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COMMENTARY

A Review of the Diagnostic and Therapeutic Gaps in Rosacea Management: Consensus Opinion

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ABSTRACT

Rosacea is a common, chronic inflammatory disease characterized by both fluctuating and fixed heterogeneous signs such as facial erythema, papules/pustules, telangiectasia, acute vasodilation (flushing), and phymatous changes, and symptoms such as cutaneous stinging and burning. The shift to a phenotype-based approach to rosacea management has improved the consistency of recommendations across recent published guidelines. Consistent and thorough guidance for the classification, diagnosis, and management of the disease is difficult, as the mechanisms underlying the development of rosacea are still not completely understood nor universally accepted. Here, we provide a critical review of current published guidance, and gaps in the knowledge and management of rosacea. We present the recently approved microencapsulated benzoyl

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peroxide as an effective topical treatment option for papulopustular rosacea. Benzoyl peroxide (BPO) has been used in acne management for many years; however, many clinicians perceive treatment of rosacea with any BPO formulation to be counterintuitive because of concerns of potential skin irritation, while the lack of an accepted mechanism of action on rosacea pathophysiology means that others may be hesitant to use BPO as a treatment. Minocycline foam 1.5% is also an option for the treatment of inflammatory lesions in rosacea, with a decreased risk of systemic adverse events compared with oral minocycline.

Keywords: Expert opinion; Guidelines; Management; Microencapsulated benzoyl peroxide; Minocycline foam; Rosacea

Key Summary Points

Future recommendations and guideline updates for rosacea should aim to establish consensus and promote consistent management across the dermatologic community, including the importance of patient-centric management and education to improve adherence and treatment success.

The recent approval of new treatment options for rosacea, including microencapsulated benzoyl peroxide (E-BPO) as an effective and tolerable treatment for papulopustular rosacea and minocycline foam for inflammatory lesions of rosacea, warrant a revision to current published guidelines.

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INTRODUCTION

Rosacea is a common, chronic disease that, despite having an estimated prevalence of 3.2% in the USA, is still poorly understood [1, 2]. It is characterized by heterogeneous signs and symptoms that cycle between remission and exacerbation, including fixed and transient facial erythema, flushing, papules, pustules, phymatous changes, telangiectasias, and stinging and burning [1, 3–5]. Management should be individualized to the patient, primarily on the basis of current clinical presentation (phenotype); and, when appropriate, multiple therapies should be integrated to optimally target the patient-specific clinical manifestations of rosacea [3–5]. In this opinion piece, we provide a critical review of published guidelines, particularly those published by the American Acne and Rosacea Society (AARS) and the Global Rosacea Consensus (ROSCO) panel. We also discuss the more recently approved microencapsulated benzoyl peroxide (E-BPO) and minocycline foam as effective and well-tolerated treatment options for rosacea. The existence of safe and effective treatments for rosacea that were not available at the time of the last AARS and ROSCO guideline updates warrants revision. This article is based on previous studies and does not include new research by the authors involving human participants or animals.

KNOWLEDGE GAPS IN ROSACEA

Psychosocial associations Since the last AARS and ROSCO updates in 2019 [4, 6], the 2020 Beyond the Visible report has highlighted the psychological and invisible burden of rosacea [7]. It revealed that 89% of patients with rosacea considered their disease to be uncontrolled to some extent, and 58% experienced a significant daily life impact. Patients with rosacea had missed 4% of work time in the past year, equating to nearly 10.5 working days annually [7].

Beyond the psychological burden There are several gaps in our rosacea understanding that necessitate attention. Understanding the

development of rosacea is pivotal for effective treatment for patients; however, data gaps persist in its pathophysiology and classification of severity for ocular, phymatous, and granulomatous rosacea, which can limit treatment options. Additionally, the quality of evidence for the treatment of phymatous and granulomatous rosacea is low, as there are limited trial data [6].

Association between phyma and carcinomas Previous research has suggested that there is an unexplored link between phyma and skin cancer. Rhinophyma has been observed to hide the emergence of basal and squamous cell carcinomas developing in the nasal area of the elderly population; however, it is possible that this is coincidental [8, 9]. Regardless, vigilance by dermatologists during treatment of phymatous rosacea is crucial for early cancer detection [8].

Cutaneous microbiome Another incompletely understood area of rosacea is the effect of the skin microbiome on the pathophysiology and presentation of the disease. Woo et al. found a link between lower *Cutibacterium acnes* and increased rosacea severity [10]. Proliferation of *Demodex folliculorum* and its associated bacteria (e.g., *Bacillus oleronius*) may contribute to early inflammation in rosacea [11, 12]. The secretome of Gram-negative *Bacillus oleronius* may stimulate peripheral blood cell proliferation and neutrophil accumulation in rosacea skin, leading to inflammation and, in the case of the latter, tissue degradation [13, 14]. However, the role of *B. oleronius* in rosacea is not as widely accepted as *D. folliculorum*, warranting additional research. Additionally, increased facial skin temperature in patients with rosacea, caused by increased blood flow, is thought to promote inflammatory β-hemolytic protein production by *Staphylococcus epidermidis* [15].

Cathelicidin cascade The role of cathelicidin antimicrobial peptides in rosacea warrants further exploration—Yamasaki et al. discovered that patients with rosacea often express higher levels of abnormally processed cathelicidins in their facial skin, correlating to increased inflammation [16]. Toll-like receptor activation may contribute to this process, triggering various immune and vascular responses that promote angiogenesis, inflammation, and skin microbiome changes [16, 17].

Transient receptor potential (TRP) protein channels Immunostaining has shown increased *TRPV* gene expression in dermal inflammatory cells in patients with rosacea [18]. Activation of some TRPV channels owing to heat may explain rosacea symptoms triggered by environmental warmth or dietary factors [18–20]. This activation may trigger an inflammatory cascade, releasing proinflammatory cytokines such as interleukin-1, prostaglandin E2, and matrix metalloproteinases 1 [18]. Further investigation may elucidate this link.

OVERVIEW OF CURRENT PUBLISHED GUIDANCE

Since its introduction in 2008, there have been several updates to the AARS guidelines to address the use of newly approved therapies and other management options for the treatment of rosacea [6, 21–25]. However, since the last guideline update in 2019, new treatments have been approved for the treatment of rosacea, including E-BPO cream and minocycline foam, which highlights the need for updated guidelines.

Several consensus publications support a shift from a subtype-led to a phenotype-based approach for rosacea management [1, 25–28]. Published data support the use of topical alpha-agonists and/or device therapy for the management of rosacea presenting with persistent central facial erythema (PFE), while there is a plethora of data suggesting that papulopustular lesions with perilesional erythema should be treated with topical and/or oral treatments that target inflammation [1, 4, 6, 29].

Combination therapy approaches Clinical evidence supports the use of combination therapies to treat signs and symptoms of rosacea effectively, especially for severe or unresponsive cases [4–6, 23, 24, 26, 30]. An individualized phenotypic approach to rosacea treatment is essential to improve the overall effectiveness of therapy; additional research and real-world data collection can help us understand how to optimize treatment outcomes by combining

available treatments in the rosacea armamentarium. Various combination treatments have been explored: oral and topical therapies for faster control of papulopustular rosacea; alpha-agonist and topical therapies for specific unresponsive manifestations of papulopustular rosacea; and alpha-agonist treatment with a selective physical modality to address PFE and telangiectasias [30–33].

Skin barrier dysfunction Patients with rosacea have an impaired skin barrier and sensitive skin [34]. Discussions surrounding skin barrier function often focus on the epidermal permeability barrier; however, alterations in the microbiome and immune-response barriers may also contribute [10–15, 35]. A comprehensive skin care routine is essential for successful rosacea treatment [5, 36]. Using appropriate cleansers, moisturizers, and photoprotection can reduce skin irritation and barrier impairment, improving therapeutic outcomes and patient adherence [5, 6, 21, 22, 25, 26].

More uncommon rosacea types Current publications describe management options for ocular rosacea, including lid hygiene, various topical ophthalmic agents, oral doxycycline therapy, and topical ivermectin specifically for the treatment of blepharitis [4, 6, 37–42]. Existing recommended management options for phymatous and granulomatous rosacea are limited, with guidance suggesting the use of oral tetracyclines and low-dose isotretinoin or device therapy and surgical therapy, respectively [6, 23].

Physical devices The use of energy devices to improve skin quality and manage PFE and telangiectasias of rosacea is explored in the ROSCO and AARS guidelines [4, 24]. The AARS guidelines cover physical modalities and devices, including tangential excision, electroscalpel, and dermabrasion [24]. However, treatment with energy devices can lead to paradoxical cutaneous concerns such as swelling, erythema, bruising, dyspigmentation, and scarring, highlighting the importance of proper device use by an experienced operator [24, 43, 44]. Additionally, intradermal botulinum A can treat rosacea with PFE and flushing that are poorly responsive to other therapies or prone to tolerability issues [6, 45].

GAPS IN CLINICAL EVIDENCE, GUIDELINES, AND OVERALL ROSACEA TREATMENT

There are several gaps in the current management landscape of rosacea, as summarized in Table 1. First, patients who desire fast-acting, long-term control of their rosacea have limited treatment options. Establishing realistic patient expectations at treatment initiation is crucial, especially for those hoping for a rosacea "cure." Patients seeking rapid improvement, including those who have previously used topical therapies, are often prescribed oral systemic agents alongside topical treatments. This is continued until symptom control is achieved, with an eventual transition to topical monotherapy for maintenance [46]. Generally, topical medications are preferred in most cases for the treatment of rosacea, considering the chronic nature of the disease; oral systemic therapy has risks such as systemic adverse events and antibiotic resistance with prolonged full-dose antibiotic use [46]. Therefore, there is a need to explore quick yet effective and long-lasting topical therapies for papulopustular rosacea.

There are limited data available from well-designed, two-arm clinical studies evaluating the efficacy and safety of long-term treatment of rosacea beyond the typical clinical trial length of pivotal studies (12–16 weeks) [47, 48]. In addition, the limited data available primarily address rosacea presenting with papulopustular lesions. This has led to a limited understanding of real-world rosacea presentations, and inconsistencies in recommendations related to standardized care, especially for the long-term management of rosacea [25, 48]. To improve this, we recommend conducting well-designed comparative retrospective studies to establish optimal first-line and maintenance treatments for rosacea [49].

Published guidelines lack specific guidance on alternative therapies, treatment adjustments, and treatment for specific patient types. Current guidance was developed using clinical trial data from treatment-naïve patients or those who had been off treatment for multiple weeks/months [25]. Additional data are needed

Table 1 Gaps in current guidance

Gaps in rosacea management	Rationale
Fast-acting, long-lasting, and tolerable topical treatments	Quick improvement of symptoms is often achieved with combination treatments of topical and systemic therapies, which come with additional risk of systemic adverse events [46]
Maintenance therapy beyond 12–16 weeks	Limited active- and vehicle-controlled trial data on the effectiveness and tolerability of treatment beyond 12–16 weeks [48]
Additional data on combination therapies	Many current treatments are only indicated to treat a single feature of rosacea. As a multifactorial disease process, guidance on designing treatment regimens that address each individual patient's signs and symptoms of rosacea is needed [48]; more data on optimal integration of individual therapies are needed
Treatment of nonresponders	Current guidance is based on evidence from adult patients with rosacea who have not been previously treated/have been off treatment for weeks to months [25]
Clarity on diagnosis and treatment of rosacea in patients with skin of color	There is a risk of misdiagnosis or delayed diagnosis in patients with darker phototypes during clinical assessment, as erythema and telangiectasia are more difficult to visualize; there are limited data on the treatment of rosacea in patients with skin of color [50]
Patient-centric approach to rosacea management	There is a need for increased guideline emphasis on patient education, psychosocial support, and individualized treatment plans that incorporate patient-specific needs, preferences, and expectations [48]
Availability and accessibility of recommended management options	Current guidance does not take into consideration the difficulties that patients may have when trying to access certain treatments, which can have a major impact on treatment adherence and patient outcomes

regarding successful treatment of nonresponders to inform future guideline updates. Emphasizing the diagnosis and management of rosacea in patients with skin of color is also recommended, as facial erythema and telangiectasias can be more difficult to visualize in darker skin, leading to underdiagnosis, delayed diagnosis and treatment, and worsening

chronic manifestations of rosacea, such as ocular or phymatous changes [50].

Although the consistency of recommendations for rosacea management has improved with the phenotype approach, it is important to standardize definitions and specific criteria to avoid confusion among clinicians. Guidelines should also include patient-centric recommendations as vital management components, including patient education, psychosocial support, and individualized treatment plans that consider patients' preferences, needs, and expectations [48]. Developing a shared decision-making model that incorporates social determinants of health, such as home environment, medical care access, and education level, may accommodate a comprehensive patient-centric approach to rosacea management. Respective of the prior scientific and clinical updates, considerations for the availability, accessibility, and affordability of treatment options may have a significant impact on patients' ability to access care, receive optimal therapy, and adhere to treatment. Foremost, however, is the need for more frequent updates to consensus recommendations and guidelines that include new, clinically relevant information on rosacea pathophysiology, diagnosis, skin care, potential comorbidities, and therapeutic advances, including emerging treatments and management options.

NOVEL TOPICAL TREATMENTS IN THE ROSACEA ARMAMENTARIUM MICROENCAPSULATED BENZOYL PEROXIDE (E-BPO): A NOVEL TOPICAL THERAPY OPTION FOR PAPULOPUSTULAR ROSACEA

In April 2022, the Food and Drug Administration (FDA) approved E-BPO cream, 5% for the treatment of papulopustular lesions of rosacea [51]. Since then, visible and well-tolerated improvements have been observed with long-term treatment, as demonstrated in our real-world case study in Fig. 1; further information is provided in Supplementary Material 1.

Unencapsulated traditional formulations of benzoyl peroxide (BPO) have been recognized as an effective topical management option for rosacea since 1961 [52]. Upon contact with skin, it is believed that BPO penetrates the stratum corneum and enters the pilosebaceous duct, degrading into benzoic acid and oxygen [53]. Additionally, reduction in *D. folliculorum* was observed in a clinical study of BPO and erythromycin versus metronidazole [54]. Efficacy for the treatment of moderate-to-severe rosacea was highlighted in another study assessing once-daily application of BPO, 5%, and clindamycin, 1% topical gel, with adverse application-site reactions occurring in 14.8% of active-arm patients [55]. Although BPO efficacy has been proven in clinical trials, use in clinical practice has historically been limited by tolerability [53]. Direct skin application can cause high transient exposure leading to local cutaneous reactions, including erythema, stinging, burning, and itching.

Silica microencapsulation of BPO (E-BPO) is a novel technology demonstrated in clinical trials to be effective and tolerable in the skin of patients with rosacea [56–58]. This microencapsulation process sequesters BPO in an amorphous silica shell of predetermined size and thickness, creating a permeable barrier between the medication and skin for gradual release to control the rate of skin exposure and decrease the risk of local adverse reactions [56, 59–61].

In two phase 3 trials, E-BPO cream, 5%, was statistically superior to vehicle in treating subjects with papulopustular rosacea [57, 58]. E-BPO exhibited a rapid onset of clinical effects in both co-primary endpoints, viz. Investigator's Global Assessment (IGA) success and mean inflammatory lesion count change. IGA scoring included the number of papules/pustules and erythema severity, while success was defined as a patient scoring 0 ("clear") or 1 ("almost clear") on a five-point scale (0–4). IGA success was achieved by over 25% of subjects treated with E-BPO cream, 5%, by week 4 in both phase 3 trials, versus 6.5% and 14.1% in the vehicle groups ($P < 0.001$ and $P = 0.009$). Subjects who received E-BPO cream, 5%, demonstrated a 67.9% greater reduction in the mean number of

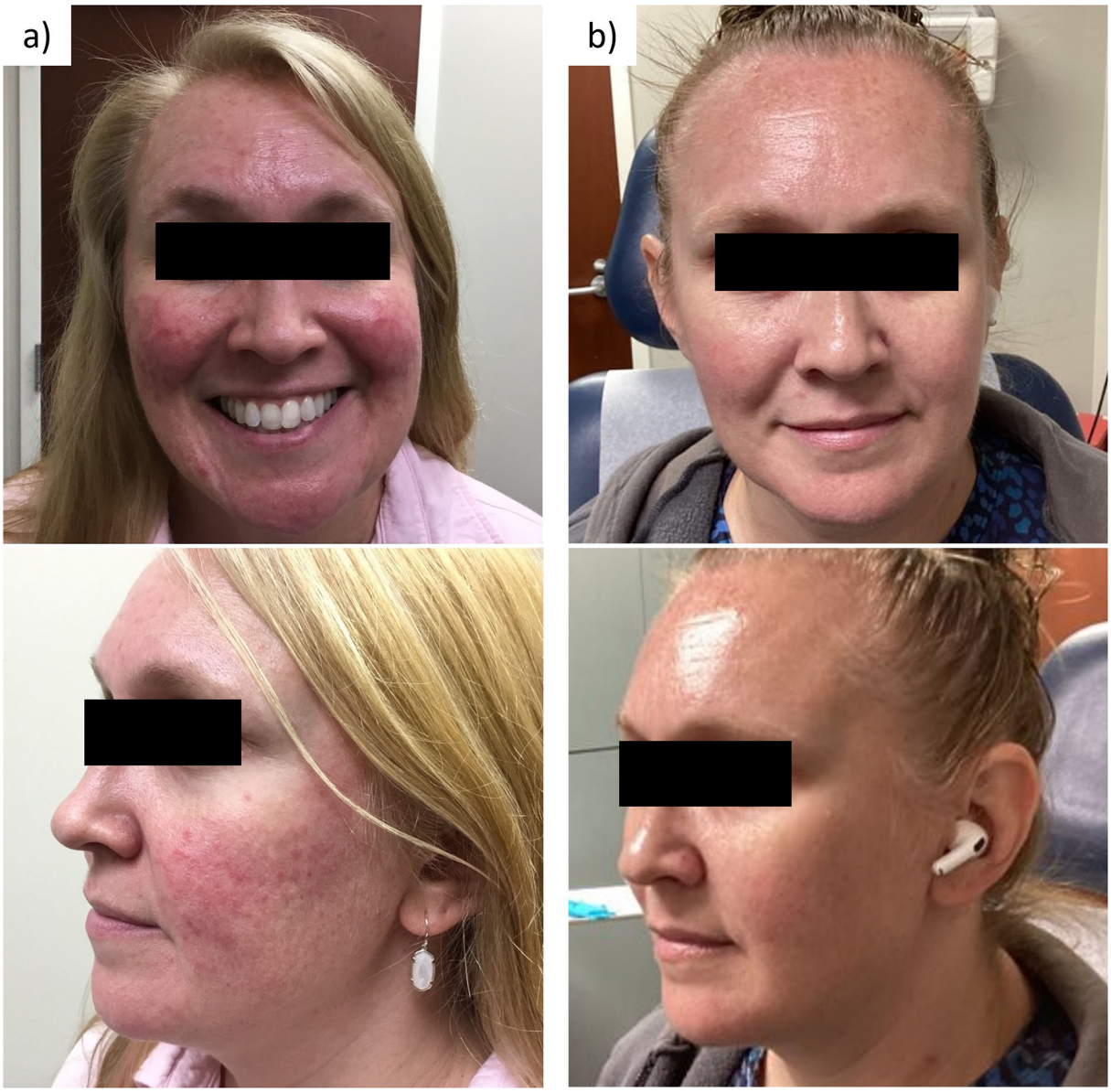

Fig. 1 Clinical photographs of a patient showing improvement in visible signs of rosacea before and after combination treatment with once-daily E-BPO cream, 5%. The patient presented with papules, PFE, and perilesional erythema with intermittent flushing episodes, and sensory symptoms of burning. Once-daily combination treatment of oral doxycycline 40 mg, carvedilol, oxymetazoline cream, 1% and E-BPO, 5% markedly improved the patient's overall facial erythema by 12-month follow-up, with flushing and burning symptoms also well controlled. **a** Pretreatment. **b** Posttreatment (12-month follow-up). Further details of this patient case study can be found in the Supplementary Material

inflammatory lesions from baseline to week 12 versus vehicle treatment in both trials (−17.4 versus −9.5 and −20.3 versus −13.3, respectively; $P < 0.001$). Generally, E-BPO cream, 5%, was safe and well tolerated in phase 3 trials [57]. Additionally, a phase 3 extension study demonstrated that E-BPO is effective in the reduction of papules, pustules, and erythema, and well tolerated for up to 52 weeks of treatment with limited cutaneous irritation [58].

We have provided a case study that depicts visible improvements in a patient presenting with papules, pustules, and PFE after 1 year of continued combination therapy including once-daily use of E-BPO cream, 5%, which clinically suggests a reduction in perilesional erythema and PFE. However, more data are needed to evaluate the potential therapeutic contributions of E-BPO cream, 5%, for the reduction of overall facial erythema with continued use in patients with inflammatory lesions, as monotherapy or in combination with other therapies. There is scientific basis for this consideration: cathelicidin-induced inflammation in lesions can contribute to the progressive increase in PFE via mechanisms induced by variant peptides [16, 62]. Similar to what has been observed with ivermectin treatment for mild–moderate inflamed rhinophyma [63], further investigations could be conducted into the use of E-BPO cream, 5%, for the treatment of clinically inflamed phyma.

Symptoms of rosacea such as burning, stinging, and itching were captured as tolerability parameters in phase 3 clinical trials, showing improvement with E-BPO cream, 5%, treatment. The case study corroborates findings from the phase 3 trials: improvements in burning symptoms accompanying flushing episodes were observed within 3 months of once-daily topical E-BPO treatment initiation.

E-BPO cream, 5%, is a relatively new rosacea treatment with limited available data. Unpublished data suggest enduring changes to the skin barrier and microbiome after 8 weeks of E-BPO treatment, with decreases in the relative abundance of *Staphylococcus* and increases in *Cutibacterium*; however, the significance of these changes in pathophysiology requires further investigation. Moreover, the efficacy of E-BPO on inflammatory lesions and associated erythema support antiinflammatory activity and warrant further characterization, particularly its role in addressing specific sources of erythema and for long-term management, including in patients with early and/or visible inflamed phyma. Further research is encouraged for the effect of E-BPO cream, 5%, on granulomatous rosacea, and its utilization for treating papulopustular rosacea in nonresponders.

MINOCYCLINE FOAM, 1.5%: ANOTHER TOPICAL OPTION FOR THE TREATMENT OF INFLAMMATORY LESIONS IN ROSACEA

Minocycline foam, 1.5%, is a topical tetracycline-class drug approved in 2020 for the treatment of inflammatory lesions in adult patients with moderate-to-severe rosacea [64, 65]. Tetracyclines can provide therapeutic relief for rosacea through their antiinflammatory properties, including regulating cathelicidin production. One study has shown that minocycline can significantly reduce cathelicidins in human bone marrow-derived mesenchymal stromal/stem cells ($P < 0.001$) [66].

Previously, oral tetracyclines were indicated for the treatment of papulopustular rosacea but have been associated with systemic adverse events such as pill esophagitis, dose-related phototoxicity, and cutaneous hyperpigmentation. Oral minocycline treatment has been associated with cutaneous hyperpigmentation and acute vestibular adverse events such as vertigo and dizziness, and uncommon immunologic adverse events such as drug-induced lupus-like syndrome and autoimmune hepatitis [23].

Topical administration of minocycline was found to circumvent these systemic adverse events. Two pivotal phase 3 studies found that there were no reported cases of hyperpigmentation after once-daily application of minocycline foam, 1.5%, for 12 weeks. Generally, minocycline foam, 1.5%, was safe and well tolerated in phase 3 trials. Most treatment-emergent adverse events were mild to moderate, with diarrhea, pruritus, and viral upper respiratory tract infection being the most frequently reported events [64, 65]. Subjects had improved local tolerability signs at week 12 when treated with minocycline foam, 1.5%. Localized symptoms such as erythema, telangiectasia, and flushing were mild-to-moderate at weeks 12 and 40, as observed in an open-label extension study [65].

Additionally, the proven efficacy of minocycline for the treatment of inflammatory

lesions in rosacea was maintained with topical application, with clinical efficacy established as early as week 4 [65]. Subjects treated with minocycline foam, 1.5%, demonstrated a 18.4% greater reduction in the mean number of inflammatory lesions versus vehicle treatment from baseline to week 12 in both trials (−17.57 versus −15.65; $P = 0.0031$ and −18.54 versus −14.88; $P < 0.0001$, respectively). At week 12, IGA success was achieved by roughly half of subjects treated with minocycline foam, 1.5%, in both trials, compared with 43% and 39% treated with vehicle ($P = 0.0273$ and $P = 0.0077$) [65].

CONCLUSIONS

It is important to note that current gaps in published consensus recommendations and guidelines are primarily driven by limitations in data from clinical trials, including evaluation of long-term treatment, phenotype-specific combination therapy approaches, and treatments for nonresponders. Moreover, patient and clinician education are important to improve the overall management of rosacea and inform on the full spectrum of general management suggestions and available treatments. Future updates could focus on the importance of patient-centric management and education, including the need for an optimized skin care routine (for barrier repair and sun protection), and its impact on adherence and success. They should also aim to promote consistent therapeutic approaches by establishing up-to-date consensus for the classification, diagnosis, and treatment of rosacea.

Our understanding of rosacea, its pathophysiology, and the current treatment landscape have come a long way since the original publication of rosacea subtypes in 2002 [67]. In addition, with their recent approvals, we believe that any updates to management guidelines should include E-BPO cream, 5%, as an available option for the topical treatment of papulopustular rosacea with limited cutaneous irritation, and minocycline foam, 1.5%, for the treatment of inflammatory lesions in papulopustular rosacea, with a decreased risk of systemic adverse events compared with oral minocycline [65]. This article also suggests how additional investigations of E-BPO cream, 5%, may help to address some of the identified gaps in our understanding of rosacea pathophysiology and its management.

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Declarations

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The patient presented in the case study has consented to their anonymized medical details, treatment plan, and patient photos to be published.

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