesions and had a higher rate of treatment success (18.8% vs 16.7%) at week 12; these comparisons, however, did not reach statistical significance. Application-site pain (2.9% vs 4.2%), erythema, exfoliation, and dryness (0% vs 1.4% for each) were less frequent in patients treated with tazarotene 0.045% lotion than tazarotene 0.1%; furthermore, no patients treated with tazarotene 0.045% lotion discontinued treatment due to AEs. A pooled analysis of two identical phase III, double-blind, randomized, vehicle-controlled studies of tazarotene 0.045% lotion versus vehicle confirmed its statistically significant superiority to vehicle [72]. Among AEs deemed treatment-related, the most common in the tazarotene 0.045% lotion arm were application-site pain (5.3%), dryness (3.6%), exfoliation (2.1%), and erythema (1.8%). There were 13 (1.8%) and 6 (0.8%) discontinuations in the tazarotene arm due to application-site pain and erythema, respectively. Tazarotene 0.045% lotion received FDA approval for use in the topical treatment of acne in December 2019 (Table 2; Fig. 1).

## 5 Conclusions

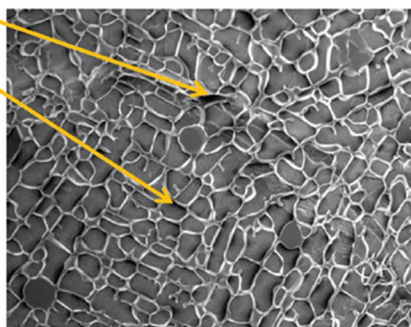
In the 50 years since the initial approval of tretinoin, topical retinoids—alone or in combination with other agents—have become the mainstay of acne treatment and have provided treatment options for other dermatological indications not addressed herein. Studies have shown, however, that adherence to these widely prescribed agents in acne vulgaris is

A



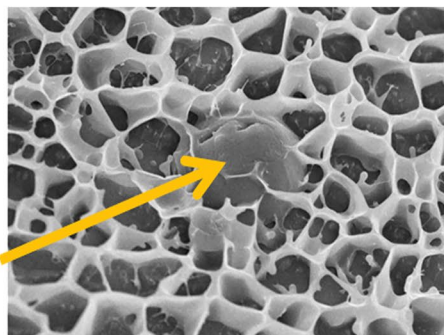
B

*Polymeric matrix traps  
micronized tretinoin  
particles*



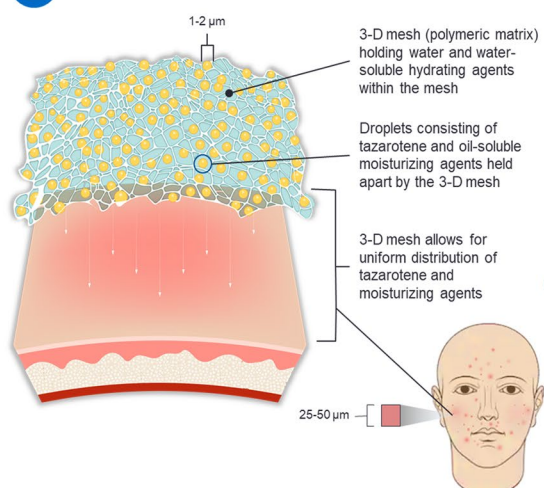
C1

*10,000X magnification  
of honeycomb mesh  
showing emulsion  
droplet*



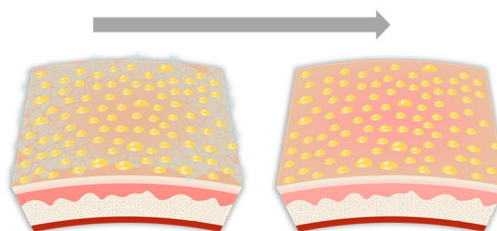
C2

### 1 Uniform Distribution



### 2

3-D mesh dissolves instantly upon contact with salts on skin



### 3

Tazarotene and moisturizing/hydrating agents uniformly absorbed by skin



**Fig 2** Retinoid formulations. **a** Microsponge. Adapted from Embil and Nacht, 1996 [64]. Scanning electron micrograph of a micro-sponge particle approximately 25 microns in diameter ( $\times 5000$ ). Inset: The ultrastructure of a fractured microsponge ( $\times 6000$ ). **b** Micronized tretinoin [62]. Cryo scanning electron microscopy imaging of the polymeric matrix ( $\times 1000$ ). Micronized tretinoin particles are predominantly  $< 10$  microns in diameter. **c** Polymeric emulsion (for tazarotene) [70]. Part 1: Cryo-scanning electron microscopy imaging showing oil-in-water emulsion droplet (approximately 1- to 2-micron diameter) separated within a polymeric matrix ( $\times 10,000$ ). Part 2: This highly spreadable lotion formulation was developed to allow for even skin distribution and more efficient delivery of tazarotene into dermal layers while reducing the potential for skin irritation

remarkably low, with perhaps 30% of prescriptions never filled [55], and almost one-half of all patients poorly adherent with the prescribed regimen [50, 58]. The local irritation associated with topical retinoids, which is most prominent in the first few weeks of therapy, has been associated with poor adherence [53, 54]. Among the avenues explored to minimize irritation and maximize adherence, neither the theory that irritancy inherently paralleled efficacy for topical retinoids nor the idea that adverse events were due to insufficient retinoid receptor subtype selectivity have proven to be true. Half a century of research has resulted in new generations of retinoids with improved stability (primarily through structural modification) and greater tolerability (largely a result of improved formulation technologies).

**Acknowledgements** Medical writing support was provided by Robert M. Rydzewski, CMPP and Lynn M. Anderson, PhD (Prescott Medical Communications Group, Chicago, IL, USA) with financial support from Ortho Dermatologics. Ortho Dermatologics is a division of Bausch Health US, LLC.

## Declarations

**Funding** Medical writing support for this review article was funded by Ortho Dermatologics.

**Conflict of Interest** Hilary Baldwin has served as advisor, investigator, and on speakers' bureaus for Almirall, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharmaceuticals. Guy Webster has served as a consultant, speaker, or investigator for Ortho Dermatologics, Galderma, Almirall, Foamix Pharmaceuticals, and Sol-Gel Technologies. Linda Stein Gold has served as investigator, consultant, or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharmaceuticals, UCB, Arcutis, and Lilly. Valerie Callender has served as an investigator, consultant, or speaker for Allergan, Galderma, L'Oréal, and Ortho Dermatologics. Fran E. Cook-Bolden has served as consultant, speaker, or investigator for Galderma, LEO Pharma, Almirall, Cassiopea, Ortho Dermatologics, Investigators Encore, Foamix Pharmaceuticals, Hovione, Aclaris, and Cutanea. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company.

**Availability of Data** Not applicable.

**Ethics Approval** Not applicable.

**Consent** Not applicable.

**Author Contributions** All authors made substantial contributions to the conception or design of the work; drafted the work/revised it critically; approved the version to be published; and agree to be accountable for all aspects of the work.

## References

1. US Food and Drug Administration. Drugs@FDA-Approved Drugs. 2020. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016921>. Accessed 28 Apr 2020.
2. Leyden J, Stein-Gold L, Weiss J. Why topical retinoids are mainstay of therapy for acne. *Dermatol Ther (Heidelb)*. 2017;7(3):293–304.
3. Nast A, Dreno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, *et al*. European evidence-based (S3) guidelines for the treatment of acne. *J Eur Acad Dermatol Venereol*. 2012;26(Suppl 1):1–29.
4. Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden JJ, *et al*. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol*. 2009;60(5 Suppl):S1–50.
5. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, *et al*. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945–73 e33.
6. Kligman AM. The treatment of acne with topical retinoids: one man's opinions. *J Am Acad Dermatol*. 1997;36(6 Pt 2):S92–5.
7. Tan J, Tangheiti E, Baldwin H, Stein Gold L, Lain E. The role of topical retinoids in prevention and treatment of atrophic acne scarring: understanding the importance of early effective treatment. *J Drugs Dermatol*. 2019;18(3):255–60.
8. Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. *J Clin Aesthet Dermatol*. 2010;3(7):20–31.
9. Riahi RR, Bush AE, Cohen PR. Topical retinoids: therapeutic mechanisms in the treatment of photodamaged skin. *Am J Clin Dermatol*. 2016;17(3):265–76.
10. Ogbechie-Godec OA, Elbuluk N. Melasma: an up-to-date comprehensive review. *Dermatol Ther (Heidelb)*. 2017;7(3):305–18.
11. Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. *Nat Rev Dis Primers*. 2015;1:15029.
12. Boswell CB. Skincare science: update on topical retinoids. *Aesthet Surg J*. 2006;26(2):233–9.
13. Leyden JJ, Shalita A, Thiboutot D, Washenik K, Webster G. Topical retinoids in inflammatory acne: a retrospective, investigator-blinded, vehicle-controlled, photographic assessment. *Clin Ther*. 2005;27(2):216–24.
14. Germain P, Chambon P, Eichele G, Evans RM, Lazar MA, Leid M, *et al*. International union of pharmacology. LX. Retinoic acid receptors. *Pharmacol Rev*. 2006;58(4):712–25.
15. Elder JT, Fisher GJ, Zhang QY, Eisen D, Krust A, Kastner P, *et al*. Retinoic acid receptor gene expression in human skin. *J Invest Dermatol*. 1991;96(4):425–33.
16. Fisher GJ, Voorhees JJ. Molecular mechanisms of retinoid actions in skin. *FASEB J*. 1996;10(9):1002–13.
17. Khalil S, Bardawil T, Stephan C, Darwiche N, Abbas O, Kibbi AG, *et al*. Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. *J Dermatolog Treat*. 2017;28(8):684–96.

18. Shroet B. Pharmacodynamics and pharmacokinetics of topical adapalene. *J Am Acad Dermatol*. 1998;39(2 Pt 3):S17–24.
19. Dreno B, Gollnick HP, Kang S, Thiboutot D, Bettoli V, Torres V, *et al*. Understanding innate immunity and inflammation in acne: implications for management. *J Eur Acad Dermatol Venereol*. 2015;29(Suppl 4):3–11.
20. Kligman AM, Fulton JE Jr, Plewig G. Topical vitamin A acid in acne vulgaris. *Arch Dermatol*. 1969;99(4):469–76.
21. Bershad S. Developments in topical retinoid therapy for acne. *Semin Cutan Med Surg*. 2001;20(3):154–61.
22. Rigopoulos D, Ioannides D, Kalogeromitros D, Katsambas AD. Comparison of topical retinoids in the treatment of acne. *Clin Dermatol*. 2004;22(5):408–11.
23. Chen S, Ostrowski J, Whiting G, Roalsvig T, Hammer L, Currier SJ, *et al*. Retinoic acid receptor gamma mediates topical retinoid efficacy and irritation in animal models. *J Invest Dermatol*. 1995;104(5):779–83.
24. Chandraratna RA. Rational design of receptor-selective retinoids. *J Am Acad Dermatol*. 1998;39(4 Pt 2):S124–8.
25. Ellis CN, Voorhees JJ. Etretinate therapy. *J Am Acad Dermatol*. 1987;16(2 Pt 1):267–91.
26. Dogra S, Yadav S. Acitretin in psoriasis: an evolving scenario. *Int J Dermatol*. 2014;53(5):525–38.
27. US Food and Drug Administration. NDA-20-338. 1996. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/pre96/020338Orig1s000rev.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020338Orig1s000rev.pdf). Accessed 29 Apr 2020.
28. Shroet B, Michel S. Pharmacology and chemistry of adapalene. *J Am Acad Dermatol*. 1997;36(6 Pt 2):S96–103.
29. Allec J, Chatelus A, Wagner N. Skin distribution and pharmaceutical aspects of adapalene gel. *J Am Acad Dermatol*. 1997;36(6 Pt 2):S119–25.
30. Latriano L, Tzimas G, Wong F, Wills RJ. The percutaneous absorption of topically applied tretinoin and its effect on endogenous concentrations of tretinoin and its metabolites after single doses or long-term use. *J Am Acad Dermatol*. 1997;36(3 Pt 2):S37–46.
31. Saurat JH, Sorg O. Topical natural retinoids. The “proligand-nonligand” concept. *Dermatology*. 1999;199(Suppl 1):1–2.
32. Cunliffe WJ, Poncet M, Loesche C, Verschoore M. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. *Br J Dermatol*. 1998;139(Suppl 52):48–56.
33. Tazorac® [package insert]. Irvine: Allergan, Inc.; 1997.
34. Hecker D, Worsley J, Yueh G, Kuroda K, Lebwohl M. Interactions between tazarotene and ultraviolet light. *J Am Acad Dermatol*. 1999;41(6):927–30.
35. Webster GF, Berson D, Stein LF, Fivenson DP, Tangheiti EA, Ling M. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. *Cutis*. 2001;67(6 Suppl):4–9.
36. Webster GF, Guenther L, Poulin YP, Solomon BA, Loven K, Lee J. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. *Cutis*. 2002;69(2 Suppl):4–11.
37. Shalita A, Miller B, Menter A, Abramovits W, Loven K, Kakita L. Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. *J Drugs Dermatol*. 2005;4(2):153–8.
38. Kolli SS, Pecone D, Pona A, Cline A, Feldman SR. Topical retinoids in acne vulgaris: a systematic review. *Am J Clin Dermatol*. 2019;20(3):345–65.
39. Tolaymat L, Zito PM. Adapalene. [Updated 2020 Sep 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021-Jan. <https://www.ncbi.nlm.nih.gov/books/NBK482509/>
40. Latter G, Grice JE, Mohammed Y, Roberts MS, Benson HAE. Targeted topical delivery of retinoids in the management of acne vulgaris: current formulations and novel delivery systems. *Pharmaceutics*. 2019;11(10):490.
41. The medical letter on drugs and therapeutics. Trifarotene (Aklief®)—A new topical retinoid for acne. *JAMA*. 2020;323(13):1310–1.
42. Tan J, Thiboutot D, Popp G, Gooderham M, Lynde C, Del Rosso J, *et al*. Randomized phase 3 evaluation of trifarotene 50 µg/g cream treatment of moderate facial and truncal acne. *J Am Acad Dermatol*. 2019;80(6):1691–9.
43. Aklief® [package insert]. Galderma Laboratories L, Switzerland; 2019.
44. Culp L, Moradi Tuchayi S, Alinia H, Feldman SR. Tolerability of topical retinoids: are there clinically meaningful differences among topical retinoids? *J Cutan Med Surg*. 2015;19(6):530–8.
45. Loesche C, Pernin C, Poncet M. Adapalene 0.1% and benzoyl peroxide 2.5% as a fixed-dose combination gel is as well tolerated as the individual components alone in terms of cumulative irritancy. *Eur J Dermatol*. 2008;18(5):524–6.
46. Feldman SR, Werner CP, Aljo Saenz AB. The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2 multicenter, randomized, vehicle-controlled, double-blind studies. *J Drugs Dermatol*. 2013;12(4):438–46.
47. Leyden J, Grove G, Zerweck C. Facial tolerability of topical retinoid therapy. *J Drugs Dermatol*. 2004;3(6):641–51.
48. Thielitz A, Gollnick H. Topical retinoids in acne vulgaris: update on efficacy and safety. *Am J Clin Dermatol*. 2008;9(6):369–81.
49. Pomerantz H, Weinstock MA, VATTC. Predictors of local adverse effects caused by topical tretinoin cream 0.1% in the Veterans Affairs Topical Tretinoin Chemoprevention trial. *Br J Dermatol*. 2014;171(3):642–5.
50. Dreno B, Thiboutot D, Gollnick H, Finlay AY, Layton A, Leyden JJ, *et al*. Large-scale worldwide observational study of adherence with acne therapy. *Int J Dermatol*. 2010;49(4):448–56.
51. Krejci-Manwaring J, Tusa MG, Carroll C, Camacho F, Kaur M, Carr D, *et al*. Stealth monitoring of adherence to topical medication: adherence is very poor in children with atopic dermatitis. *J Am Acad Dermatol*. 2007;56(2):211–6.
52. Raebel MA, Schmittiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care*. 2013;51(8 Suppl 3):S11–21.
53. Hoffman LK, Bhatia N, Zeichner J, Kircik LH. Topical vehicle formulations in the treatment of acne. *J Drugs Dermatol*. 2018;17(6):S6–10.
54. Del Rosso JQ, Kircik LH, Zeichner J, Stein GL. The clinical relevance and therapeutic benefit of established active ingredients incorporated into advanced foam vehicles: vehicle characteristics can influence and improve patient outcomes. *J Drugs Dermatol*. 2019;18(2s):S100–7.
55. Anderson KL, Dothard EH, Huang KE, Feldman SR. Frequency of primary nonadherence to acne treatment. *JAMA Dermatol*. 2015;151(6):623–6.
56. Tan X, Al-Dabagh A, Davis SA, Lin HC, Balkrishnan R, Chang J, *et al*. Medication adherence, healthcare costs and utilization associated with acne drugs in Medicaid enrollees with acne vulgaris. *Am J Clin Dermatol*. 2013;14(3):243–51.
57. Peterson AM, Nau DP, Cramer JA, Benner J, Gwady-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007;10(1):3–12.
58. Dikicier BS. Topical treatment of acne vulgaris: efficiency, side effects, and adherence rate. *J Int Med Res*. 2019;47(7):2987–92.

59. Veraldi S, Barbareschi M, Benardon S, Schianchi R. Short contact therapy of acne with tretinoin. *J Dermatolog Treat.* 2013;24(5):374–6.
60. Leyden J, Lowe N, Kakita L, Draeos Z. Comparison of treatment of acne vulgaris with alternate-day applications of tazarotene 0.1% gel and once-daily applications of adapalene 0.1% gel: a randomized trial. *Cutis.* 2001;67(6 Suppl):10–16.
61. Piacquadio D, Kligman A. The critical role of the vehicle to therapeutic efficacy and patient compliance. *J Am Acad Dermatol.* 1998;39(2 Pt 3):S67–73.
62. Kircik LH, Draeos ZD, Berson DS. Polymeric emulsion technology applied to tretinoin. *J Drugs Dermatol.* 2019;18(4):S148–54.
63. Kaity S, Maiti S, Ghosh AK, Pal D, Ghosh A, Banerjee S. Microsponges: a novel strategy for drug delivery system. *J Adv Pharm Technol Res.* 2010;1(3):283–90.
64. Embil K, Nacht S. The Microsponge Delivery System (MDS): a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *J Microencapsul.* 1996;13(5):575–88.
65. Nighland M, Grossman R. Tretinoin microsphere gel in facial acne vulgaris: a meta-analysis. *J Drugs Dermatol.* 2008;7(8 Suppl):S2–8.
66. Kircik LH. The microsponge delivery system reduces facial oiliness and shine during acne therapy. *J Drugs Dermatol.* 2013;12(11):1268–70.
67. Lucky AW, Cullen SI, Jarratt MT, Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter double-blind, parallel study. *J Am Acad Dermatol.* 1998;38(4):S17–23.
68. Torok HM, Pillai R. Safety and efficacy of micronized tretinoin gel (0.05%) in treating adolescent acne. *J Drugs Dermatol.* 2011;10(6):647–52.
69. Tying SK, Kircik LH, Pariser DM, Guenin E, Bhatt V, Pillai R. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of efficacy and safety in patients aged 9 years and older. *J Drugs Dermatol.* 2018;17(10):1084–91.
70. Tanghetti EA, Stein Gold L, Del Rosso JQ, Lin T, Angel A, Pillai R. Optimized formulation for topical application of a fixed combination halobetasol/tazarotene lotion using polymeric emulsion technology. *J Dermatolog Treat.* 2019:1–8.
71. Tanghetti EA, Kircik LH, Green LJ, Guenin E, Harris S, Martin G, *et al.* A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol.* 2019;18(6):542.
72. Tanghetti EA, Werschler WP, Lain T, Guenin E, Martin G, Pillai R. Tazarotene 0.045% lotion for once-daily treatment of moderate-to-severe acne vulgaris: results from two phase 3 trials. *J Drugs Dermatol.* 2020;19(1):70–7.
73. Data on file, Bausch Health Americas, Inc. Studies V01-121A-301 and V01-121A-302.
74. Data on file, Bausch Health Americas, Inc. Studies V01-123A-301 and V01-123A-302.
75. Eichenfield LF, Jarratt M, Schlessinger J, Kempers S, Manna V, Hwa J *et al.* Adapalene 0.1% lotion in the treatment of acne vulgaris: results from two placebo-controlled, multicenter, randomized double-blind, clinical studies. *J Drugs Dermatol.* 2010;9(6):639–46.