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Review Article

The Right Formula for Acne: Importance of Vehicle Formulation in Tazarotene 0.045% Lotion Design, Application, Tolerability, and Efficacy

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The vehicles used for topical dermatological treatments can significantly contribute to treatment effects while also delivering ingredients to maintain skin barrier function and reduce irritation. Tazarotene 0.045% lotion was developed using proprietary polymeric emulsion technology to provide uniform and efficient delivery of the active ingredient as well as improved safety and tolerability compared to higher-dose tazarotene formulations. The lotion vehicle additionally provides rapid and sustained improvements in moisturization and skin barrier function with patient-friendly application and cosmetic properties. Compared with trifarotene 0.005% cream, tazarotene 0.045% lotion demonstrated ~30% greater spreadability and a lower potential for irritation. In clinical trials and investigator-initiated studies, tazarotene 0.045% lotion demonstrated efficacy in the treatment of facial and truncal acne and improved skin oiliness. Facial acne improvements were similar among study participants grouped by sex, race, ethnicity, or age. In a head-to-head study, efficacy was comparable to tazarotene 0.1% cream with approximately half the rate of treatment-emergent adverse events. Tazarotene 0.045% lotion is a beneficial acne treatment option for patients of varying ages, races, ethnicities, and skin types, delivered in a formulation that can be easily used on the face, back, and chest.

1. Introduction

Topical retinoids were first approved for the treatment of acne over 50 years ago [1]. They address multiple pathogenic factors in acne [2–4], are recommended as first-line treatment by the American Academy of Dermatology [5], and have become a mainstay in acne treatment and management [3]. However, their clinical effectiveness can be limited by tolerability concerns and poor adherence to treatment [1, 6, 7]. As acne can have long-lasting physical and psychosocial impacts, there is ongoing need for topical treatments that are efficacious, well tolerated, and promote patient adherence. In recent history, there have been few novel molecules developed for acne treatment; rather, newer treatments have utilized different concentrations of well-established active ingredients and taken advantage of advanced drug delivery systems and enhancements in vehicle technology to improve treatment outcomes [1, 8].

Topical dermatological treatments are somewhat unique in that the vehicle, which comprises most of the formulation, can contribute significantly to treatment outcomes while delivering moisturizing and hydrating excipients that can help maintain skin barrier function and reduce irritation [4, 9]. Moreover, vehicle choice has a number of impacts on the active drug, including its stability during storage, release onto the skin upon application, penetration across stratum corneum, and dermal absorption [8–11]. Efficient drug delivery may permit the use of lower-dose formulations, which could also reduce treatment-related irritation [12, 13]. A vehicle's physical properties—including ease of application, spreadability, cosmetic elegance, and skin feel after application—play an important role in patient perception and acceptance of, as well as adherence to, a topical treatment [8, 14]. Despite the well-established importance of vehicle in topical formulations, vehicle design is often an afterthought in the development of topical formulations [15], potentially as a means to reduce development costs. Conversely, optimization of the vehicle used in topical dermatological formulations represents an opportunity to maximize therapeutic benefits (Figure 1).

Tazarotene 0.045% lotion is the most recently approved single-agent topical retinoid for the treatment of acne [1], having received FDA approval in December 2019 [16]. It was developed using proprietary polymeric emulsion technology to provide uniform and rapid delivery of the active ingredient in a lower-dose formulation to meet the need for an efficacious topical acne therapy with patient-friendly aesthetics, safety, and tolerability across all skin types.

This review will describe the physical and clinical features of tazarotene 0.045% lotion—how the vehicle lotion impacts spreadability on the skin, skin barrier function, patient acceptance, and delivery of the active ingredient into the epidermis—as well as safety/tolerability and efficacy data from clinical trials.

2. Tazarotene 0.045% Lotion Vehicle

2.1. Polymeric Emulsion-Based Vehicle Technology. The majority (80–90%) of the vehicle for tazarotene 0.045% lotion is water, which provides for easier application but results in a less occlusive and less hydrating vehicle base compared with vehicles having higher oil content [14]. Moreover, the aqueous medium presents a challenge to suspending and dispersing both active ingredients and lipophilic hydrating agents in a homogenous and stable way. To address this, tazarotene 0.045% lotion utilizes proprietary polymeric emulsion technology that allows for the active ingredient to be encapsulated within the same oil droplets as moisturizing excipients (Figure 2) [17]. These droplets are evenly distributed, along with water-soluble hydrating ingredients, throughout a three-dimensional mesh matrix, which breaks apart instantly upon contact with salts on the skin to provide rapid and uniform delivery of the active ingredient, moisturizers, and hydrating agents onto the skin and into dermal layers. Carbomer homopolymers A and B allow for the suspension of insoluble ingredients in a high proportion of water as well as optimization of release properties of active ingredients and rheological characteristics (see below) [18, 19]. The mesh matrix, excipients, and other design characteristics of the polymeric emulsion lotion are described in further detail by Tanghetti et al. [17]. Formal stability testing of tazarotene 0.045% lotion suggests a shelf life of 36 months at up to 25°C [19].

2.2. Spreadability. Spreadability of a topical formulation is closely related to sensory and aesthetic attributes—such as texture, ease of application, and overall skin feeling after application—that can influence patient preference [20, 21] and can also impact efficacy, tolerability, and cost-effectiveness of treatment. Thick or uneven applications may contain "wasted" drug that is never able to contact, much less penetrate, the skin, or can lead to hot spots of higher drug concentration at the skin surface that can lead to increased irritation [22]. From a practical standpoint, highly spreadable formulations are appropriate for use both on the face and on larger skin surfaces such as the chest and back. Greater spreadability effectively increases the number of applications per unit volume of a formulation, decreasing the cost per application. Two studies—one in vitro and one in vivo—were performed to compare the spreadability of tazarotene 0.045% lotion to trifarotene 0.005% cream, another recently approved topical retinoid for acne.

2.2.1. In Vitro Rheological Characterization of Tazarotene 0.045% Lotion versus Trifarotene 0.005% Cream. The spreadability of a topical formulation on skin can be rapidly and objectively quantified in vitro by assessing its rheology—how its flow characteristics change under applied stress or force [23, 24]. The rheological profiles of tazarotene 0.045% lotion and trifarotene 0.005% cream were assessed to predict their spreadability on skin [25]. Compared to trifarotene 0.005% cream, tazarotene 0.045% lotion was found to be 73% less viscous and 87% less rigid and had yield stress and yield strain measurement that were 77% lower and 64% higher, respectively. Collectively, these results indicate that tazarotene 0.045% lotion is thinner, deforms more easily, and requires less force to initiate spread than trifarotene 0.005% cream. Such rheological characteristics are predictive of a formulation that is able to form a smoother, more uniform layer with overall greater spreadability when applied to the skin.

2.2.2. In Vivo Spreadability of Tazarotene 0.045% Lotion and Trifarotene 0.005% Cream on Skin. In vivo spreadability of tazarotene 0.045% lotion and tazarotene 0.005% cream was assessed in a double-blind, split-body study of 30 healthy adults [25]. After equal amounts of each product were applied to opposite sides of the back, tazarotene 0.045% lotion was able to cover a greater body surface than trifarotene 0.005% cream. For all participants, area of spread with tazarotene 0.045% lotion was either equivalent to or greater than trifarotene 0.005% cream, consistent with the in vivo rheological assessment. On average, tazarotene 0.045% lotion covered nearly 30% greater body surface than

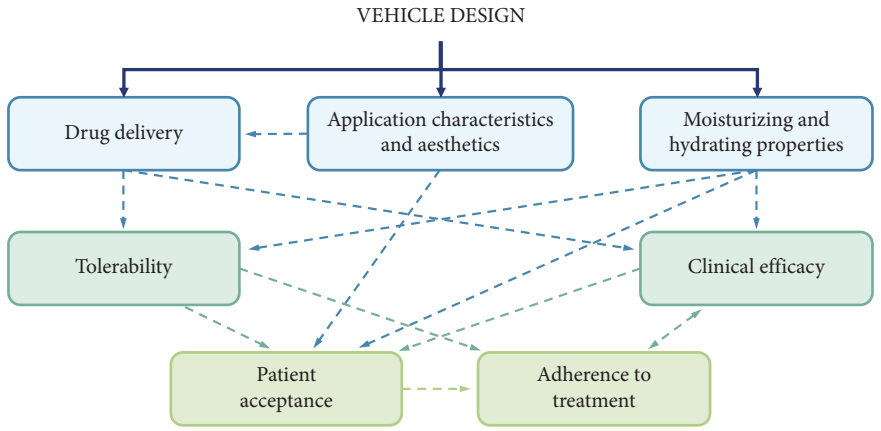

Figure 1: Topical vehicle design impacts drug delivery, clinical outcomes, and patient acceptance. Topical formulations involve complex interactions among vehicle properties, clinical effects, and patient acceptance.

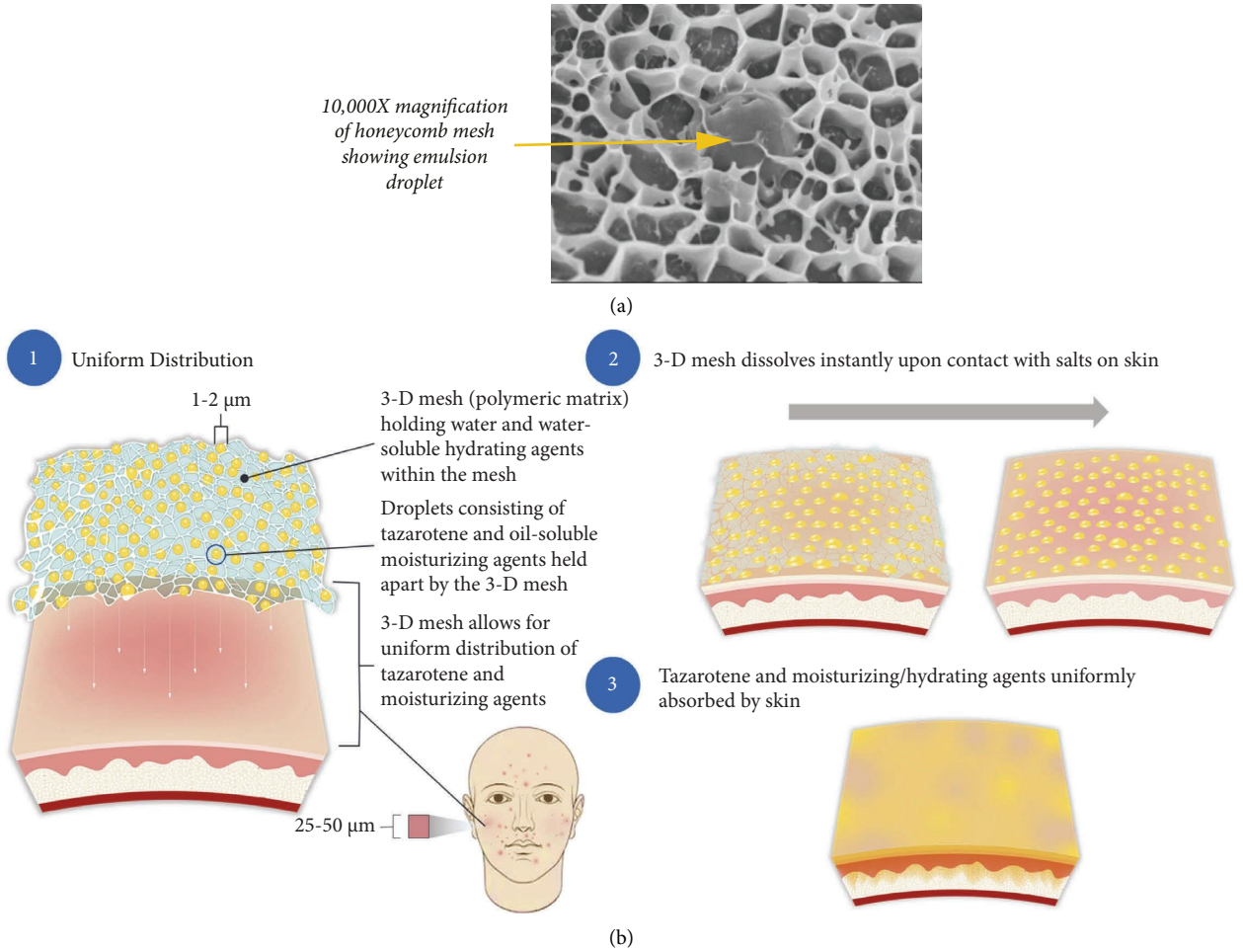

Figure 2: Polymeric emulsion technology for tazarotene 0.045% lotion. (a) Cryoscanning electron micrograph (10,000x magnification) showing an oil-in-water droplet (diameter ~1-2 micron) within the 3-d polymeric mesh. (b) This highly spreadable lotion formulation was developed to provide rapid and uniform distribution of tazarotene and moisturizing/hydrating agents while reducing the potential for skin irritation. Reprinted with permission from Eric Guenin: Springer, *Am J Clin Dermatol*; 50 Years of Topical Retinoids for Acne: Evolution of Treatment; Baldwin et al. [1] Copyright 2021.

trifarotene 0.005% cream ($P < 0.001$). This favorable spreadability profile, along with data demonstrating efficacy in the treatment of acne on the chest and/or back (see below) [26], suggests a role for tazarotene 0.045% lotion in the treatment of truncal acne.

2.3. Moisturization and Epidermal Barrier Function. Repeated application of topical retinoids can compromise epidermal barrier function and increase transepidermal water loss (TEWL), which may contribute to irritation/tolerability concerns [4, 27]. This effect can be countered by using vehicles containing moisturizing and hydrating humectants, which help restore and maintain stratum corneum barrier function and reduce retinoid-related irritation [4, 9]. Unfortunately, choosing a topical vehicle may involve a tradeoff between moisturizing/hydrating properties and patient-friendly cosmetic properties such as skin feel, spreadability, and non-greasiness [14].

Tazarotene 0.045% lotion delivers a number of excipients to augment skin moisturization and hydration [17]. In a study of 30 healthy females, the lotion vehicle provided rapid and sustained improvements in moisturization (assessed via corneometry) and barrier function (assessed via TEWL) as compared to an untreated control site (Figure 3) [17, 28]. At the lotion-treated site, significant improvements versus control in corneometry score (>2-fold increase) and TEWL were observed, beginning 15–30 minutes post-application. TEWL improvements were greatest 8 hours post-application (~50% decrease). For both measurements, significant improvements persisted through 24 hours of follow-up, indicating prolonged enhancement of skin barrier function with tazarotene 0.045% lotion vehicle.

2.4. Patient Preference of Vehicle Lotion. Patient preference is an important consideration in the choice of topical therapies for acne [5, 29] and is strongly influenced by vehicle attributes such as moisturization, fast absorption, non-greasiness, and ease of use [14, 30–33]. In a patient perception study of tazarotene 0.045% lotion vehicle, 15 healthy adult females answered a questionnaire on various properties of the lotion base after application to one side of the face [17]. Acceptability of the lotion was very high; 93–100% of respondents agreed or strongly agreed in response to all questions, which addressed lotion application (e.g., "the product absorbs quickly"), feel and aesthetics (e.g., "the product has a lightweight after feel"), and moisturizing/hydrating properties (e.g., "my skin feels moisturized"). In a separate study of 19 adults with acne of the chest and/or back who were treated with tazarotene 0.045% lotion, two thirds of the participants stated that lotions were their top preference for topical vehicles [26]. In particular, tazarotene 0.045% lotion was rated by 94–100% of the participants as "good" or "excellent" for its ease of use and spreadability. In comparison to other acne medicines, tazarotene 0.045% lotion was rated as "good" or "excellent" by ≥80% of the respondents with respect to ease of use, ability to continue daily activities, and the large surface area of application [26, 34].

2.5. Tazarotene Percutaneous Penetration and Deposition. Once applied, topical formulations must overcome the skin barrier to maximize the amount of drug delivered into the skin, as drug remaining on the skin surface is not just unavailable to contribute to clinical efficacy but can cause irritation [22]. Skin penetration can be significantly enhanced by the vehicle [35]; ideally, topical vehicles should uniformly and efficiently release the active drug for more controlled and targeted absorption into the skin [10]. Improving the percutaneous penetration and deposition of the active ingredient in the skin could allow the use of lower-dose formulations, which has been associated with lower rates of adverse events in clinical trials of retinoids [12, 13].

In an ex vivo study, percutaneous absorption of tazarotene in human cadaverous skin was measured after the application of either tazarotene 0.1% cream or polymeric emulsion lotion containing tazarotene 0.09% and halobetasol propionate 0.01% [17]. Twenty-four hours after application, the lotion demonstrated greater permeation efficiency of tazarotene, with 20.8% of the applied dose recovered, compared to 12.3% with the cream. In an in vivo study, epidermal deposition of tazarotene was measured in 10 healthy adults after the application of tazarotene 0.045% lotion and 0.1% cream to opposite forearms [36]. To measure penetration of tazarotene, layers of epidermis were serially removed using tape strips, which were processed and analyzed for tazarotene content (Figure 4). A numerically greater percentage of the applied dose of tazarotene was recovered from throughout epidermis six hours after application of tazarotene 0.045% lotion than with tazarotene 0.1% cream (15.5% vs. 13.8%), which may be due to the unique polymeric emulsion technology used to develop the lotion formulation. Despite containing less than half the concentration of tazarotene overall, the 0.045% lotion formulation delivered a similar concentration of drug to deeper epidermal layers as the 0.1% cream. Furthermore, the 2-fold lower concentration of tazarotene remaining at superficial epidermal layers may contribute to the improved tolerability with 0.045% lotion versus 0.1% cream observed in a phase 2 clinical study (see clinical safety below) [37].

3. Tazarotene 0.045% Lotion: Tolerability, Safety, and Efficacy

3.1. Irritation and Sensitization Potential of Tazarotene 0.045% Lotion. The potential for sensitization (e.g., allergic potential) and irritation due to epidermal damage after repeated application of tazarotene 0.045% lotion was assessed in two dermal safety studies [38]. In a repeat insult patch test (RIPT), tazarotene 0.045% lotion was not associated with significant irritation and no participants were classified as having allergic sensitization. In a cumulative irritation patch test (CIPT), despite greater overall drug exposure than in the RIPT, tazarotene 0.045% lotion was deemed only "slightly irritating." The irritation profile of tazarotene 0.045% lotion in these studies was

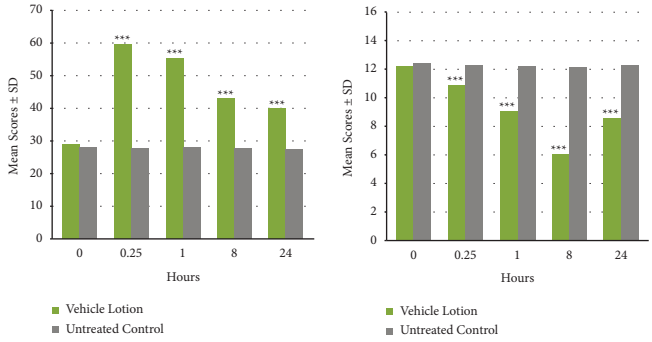

Figure 3: Skin moisturization and barrier maintenance with the vehicle lotion. The polymeric emulsion vehicle used for tazarotene 0.045% lotion was assessed for (a) moisturizing properties via corneometry and (b) skin barrier maintenance via TEWL in 30 healthy participants [16]. For both assessments, skin treated with the vehicle lotion was superior to an untreated control site 15 minutes post-application and continuing through 24 hours post-application. *** $P < 0.001$ vs. untreated control. SD, standard deviation; TEWL, transepidermal water loss.

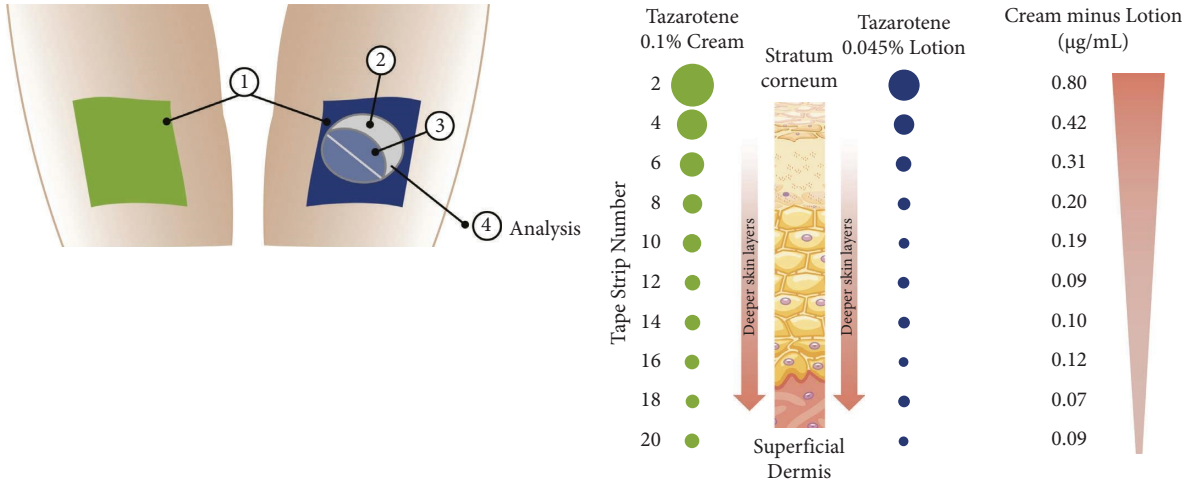

Figure 4: Tazarotene deposition in the skin after application of 0.045% lotion and 0.1% cream. (a) Methods: (1) ~0.1 g of tazarotene 0.1% cream and 0.045% lotion were applied to opposite volar forearms. (2) 6 hours post-application, D-Squame 7/8" tape strips applied to treated areas and held under controlled pressure (225 g/cm^2) for 10 seconds to ensure contact between tape and skin. (3) Tape strips removed; first strip discarded; 20 additional strips taken at same sampling location. (4) Even-numbered tape strips processed and analyzed for the tazarotene content using liquid chromatography-mass spectrometry. Detailed study methods are available in Draelos et al. [33]. (b) Concentration of tazarotene recovered measured at each tape strip 6 hours post-application. Size of each dot corresponds to tazarotene concentration. Differences in tazarotene concentrations were greatest at superficial skin layers. Skin layers are for illustrative purposes only; exact location of tape strip sampling within the skin was not assessed.

comparable to findings from a similarly designed study of a 0.1% lotion formulation of adapalene [39], which is considered one of the best-tolerated topical retinoids for acne [13, 40]. In a separate set of modified CIPT studies, irritation with tazarotene 0.045% lotion was compared head to head against adapalene 0.3% gel and trifarotene 0.005% cream [41]. After 12 days of exposure, tazarotene 0.045% lotion was found to be significantly less irritating than trifarotene 0.005% cream and numerically less irritating than adapalene 0.3% gel (Figure 5). Thus, under the exaggerated conditions of these studies, tazarotene 0.045% lotion was well tolerated and not associated with substantial irritation.

3.2. Clinical Safety, Tolerability, and Efficacy of Tazarotene 0.045% Lotion in the Treatment of Acne

3.2.1. Clinical Trials in the Treatment of Facial Acne. Results from one phase 2 and two phase 3 clinical trials are consistent with the beneficial properties of the polymeric emulsion vehicle used for tazarotene 0.045% lotion. Study participants treated with tazarotene 0.045% lotion experienced significantly greater reductions from the baseline in inflammatory and noninflammatory lesion counts and significantly greater rates of treatment success (≥2-grade reduction (improvement) in Evaluator's Global Severity Score and "clear" or "almost clear" skin) than those treated

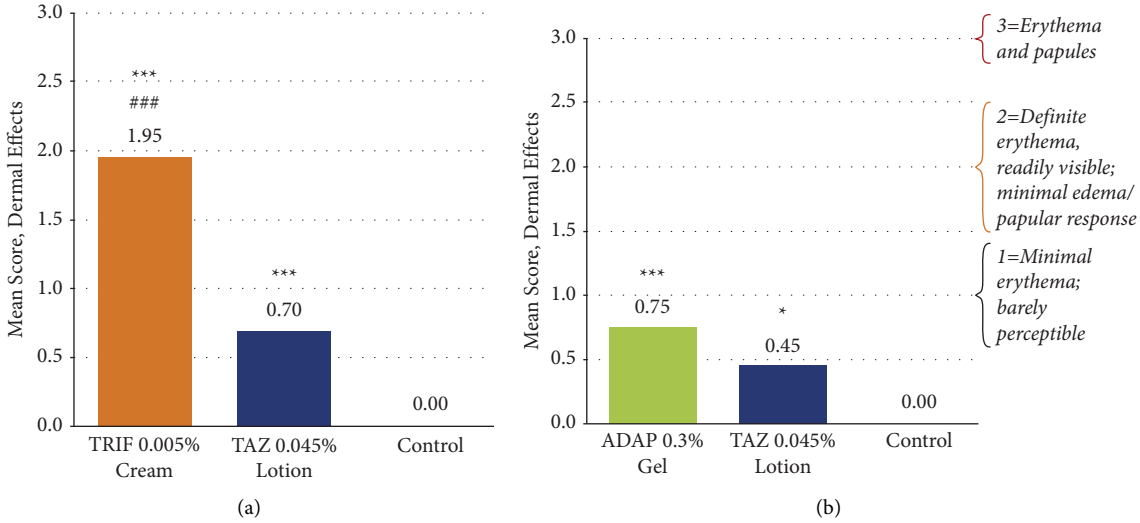

Figure 5: Irritation potential of tazarotene 0.045% lotion vs. trifarotene 0.005% cream and adapalene 0.3% gel. At the end of 12-day modified continuous irritation patch tests, tazarotene 0.045% lotion was (a) significantly less irritating than trifarotene 0.005% cream and (b) numerically less irritating than adapalene 0.3% gel. In both studies, tazarotene 0.045% lotion was assessed as mildly irritating [39]. $^{*}P < 0.05$; $^{***}P < 0.001$ vs. control. $^{###}P < 0.001$ trifarotene 0.005% cream vs. tazarotene 0.045% lotion. ADAP, adapalene; TAZ, tazarotene; TRIF, trifarotene.

with vehicle [37, 42, 43]. Subsequent post hoc analyses have demonstrated efficacy and tolerability of tazarotene 0.045% lotion among phase 3 study participants grouped by sex, race, ethnicity, and age [44–49]. An additional post hoc analysis based on skin type demonstrated that most participants who self-reported oily skin at the baseline also reported improvement to "moderately oily" or "low/not oily" skin [50]. This effect may be attributable to properties of the polymeric emulsion lotion itself, as over 70% of participants in both the tazarotene 0.045% lotion and vehicle lotion groups reported improvement.

Lower active drug concentrations have been associated with lower rates adverse events with topical dermatological treatments [13]. Results of the phase 2 study of tazarotene 0.045% lotion—which included a tazarotene 0.1% cream treatment arm—are consistent with this finding [37]. Treatment with lower-dose tazarotene 0.045% lotion was associated with rates of treatment-emergent adverse events (TEAEs) and treatment-related TEAEs that were approximately half of those associated with the 0.1% cream formulation. Rates of application-site pain (2.9% vs. 4.2%) and erythema, exfoliation, and dryness (0% vs. 1.4% each) were also less frequent with the 0.045% lotion than with 0.1% cream. Discontinuations due to a TEAE occurred in 0% of the participants treated with tazarotene lotion versus 1.4% of the participants treated with cream. Notably, despite containing less than half the concentration of tazarotene, the 0.045% lotion was associated with lesion reductions (Figure 6) and treatment success rates that were statistically comparable—though numerically superior—to tazarotene 0.1% cream, perhaps due to deposition of similar concentrations of tazarotene at deeper epidermal layers with both formulations [36]. In general, rates of TEAEs commonly reported in clinical trials of topical retinoids (e.g., burning, irritation, erythema, and dry skin) were lower with tazarotene 0.045% lotion than in studies of other tazarotene formulations [42] or other topical retinoids [1] though differences in study designs and populations must be taken into consideration.

Across the three clinical trials, investigator-assessed scaling, erythema, hypopigmentation, and hyperpigmentation and participant-assessed itching, burning, and stinging were of overall mild severity [37, 42, 43]. Mean scores for all cutaneous safety/tolerability assessments were between 0 (none) and 0.6 at all study visits (score of 1 = mild). As is common with topical retinoid treatment [4], transient increases in signs of cutaneous safety and tolerability were observed within the first few weeks of treatment; however, all improved or returned to the baseline by the final assessment at week 12. In the phase 2 study, increases in participant-assessed burning and stinging were numerically less severe with tazarotene 0.045% lotion than with tazarotene 0.1% cream, and no increases from the baseline in itching were observed (Figure 7); increases in investigator-assessed cutaneous safety were similar for the two formulations at all study visits (data not shown).

The improved safety and tolerability profile of tazarotene 0.045% lotion compared with tazarotene 0.1% lotion—achieved without any loss of efficacy—may reflect the lower concentration of active drug used coupled with improved skin penetration and simultaneous delivery of moisturizers and humectants by the polymeric emulsion-based vehicle. That efficacy was not sacrificed for improved tolerability is of great importance; in a study of adherence to topical acne treatments, almost two thirds of patients who discontinued treatment cited ineffectiveness, side effects, or a combination of the two as the reason for discontinuation [51]. A thorough compilation of efficacy and safety data from

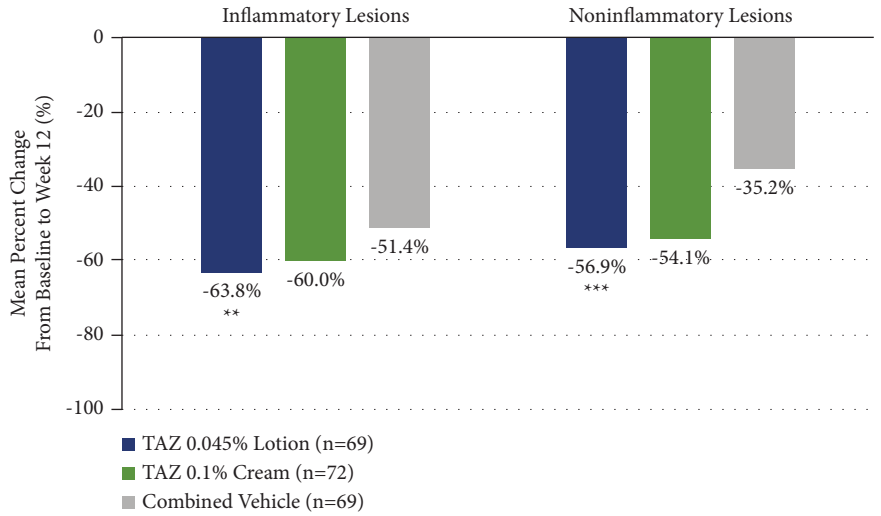

Figure 6: Lesion count reductions from the baseline with tazarotene 0.045% lotion and tazarotene 0.1% cream (phase 2 study). $^{**}P < 0.01$; $^{***}P < 0.001$ vs. combined vehicle. TAZ, tazarotene.

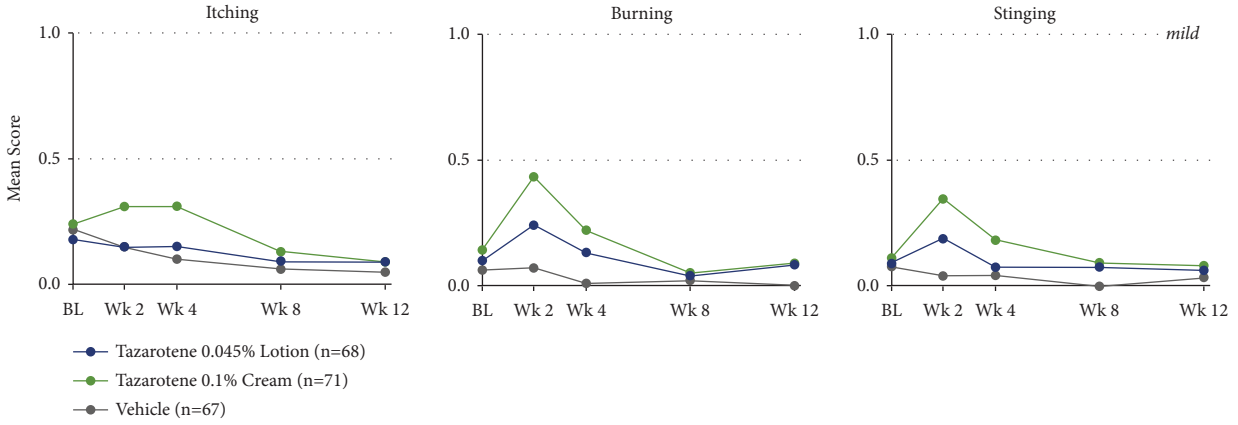

Figure 7: Assessments of cutaneous tolerability of tazarotene 0.045% lotion vs. tazarotene 0.1% cream (phase 2 study). Study participants assessed itching, burning, and stinging on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). BL, baseline; Wk, week.

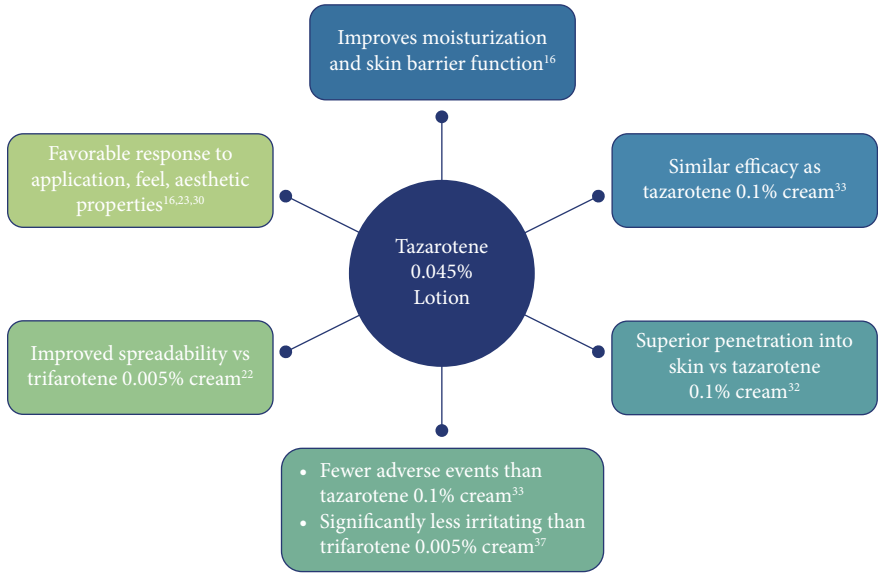

Figure 8: Summary of tazarotene 0.045% polymeric emulsion lotion benefits in the treatment of acne.

clinical trials of tazarotene 0.045% lotion and other topical retinoid formulations for acne has been published by Baldwin et al. [1] though it should be noted that few head-to-head trials have been reported and cross-trial comparisons are complicated by differences in study designs and baseline participant demographics.

3.2.2. Truncal Acne Treatment. Truncal acne, occurring on the chest and/or back, can involve much larger skin areas than facial acne, requiring formulations that are easy to apply and highly spreadable. In a study of 19 participants, tazarotene 0.045% lotion was well tolerated and efficacious in the treatment of moderate truncal acne [26]. There were no significant changes from the baseline to week 12 in any tolerability assessment (erythema, dryness, peeling, oiliness, pruritus, and burning) and no adverse events were related to tazarotene treatment. At week 12, participants experienced over 80% reductions from the baseline in total lesion counts, with 89% of participants achieving clear or almost clear skin.

4. Conclusions

In the topical treatment of acne and other dermatological conditions, success hinges upon minimizing irritation, enhancing therapeutic outcomes, and fostering patient adherence [52]. Optimizing topical formulations involves a complex interplay between the active ingredient(s); the vehicle's design, physical properties, and patient preference; and clinical safety, tolerability, and efficacy. Tazarotene 0.045% lotion is easy to apply and has sensory and aesthetic properties preferred by patients. The lotion vehicle utilizes proprietary polymeric emulsion technology to uniformly distribute the active ingredient and hydrating/moisturizing excipients across the skin and to efficiently deliver tazarotene into the skin in a lower-dose formulation. This allows for low irritation potential, moisturization with improvements in skin oiliness, and a favorable safety/tolerability profile without sacrificing clinical efficacy (Figure 8). Tazarotene 0.045% lotion is a beneficial option for the treatment of acne in patients of varying ages, races, ethnicities, and skin types, delivered in a formulation that can be easily used on the face, back, and chest.

Conflicts of Interest

Zoe Draelos has received funding from Ortho Dermatologics. Leon Kircik has served as either a consultant, speaker, advisor, or an investigator for Allergan, Almirall, Epi Health, Galderma, Novartis, Ortho Dermatologics, and Sun. Joshua Zeichner has served as advisor, consultant, or speaker for AbbVie, Allergan, Dermavant, Dermira, EPI Health, Galderma, Incyte, Johnson and Johnson, L'Oreal, Ortho Dermatologics, Pfizer, Procter and Gamble, Regeneron, Sun Pharma, UCB, Unilever, and Vyne. Radhakrishnan Pillai and Arturo Angel are employees of Bausch Health US, LLC, and may hold stock and/or stock options in its parent company. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Emil Tanghetti has served as speaker for Novartis, Ortho Dermatologics, Sun Pharma, Lilly, Galderma, AbbVie, and Dermira; served as a consultant/clinical studies for Hologic, Ortho Dermatologics, and Galderma; and is a stockholder for Accure.

Authors' Contributions

All authors were involved in the interpretation of data and the critical review of all manuscript drafts. All authors have approved the final manuscript draft for submission and are responsible for the integrity of this work.

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