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Authors

Desai, Seemal

Baldwin, Hilary

Del Rosso, James

et al.

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REVIEW ARTICLE

Microencapsulated Benzoyl Peroxide for Rosacea in Context: A Review of the Current Treatment Landscape

Seemal R. Desai[1] · Hilary Baldwin[2] · James Q. Del Rosso[3] · Richard L. Gallo[4] · Neal Bhatia[5] · Julie C. Harper[6] · Jean Philippe York[7] · Linda Stein Gold[8]

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Abstract

Rosacea, a chronic skin condition affecting millions of people in the USA, leads to significant social and professional stigmatization. Effective management strategies are crucial to alleviate symptoms and improve patients' quality of life. Encapsulated benzoyl peroxide 5% (E-BPO 5%) is a newly FDA-approved topical treatment for rosacea that shows promise in enhancing therapeutic response and minimizing skin irritation. This review aims to assess the role of recently FDA approved E-BPO 5% in the current treatment landscape for rosacea management, as it is not yet included in clinical guidelines that predominantly rely on older approved therapies. The review focuses on randomized controlled trials conducted in English-speaking adults. It evaluates the efficacy, safety, and tolerability of various US Food and Drug Administration (FDA)-approved agents used for rosacea treatment, including E-BPO cream, metronidazole gel, azelaic acid gel and foam, ivermectin cream, minocycline foam, oral doxycycline, brimonidine gel, and oxymetazoline HCl cream. Existing therapies have been effective in reducing papulopustular lesions and erythema associated with rosacea for many years. E-BPO 5% offers a promising addition to the treatment options due to its microencapsulation technology, which prolongs drug delivery time and aims to improve therapeutic response while minimizing skin irritation. Further research is necessary to determine the exact role of E-BPO 5% in the therapeutic landscape for rosacea. However, based on available evidence, E-BPO 5% shows potential as a valuable treatment option for managing inflammatory lesions of rosacea, and it may offer benefits to patients including: rapid onset of action, demonstrated efficacy by Week 2, excellent tolerability, and sustained long-term results for up to 52 weeks of treatment.

Key Points

E-BPO 5% uses a novel microencapsulation technology to improve therapeutic effects and reduce inflammatory lesions of rosacea.

E-BPO 5% is an important addition to the current therapeutic options for rosacea and demonstrates improved patient outcomes along with the potential to reduce treatment-associated irritation.

✉ Jean Philippe York
jp.york@galderma.com

1 Innovative Dermatology, Plano, TX, USA

2 Acne Treatment and Research Center, Brooklyn, NY, USA

3 JDR Dermatology Research, Las Vegas, NV, USA

4 University of California San Diego, San Diego, CA, USA

5 Therapeutics Clinical Research, San Diego, CA, USA

6 The Dermatology and Skin Care Center of Birmingham, Birmingham, AL, USA

7 Galderma Laboratories, Dallas, TX, USA

8 Henry Ford Health System, Detroit, MI, USA

1 Introduction

Rosacea is a chronic relapsing facial skin disease that presents with one or more of the following features: recurrent flushing, erythema, inflammatory lesions (papules and

pustules), phymas, and telangiectasias. An estimated 16 million people in the USA have rosacea, and there are a lot more undiagnosed cases, especially in skin of color [1, 2]. As a disease that affects the face, rosacea can make a lasting impression in social and professional settings [3]. The stigmatization seen with rosacea is evident from a global perception survey, in which individuals with central facial redness were judged more negatively than those without [4].

Long-term avoidance of common triggers, use of gentle skin care, and adherence to pharmacologic treatment are fundamental strategies for rosacea control [5]. Phenotype-based medical management of rosacea was first proposed by Del Rosso et al. in 2013 from the American Acne and Rosacea Society [6]. Treatment guided by phenotype has recently been endorsed by Schaller et al. in 2020 from the global Rosacea Consensus (ROSCO) panel, an international group that includes North American dermatology experts [7]. Rather than follow an algorithm, optimal therapy is tailored by the signs and symptoms the clinician observes and the patient finds most troubling [5]. Topical therapy is often the preferred initial treatment, though more severely affected patients may initially need topical therapy plus a systemic agent to gain more rapid control of rosacea.

The objective of this review is to explore how encapsulated benzoyl peroxide 5% (E-BPO 5%) contributes to the current rosacea treatment landscape by enabling the effective and well-tolerated delivery of benzoyl peroxide to the skin through a novel microencapsulation technology. E-BPO 5% is the newest topical agent for rosacea following its approval by the US Food and Drug Administration (FDA) in 2022. E-BPO 5% was developed using the solgel process that encloses BPO in a silica microcapsule, which extends drug delivery time to increase therapeutic response and reduce the risk of skin irritation. E-BPO 5% is not mentioned in published rosacea clinical management guidelines, which have not yet been updated. Additionally, minocycline foam is also a newer topical therapeutic option, which was FDA approved for rosacea in 2020.

2 Methods

The studies for review are English-language randomized controlled trials of adults of any ethnic group or sex. Our search included treatments with anti-inflammatory efficacy in rosacea that specifically included treatment outcomes for inflammatory lesions. PubMed and Google Scholar databases were searched for original clinical trials with the following FDA-approved agents: metronidazole 0.75% or 1%; azelaic acid gel 15% and azelaic acid foam 15%; ivermectin cream 1%; minocycline foam 1.5%; E-BPO cream 5%; oral doxycycline modified release 40 mg capsules; brimonidine gel 0.33%; and oxymetazoline HCl cream 1%. Excluded criteria were non-FDA-approved therapies, pediatric studies, and studies for ocular rosacea.

The gap specifically being addressed during the review process was to find recent treatments approved since the publication of updated guidance for rosacea management (ROSCO 2019). Studies selected for inclusion in this review focused on (1) efficacy, measured by improvement in the number of inflammatory lesions or investigator global assessment (IGA) scores; (2) safety, including serious adverse events and treatment-induced adverse events such as stinging, burning, or worsening of erythema or of inflammatory lesions; and (3) tolerability of the treatment. This review updates FDA-approved acute and chronic rosacea management options, with emphasis on treatment outcomes of rosacea-associated inflammatory lesions.

3 Results: FDA-Approved Therapy for Inflammatory Lesions of Rosacea (Table 1)

3.1 Metronidazole

Available since 1989, topical metronidazole is an antimicrobial that can also inhibit inflammatory mediators generated by neutrophils [8]. It is effective in reducing inflammatory lesions and the perilesional erythema associated with rosacea. As a mainstay of topical rosacea therapy for several decades, metronidazole 0.75% and 1.0% formulations have been well studied in more than 500 patients [9]. An early study [10] demonstrated superiority of metronidazole 1% over vehicle. In a later 9-week split-face study, 40 adults with symmetric distribution of inflammatory lesions applied metronidazole 0.75% twice daily to one side of their face and vehicle to the other [11]. Improvement with metronidazole was noted as early as 3 weeks [11]. "Clear" (IGA 0) or "almost clear" (IGA 1) criteria were not used (IGA 5-point scale). At the study conclusion, metronidazole produced a 65% decrease in inflammatory lesion counts compared with a 15% reduction for vehicle [11]. A longer 6-month double-blind placebo-controlled study confirmed long-term efficacy and safety of metronidazole as monotherapy for control of inflammatory lesion associated with rosacea [12]. When metronidazole 0.75% and 1.0% strengths were blindly compared, both were equally effective when used once daily [13].

Table 1 Baseline and end-of-study characteristics of study participants receiving active therapy for inflammatory papules and pustules

Therapy	Study (Original Investigation)	Size	Duration (weeks)	Race, White (%)	Rosacea severity in treated groups		End-of-study efficacy	
					Moderate/Severe disease (%)	Baseline lesions (mean)	End-of-study lesions (mean)	IGA success (clear, almost clear, or 2-point IGA score improvement) (%)
Metronidazole	Nielsen [10]	81	8	NS	NS	24.4	8.9	62.5[a]
	Dahl [13]							
	Metronidazole 0.75%	72	12	100	All rated as moderate or severe	19	9	57[a]
	Metronidazole 1%					25	10	37[a]
Azelaic acid	Thiboutot et al. [16]							
	Study 1	329	12	97	76/10	17.5	6.8	51
	Study 2	335		87	76/11	17.8	8.9	46
	Draelos et al. [18]							
	2 parallel groups	961	12	95.9	86.6/13.4	21.7	8.5	32
Doxycycline 40 mg	Del Rosso et al. [23]							
	Study 301	251	16	91	52.8/40.9	19.5	7.7	45.7
	Study 302	286			54.2/33.8	20.5	11	22.5
Ivermectin 1%	Stein Gold et al. [27]							
	Study 1	683	12	96.2	82/18	30.9	7.4	38.4
	Study 2	688		95.3	75.9/24.1	32.9	8.2	40.1
Minocycline 1.5%	Stein Gold et al. [29]							
	Study 1	751	12	95.8	88.7/11.3	28.5	10.93	52.1[b]
	Study 2	771		97.3	85.1/14.9	30.0	11.46	49.1[c]
E-BPO 5%	Bhatia et al. [33]							
	Study 1	361	12	95.9	86.4/13.6	25.7	8.3	43.5
	Study 2	372		88	90.8/9.2	29.8	9.5	50.1

All studies included in this table were from properly powered and conducted individual randomized clinical trials and defined treatment success as being rating of clear, almost clear, or 2-point IGA score improvement, unless otherwise noted

E-BPO encapsulated benzoyl peroxide, *IGA* Investigator Global Assessment, *NS* not specified

[a]Percentages indicate "improved" or "much improved," or "clear to mild rosacea." "Clear" or "almost clear" terminology was not used

[b,c]The IGA scale used in the studies only assessed the papulopustular component of rosacea and did not incorporate evaluation of facial erythema as part of the investigator's static global assessment; this is an important distinction compared with IGA scales used in pivotal trials with other therapies

3.2 Azelaic Acid

Topical azelaic acid gel 15% was FDA-approved for rosacea in 2002. Azelaic acid improves rosacea by exerting anti-inflammatory activity on the cathelicidin pathway, which is upregulated in rosacea-affected skin [14]. Prior to FDA approval, azelaic acid 20% cream was studied in a split-face, 9-week study of 33 subjects [15]. At 9 weeks, complete remission or marked improvement occurred in 78.2% of the treated sides compared with 31.2% with placebo [15]. Minor local irritation was similar for both sides, though for the first 3 weeks, the treated side had more irritation [15].

The efficacy of FDA-approved azelaic acid 15% gel was reported in 2003. Two 12-week, double-blind, randomized, parallel-group, vehicle-controlled studies enrolled 664 subjects [16]. Inflammatory lesions in the actively treated group decreased from 17.5 and 17.8 at baseline to 6.8 and 8.9 at 12 weeks for studies 1 and 2. In the vehicle group, mean lesion counts decreased from 17.6 and 18.5 to 10.5 and 12.1 [16]. Investigators' rating of marked improvement or complete remission was achieved in 51% (study 1)

and 46% (study 2) of treated subjects compared with 27% (study 1) and 31% (study 2) in the vehicle group [16]. Treatment-related cutaneous adverse events were higher in the treated group; 38% of subjects experienced transient burning, stinging, or itching [16]. At the end of the study, a higher proportion of treated subjects, 44% in study 1 and 46% in study 2, had less erythema compared with those who received vehicle, an improvement thought to be due to erythema reductions associated with inflammatory lesions [16]. More subjects receiving azelaic acid stopped treatment (5%) due to cutaneous adverse reactions compared with a 2% dropout rate in the vehicle group [16]. A subsequent study demonstrated no clinical difference between once-daily and twice-daily dosing [17].

An emollient foam preparation of azelaic acid 15% was FDA approved in 2015. It was developed to be better tolerated than the gel. A 12-week, phase 3, randomized, double-blind, parallel-group, vehicle-controlled trial of twice-daily azelaic acid foam 15% was evaluated in 484 actively treated versus 477 vehicle-treated subjects [18]. At baseline, IGA scores indicated moderate (86.8%) or severe (13.2%) disease [18]. At the 12-week study conclusion, 32% of active foam subjects had a success rate of "clear" (IGA 0) or "minimal" (IGA 1) or a 2-point improvement in IGA compared with 23.5% in the vehicle group [18]. Drug-related cutaneous adverse events were experienced by 7.0% in the active group compared with 4.4% in those receiving vehicle [18]. Treatment discontinuation due to foam side effects was low, 1.2% in the active group and 2.5% in the vehicle group [18]. Cutaneous adverse events were highest in the first 4 weeks of treatment [18]. Reported adverse events and discontinuation of treatment with the azelaic acid foam were lower than those reported with azelaic acid gel, although they were not compared in a head-to-head study [18].

3.3 Doxycycline Therapy

Once-daily oral doxycycline, formulated as a 40-mg dose (30 mg immediate release and 10 mg delayed release beads), was approved for rosacea by the FDA in 2006. Tetracycline derivatives are antimicrobial and affect neutrophil chemotaxis and inhibit matrix metalloproteinases that impact the cathelicidin cascade, one of the dysregulated immune pathways in rosacea [19, 20]. Modified-release doxycycline 40 mg utilizes the drug's anti-inflammatory properties at a dose below that which can typically kill bacteria [21] and is as effective as once-daily doxycycline 100 mg for moderate-to-severe rosacea [22]. Two phase 3, randomized, double-blind, placebo-controlled trials (trials 301 and 302) [23] confirmed the efficacy and safety of once-daily doxycycline 40 mg. In 269 actively treated subjects, doxycycline led to mean inflammatory lesion reductions of 11.8 in study 301 and 9.5 in study 302, compared with reductions of 5.9 and 4.3, respectively, in placebo-treated subjects [23]. The significant improvement in lesion reduction in actively treated subjects was evident by 3 weeks [23]. The downward trend of inflammatory lesions in the treated group did not plateau by the end of the 16-week study, suggesting a longer trial might reveal additional improvement [23].

The long-term efficacy and safety of modified-release doxycycline as monotherapy was demonstrated in a two-part study [24]. Part 1 enrolled 235 adults with an IGA of moderate to severe (3 or 4 on a 5-point scale). Subjects received 12 weeks of metronidazole 1% gel plus doxycycline 40 mg. A total of 130 (55% of those in part 1), who had achieved an IGA score of clear (0) or almost clear (1), or those who had at least a 2-grade improvement in IGA, were randomized to active and placebo groups for part 2 of the study [24]. Part 2, a double-blind, placebo-controlled, 40-week study, was designed to evaluate the long-term value of oral doxycycline as monotherapy to prevent relapse [24]. By the end of the study, twice as many subjects in the placebo group (18) relapsed compared with the treated group (9), proving that once-daily doxycycline maintenance therapy enhanced long-term rosacea control. There were no serious adverse events nor treatment-associated events [24].

3.4 Ivermectin Cream 1%

Once-daily topical ivermectin 1% cream was FDA approved in 2014 for inflammatory lesions of rosacea. There is a relationship between *Demodex folliculorum* density and markers of inflammation in the skin of rosacea patients [25]. A 12-week pilot study of 20 subjects with IGA scores ≥ 3 demonstrated clinical improvement with in vivo reduction of demodex mite density and improved cutaneous inflammatory markers with once-daily ivermectin cream 1% [26]. At treatment weeks 6 and 12, diminished mite density occurred in conjunction with downregulation of inflammatory markers [26]. All subjects improved, with 16 of the 20 attaining an IGA score ≤ 1 (clear or almost clear) [26].

Following the pilot study, the clinical benefit of ivermectin was shown in a pivotal phase 3 trial. Ivermectin 1% cream versus vehicle for moderate-to-severe rosacea was examined in 2 parallel 12-week, double-blind, randomized controlled trials of 683 (study 1) and 688 (study 2) adults [27]. Treatment success, defined by IGA as "clear" (0) or "almost clear" (1) at 12 weeks, was higher in the treated subjects. Of those actively treated, 38.4% (study 1) and 40.1% (study 2) of subjects achieved treatment success compared with 11.6% and 18.8% in the vehicle groups [27]. Actively treated subjects reported fewer adverse effects, such as skin dryness, when compared with vehicle [27]. Subsequent 40-week extension studies compared safety and efficacy of daily ivermectin 1% cream with azelaic acid 15% gel [28].

Both agents were safe and well tolerated throughout the extension study, though the study design prevented direct efficacy comparisons between the 2 therapies [28]. Subjects using azelaic acid reported more skin burning, skin irritation, and dry skin [28].

3.5 Minocycline Foam

Topical minocycline 1.5% foam was FDA approved in 2020 for use in adults with moderate-to-severe rosacea. Topical minocycline is antimicrobial and may also inhibit inflammation through anti-inflammatory activity, such as other members of the tetracycline family [19]. In two phase 3, randomized, multicenter, double-blind, vehicle-controlled studies, minocycline 1.5% foam was compared with vehicle in a total of 751 (study 11) and 771 (study 12) subjects [29]. Most subjects had moderate (3) IGA scores, 88.7% (study 11) and 85.1% (study 12). Severe (IGA 4) scores were seen in 11.3% (study 11) and 14.9% (study 12). Minocycline 1.5% foam was superior to vehicle as early as 4 weeks, a benefit that was maintained until the study ended at 12 weeks. At the study conclusion, both active and vehicle groups improved, but the topical minocycline group had statistically significant greater reductions in inflammatory lesion counts [29]. At the end of the study 11, actively treated subjects had a mean reduction in lesions of 17.57 (64% reduction) compared with 15.65 (57% reduction) in the vehicle group. Study 12 actively treated subjects had a mean lesion count reduction of 18.54 (61%), while those treated with vehicle had 14.88 (50%) [29]. IGA endpoint success was defined as a dichotomized (yes/no) IGA score of clear (0) or almost clear (1) and at least a 2-grade improvement from baseline at week 12 [29]. Importantly, the IGA scale used in the study only assessed the papulopustular component of rosacea and did not incorporate evaluation of facial erythema as part of the investigator's static global assessment [29]. IGA scores improved by 52% with active treatment versus 43% with vehicle (study 11), and 49% versus 39% in study 12 [29]. An open-label, 52-week extension study confirmed the long-term safety and efficacy of minocycline 1.5% foam as maintenance therapy. The incidence of treatment-related adverse effects was low: 1.5% in the active group and 4.7% in the vehicle group [30].

3.6 Encapsulated Benzoyl Peroxide 5% Cream (E-BPO 5%)

E-BPO 5% cream was FDA approved as a topical agent for inflammatory lesions of rosacea recently in 2022. It employs a porous silica microcapsule technology designed to slow BPO absorption over time. The microcapsule can bind drugs, then release them gradually to diminish irritation [31, 32]. A phase 2 dosing study compared E-BPO 1% and 5% with vehicle. Neither strength caused significant irritation, while E-BPO 5% exhibited a superior dose-response trend [32]. Phase 3 trials confirmed benefits of E-BPO 5% in two 12-week, randomized, double-blind, vehicle-controlled trials (NCT03564119 and NCT03448939). A total of 733 adults with IGA grades moderate (3) or severe (4) were randomized to once-daily E-BPO 5% or vehicle cream [33]. Subjects were reevaluated at 2, 4, 8, and 12 weeks [33]. In study 1, a significant number of actively treated subjects were clear (IGA 0) or almost clear (IGA 1) by week 2 (9.5%), compared with those using vehicle (3.1%). In study 2, the respective results were 13.2% and 5.5% [33]. The superiority of E-BPO 5% persisted throughout all subsequent evaluations. In study 1, at 12 weeks, 44% of subjects actively treated achieved IGA success of clear (0) or almost clear (1) compared with 16% who received the vehicle. In the second parallel study, 50% of those actively treated versus 26% of vehicle-treated subjects achieved IGA success [33]. Improvement in reduction in the mean number of inflammatory lesions were observed as early as 2 weeks, which changed by as much as − 13.0 for E-BPO versus − 8.0 for vehicle (study 2), with continued improvement through 12 weeks in both studies [33]. At week 12 in study 1, the mean (SD) reductions in inflammatory lesion count for subjects treated with E-BPO 5% were − 17.4 (9.3) and − 9.5 (9.4) compared with vehicle ($P < 0.001$). The respective values for study 2 were − 20.3 (9.6) and −13.3 (9.6; $P < 0.001$) [33].

A 40-week, open-label extension study (NCT03564145) demonstrated long-term efficacy and safety [34]. Subjects from the phase 3 trial continued E-BPO 5% for up to 40 additional weeks, for a total of 52 weeks of treatment. Subjects who achieved complete clearance stopped E-BPO 5% but were allowed to restart it if relapse occurred [34]. In addition to sustained efficacy of E-BPO, subjects showed improvements in erythema with 81.3% of 209 subjects having no or mild erythema over 52 weeks [34]. Subjects with severe erythema decreased from 14.4% to 0.5% at week 52 [34]. Seventeen subjects (3.2%) had an adverse event related to the study drug [34]; 5 subjects (< 1%) discontinued E-BPO 5% due to treatment-related adverse events [34]. Results demonstrated progressive efficacy and favorable safety and tolerability for up to 52 weeks of treatment [34].

3.7 Head-to-Head Comparison Studies for Inflammatory Therapy

3.7.1 Azelaic Acid Versus Metronidazole 0.75%

Head-to-head comparisons of anti-inflammatory therapy for rosacea are rare. Azelaic acid 20% and metronidazole 0.75% were compared in a 15-week, double-blind, split-face study of 40 subjects with symmetric numbers of inflammatory

lesions [35]. Inflammatory lesions improved with either treatment. There was a 78.5% reduction in inflammatory lesions on the azelaic acid side versus a 69.4% reduction on the metronidazole side [35]. Subjects had reduced rosacea-associated skin dryness and burning with both products. There was more stinging with azelaic acid, though this did not concern subjects [35]. Physicians rated greater global improvement with azelaic acid at weeks 9 and 15, but differences achieved only borderline significance [35]. More subjects indicated they would prefer to use azelaic acid again versus metronidazole [35]. Another study involving 251 subjects compared azelaic acid gel 15% with metronidazole gel 0.75%. By the end of the 15-week study, the azelaic group had a 72.7% reduction in lesions counts compared with a 55.8% reduction for those using metronidazole [36]. Despite the clinical superiority of azelaic acid gel, 4% of subjects discontinued its use due to side effects, in contrast to none of those receiving metronidazole discontinuing [36].

3.7.2 Ivermectin 1% Versus Metronidazole 0.75%

In another head-to-head comparison, a European group investigated ivermectin 1% cream versus metronidazole 0.75% cream in a 16-week trial [37]. In part A, 478 subjects were randomized to receive once-daily ivermectin 1% cream, while 484 subjects received twice-daily metronidazole 0.75% [37]. Due to dosing differences, only investigators were blinded. At the end of the 16-week study, lesion counts were reduced by 83% in the ivermectin group versus 73.7% in the metronidazole group [37]. The ivermectin group had better IGA ratings of clear (0) or almost clear (1) in 84.9% versus 75.4% in the metronidazole group [37]. IGA scores in the ivermectin group were superior to those in metronidazole group by week 6. Neither drug showed an efficacy plateau, suggesting that continued use would provide more benefit [37]. The authors concluded that topical ivermectin provided superior results compared with metronidazole [37]. At the conclusion of part A, an extension study (part B) followed subjects with IGA scores of clear (0) or almost clear (1) every 4 weeks for up to an additional 36 weeks [38]. Treatment with the same drug used in part A was reinitiated for a relapse (IGA $\geq$ 2) [38]. Those treated in part A with ivermectin 1% had a longer time until relapse, 115 days, compared with 85 days for those treated with metronidazole, suggesting ivermectin 1% produced a more durable response [38].

The scarcity of head-to-head comparison studies makes it difficult to know which treatment provides the most benefit for rosacea. In a 2016 network meta-analysis, a quantitative comparison between ivermectin 1% cream and topical rosacea treatments that were available at the time (metronidazole 0.75% and azelaic acid 15% gel) concluded that ivermectin 1% cream is a more effective topical treatment for the inflammatory lesions of rosacea [39]. In 2019, an updated systematic review of 152 studies confirmed high-certainty evidence that ivermectin and azelaic acid reduce inflammatory lesion counts, with moderate-certainty evidence for metronidazole and topical minocycline [40]. Of FDA-approved systemic rosacea systemic therapies, there was moderate-certainty evidence for modified-release doxycycline 40 mg [40].

3.8 Topical Vasoconstrictors

The fixed vascular changes leading to the persistent facial redness of rosacea do not improve with anti-inflammatory therapy [41]. Two topical α-adrenergic agonists are FDA-approved to improve the appearance of facial erythema and also forms part of the ROSCO treatment algorithm.

3.8.1 Brimonidine Tartrate Gel 0.33%

The first, brimonidine tartrate 0.33% gel, was approved by the FDA in 2013 for once daily use. It is a selective α_2-adrenergic receptor agonist with strong vasoconstrictive effects [42]. Two identical randomized, double-blind vehicle-controlled, 8-week phase 3 trials evaluated effects of brimonidine tartrate gel 0.5% on the severity of facial erythema based on a clinician erythema assessment (CEA) and a patient self-assessment (PSA) [42]. Success was defined as a 2-grade improvement over baseline within 12 h of application, as assessed by both a clinician and the subjects [42]. Thirty percent of actively treated subjects attained treatment success compared with 10% of those who received the vehicle. Efficacy, defined as a 1-grade improvement in erythema, was seen in ~ 70% of treated subjects versus ~ 30% in the vehicle group [42]. Swift improvement in the treated group, often within 30 min, was noticed [42]. Maximal effects were seen between 3 and 6 h after application [42]. During the 4-week active treatment phase, no tachyphylaxis was noted. No significant erythema rebound was seen in the 4-week poststudy observation phase [42]. The durability of brimonidine-induced erythema reduction, without significant tachyphylaxis, was confirmed in a 1-year open-label study [43]. A postmarketing publication 1 year later reported that 10–20% of patients may experience paradoxical erythema [44]. The authors proposed an algorithm for management of this phenomenon [44]. In a study combining topical anti-inflammatory ivermectin cream 1% plus topical brimonidine 0.33% vasoconstrictor therapy, benefits were additive with no significant side effects [45].

3.8.2 Oxymetazoline HCl 1% Cream

Oxymetazoline HCl 1% cream, approved by the FDA in 2017, is a topical α_1-receptor agonist used once daily for facial erythema. Oxymetazoline vasoconstricts vascular smooth muscle, thereby diminishing the appearance of facial redness [41]. The efficacy and long-term safety of oxymetazoline was demonstrated in two 8-week phase 3 trials and one extended open-label study. The phase 3, 8-week, double-blind, randomized placebo-controlled trials compared once daily oxymetazoline 1% cream to vehicle in a total of 885 subjects [46, 47]. Subjects with moderate-to-severe constant central facial redness received active treatment or vehicle treatment for 4 weeks, followed by a 4-week observation period. Treatment success, defined as a 2-grade or greater improvement from baseline within 12 h after application, was assessed by the investigators and subjects [46, 47]. When rated on day 29, the composite success rate in the first study at hour 12 was 14.8% in the treated group and 6.0% in the vehicle group; respective values in study 2 were 12.3% and 6.1% [46, 47]. Digital photographic assessments 3 h after application showed a 25% median reduction in redness, diminishing to 9.6–14.8% median reduction at 12 h in the treated group, while the vehicle groups had 0–3.9% reduction at 3 h and a 1% reduction in redness at 12 h [46, 47]. A subsequent open-label study proved sustained efficacy, tolerability, and safety for up to 52 weeks [48]. No tachyphylaxis was reported [48]. Long-term treatment was discontinued in 3.2% of subjects due to application-site adverse events [48]. There were no rosacea flares, no increases in papules or pustules, and no worsening of telangiectasias [48].

4 Discussion

The clinical trials reviewed here support the anti-inflammatory efficacy of topical metronidazole, azelaic acid, ivermectin, minocycline foam, and systemic doxycycline 40 mg for inflammatory lesions of rosacea. The most recent FDA-approved therapy for rosacea, E-BPO 5%, demonstrated excellent tolerability and rapid improvement that was evident by week 2 of treatment and showed progressive clinical improvement for up to 52 weeks [33, 34]. Significant reductions in lesion counts and improvements in IGA occurred with active treatment in all studies. Most studies recorded improvement by 3–4 weeks. As seen in trials of azelaic acid, anti-inflammatory-dose doxycycline, ivermectin, and topical minocycline, E-BPO 5% showed no abrupt treatment-effect plateau at 12 weeks, which suggests study length may not have been sufficient to determine true therapeutic benefits [33]. Dropout rates were low with E-BPO 5%; over 90% of active and vehicle-treated subjects completed the placebo-blinded study. During the extended open-label phase 3 study, fewer than 1% of withdrawals were due to treatment-related adverse events [33].

Adverse treatment effects, particularly application-associated stinging or burning, were common and usually transient during the early phases of treatment, particularly with azelaic acid [16]. This is not surprising, since most rosacea sufferers also have sensitive skin that is easily irritated. Later tolerance may indicate that improvement in inflammation led to less skin sensitivity. The lowest treatment-related adverse events were seen with ivermectin 1%, azelaic acid foam 15%, and E-BPO 5%. Earlier unencapsulated BPO 5% formulations combined with topical clindamycin demonstrated a 71% reduction in inflammatory rosacea lesions at 12 weeks but a 14.8% incidence of treatment site reactions underscoring the efficacy of unencapsulated BPO but with high levels of irritation [49]. A retrospective study of medical and pharmacy claims for rosacea treatments also reported poor tolerability of unencapsulated BPO. Of 1084 subjects treated with unencapsulated BPO in the retrospective study, 22.5% reported treatment-related adverse effects, leading to high rates of treatment discontinuation [50]. E-BPO 5% represents an important advance in effective and tolerable rosacea therapy. A novel microencapsulation process enables a formulation of BPO that overcomes traditional limitations of poor tolerability and variable efficacy through a controlled, gradual release to the skin [33, 34]. The drug is an important therapeutic option because rapid improvement during flares, plus minimal adverse effects with long-term monotherapy, may lead to better control of inflammatory lesions of rosacea.

5 Conclusions

E-BPO 5% cream is the latest therapy for the complex and variable disease of rosacea and is demonstrated to help patients achieve clear or almost clear skin, which was a specific benchmark called for in the ROSCO 2019 consensus [7]. There is a great clinical need for effective therapy like E-BPO 5% cream to treat rosacea, since many patients are not achieving the rosacea consensus 2019 panel recommendation goal of complete clearance [7]. E-BPO 5% demonstrated rapid onset of action. Specifically, 44–50% of subjects treated with E-BPO 5% met primary endpoints of a 2-grade improvement in IGA scores to clear (0) or almost clear (1), a reduction in lesion counts by week 12, and progressive improvement to erythema, with no therapeutic plateau [33, 34]. Any of the therapies approved for inflammatory lesions (papular and pustular phenotype) of rosacea can be safely used for disease flares and for maintenance therapy. Skin irritation, especially early in treatment, should be expected with some agents. The dissatisfaction rate with

standard topical treatment options for rosacea is high; up to 89% of those who experience a treatment-related adverse effect discontinue therapy within a month [50]. E-BPO 5% demonstrated safety and tolerability comparable with its vehicle and maintained a similar profile for up to 52 weeks [33, 34]. Moderate or severe acute rosacea flares may require combination therapy, for which evidence is limited and more research is needed. When therapy is discontinued, up to two-thirds of subjects will eventually relapse [34, 38]. E-BPO 5% has been available to clinicians for less than a year. Subject populations in studies that led to E-BPO 5% approval were ethnically diverse (over 20% of subjects were Hispanic or Latino), but racial diversity was limited. Asian individuals comprised 6.7% of subjects, but fewer than 1% of participants were African American [34]. Additional clinical experience with E-BPO 5%, particularly in people with skin of color, is needed to assess whether once-daily use of this effective and tolerable formulation will encourage adherence and lead to better long-term outcomes.

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Conflict of interest The authors declare the following potential conflicts. S.R.D. serves as a consultant for Galderma. In addition, he serves in multiple other leadership and industry roles unrelated to this product. H.B. has served as an advisor and speaker for Galderma, Bausch, Sun, Almirall, and EPI, as well as an advisor and investigator to Sol-Gel Technologies Ltd. J.Q.D.R. is a consultant, researcher, and speaker for Galderma, Almirall, Bausch Health (Ortho), Beiersdorf, BioPharmX, Cassiopeia, EPI Health, Ferndale, Leo Pharma, LaRoche-Posay, L'Oreal, Main Pharma, SolGel, Sun Pharma, and Vyne. R.L.G. is a cofounder, scientific advisor, and consultant, has equity in MatriSys Biosciences, and is a consultant for Galderma. N.B. is a consultant for Abbvie, Almirall, Arcutis, Beiersdorf, Biofrontera, BMS, BI, Cara, Dermavant, EPI Health, Ferndale, Galderma, InCyte, ISDIN, J&J, LaRoche-Posay, Leo, Lilly, Ortho, Pfizer, Regeneron, Sanofi, SunPharma, and Verrica. J.C.H. has served as consultant for Cutera, Almirall, Sun, LaRoche-Posay, Ortho, EPI, BioPharmX, Cassiopeia, Cutanea, Vyne, Galderma, Dermira and Sol-Gel Technologies Ltd.; a speaker for Almirall, Ortho, EPI, Vyne, and Galderma; and an advisory board member for EPI, Cassiopeia, Cutanea, Vyne, and Galderma. J.P.Y. is an employee of Galderma Laboratories. L.S.G. is an advisor/investigator and/or consultant for Galderma, Ortho Derm, EPI Health, Vyne, Novartis, Sun, and Cutera.

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