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REVIEW

Emerging Medical Therapies in Rosacea: A Narrative Review

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ABSTRACT

Rosacea is a chronic inflammatory disease with a multifactorial pathogenesis. The wide spectrum of clinical phenotypes, including erythema, telangiectasia, inflammatory papules and pustules, and phyma, demand an individualized approach to treatment. This narrative review offers an updated reference for rosacea management by covering the latest developments in both topical and systemic treatments, including data from newly approved therapies, updates to current treatment modalities and ongoing clinical trials. Although use of benzoyl peroxide as a treatment for rosacea has typically been limited due to irritation, the improved tolerability due to microencapsulation of benzoyl peroxide 5% cream provides a new therapeutic option for patients with rosacea. Minocycline foam and topical ivermectin cream add to our armamentarium of treatment options, particularly for inflammatory papules and pustules. Sarecycline has a narrower spectrum of antibacterial activity, which might reduce the development of antibiotic resistance and disruption of the microbiome compared to other oral antibiotics. Brimonidine gel and oxymetazoline cream provide topical options for redness and flushing. There is emerging evidence about the role of hydroxychloroquine and intradermal botulinum toxin A, which may improve rosacea through their effects on mast cells. The clinical trials pipeline includes agents with a variety of mechanisms, including mast cell stabilization, antimicrobial, anti-inflammatory, and vasoconstrictive effects. However, the clinical pipeline for rosacea appears limited, and there remain important unmet needs for patients with more recalcitrant rosacea or phymatous disease. In addition, there is a need for comparative effectiveness studies to identify the highest value treatment approaches for patients with rosacea.

Keywords: Benzoyl peroxide; Botulinum toxin; Brimonidine; Hydroxychloroquine; Ivermectin; Microencapsulation; Minocycline; Oxymetazoline; Rosacea; Sarecycline

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Key Points
Microencapsulation of benzoyl peroxide has expanded its therapeutic utility for rosacea patients by minimizing skin irritation and enhancing targeted delivery.
Minocycline foam and ivermectin cream provide new topical options, particularly for inflammatory papules and pustules.
Brimonidine and oxymetazoline provide specific topical options for addressing redness and flushing.
Oral sarecycline and hydroxychloroquine might represent novel systemic options for rosacea.
The clinical pipeline for rosacea appears limited, especially for recalcitrant and phymatous forms of rosacea and further comparative effectiveness studies are necessary for optimizing treatment algorithms.

INTRODUCTION

Rosacea is a chronic inflammatory skin disease with a multifactorial pathogenesis that includes immune dysfunction, dysbiosis, and vascular hyperreactivity [1, 2]. Although rosacea has often been divided into papulopustular, erythematotelangiectatic, and phymatous rosacea subtypes, the ROSacea Consensus panel has recommended transitioning to a phenotype-based approach [3]. Such an approach instead categorizes rosacea according to a patient's presenting disease features (e.g., transient erythema, persistent erythema, telangiectasia, inflammatory papules/pustules, phyma). Since patients can present with differing combinations and severities of each feature, a phenotypic approach enables more individualized approaches to diagnosis and management than rigid subtypes. In this review, we aim to highlight recent therapeutic developments for the management of rosacea.

METHODS

A literature review as performed to identify the most recent clinical studies on novel rosacea treatments. In addition, ClinicalTrials.gov was searched to identify relevant clinical trials. Studies and trials conducted between January 2010 and August 2023 were considered for this review. 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.

SUMMARY OF NOVEL TREATMENTS

Encapsulated Benzoyl Peroxide

Background

Silica microencapsulated benzoyl peroxide 5% cream was approved by the US Food and Drug Administration (FDA) for treatment of rosacea in April 2022 [4, 5]. The use of encapsulation technology enables prolonged release and efficacy, while also potentially decreasing skin irritation [5–7]. Although benzoyl peroxide's precise mechanism of action in the treatment of rosacea is unknown, it is a potent antibacterial agent and exhibits keratolytic and comedolytic effects [8, 9].

Clinical Trial Findings

In two phase III randomized vehicle-controlled studies ($n = 733$) treatment with microencapsulated benoyl peroxide 5% cream resulted in a statistically significant greater percentage of participants achieving an Investigator Global Assessment (IGA) score of clear or almost clear at week 12 (43.5% vs. 16.1%). Additionally, microencapsulated benzoyl peroxide 5% cream resulted in a statistically significant greater decrease in inflammatory lesions (− 17.4 vs. − 9.5) [5]. The most common cutaneous adverse events within 12 weeks included application site pain (benzoyl peroxide vs. vehicle:

2% vs. 1%), erythema (2% vs. 1%), pruritis (1% vs. < 1%), and edema (1% vs. 0%) [10].

Role in Clinical Practice

Although use of benzoyl peroxide as a treatment for rosacea has typically been limited due to irritation, the improved tolerability due to microencapsulation of benzoyl peroxide 5% cream provides a new therapeutic option for patients with rosacea. In particular, encapsulated benzoyl peroxide should be a valuable option for patients with rosacea characterized by inflammatory papules and pustules. While comparative effectiveness studies are needed, given its unique mechanism of action, encapsulated benzoyl peroxide can likely complement other standard rosacea therapies, such as azelaic acid, metronidazole, and ivermectin.

Minocycline Foam

Background

Minocycline 1.5% foam was approved by the FDA for treatment of rosacea in May 2020 [11]. Similarly to other antibiotics in the tetracycline class, minocycline is believed to possess both antibacterial and anti-inflammatory properties [12–14].

Clinical Trial Findings

Two vehicle-controlled, double-blind, phase III studies (n = 1522) found that minocycline 1.5% foam resulted in a statistically significant greater percentage of participants achieving an IGA score of clear or almost clear at week 12 compared to vehicle (52.1% vs. 43% and 49.1% vs. 39.0%, respectively). In addition, minocycline 1.5% foam resulted in a statistically significant reduction in the number of inflammatory lesions at week 12 compared to vehicle (− 17.6 vs. − 15.7 and − 18.5 vs. − 14.9, respectively). Minocycline 1.5% foam was well tolerated; the most common cutaneous adverse event was pruritus (0.7% with minocycline, 0.2% with vehicle). No skin hyperpigmentation or serious adverse effects were noted [15].

Role in Clinical Practice

Topical antimicrobial agents such as metronidazole and ivermectin are mainstays of rosacea management, particularly for the treatment of inflammatory papules and pustules. Minocycline foam offers several strengths, including the potential anti-inflammatory effects of tetracyclines [13, 14, 16], which have not been available in a topical formulation, as well as the potential to overcome antimicrobial resistance to other treatments. The topical formulation should avoid the issues of systemic side effects associated with use of oral minocycline [17, 18]. However, the effect sizes for minocycline foam in the phase III studies were modest, and comparative effectiveness studies are needed to understand the relative role of minocycline foam compared to other topical antimicrobials.

Sarecycline

Background

Sarecycline is a third-generation tetracycline which was approved by the FDA for the treatment of acne vulgaris in October 2018. Sarecycline exhibits similar anti-inflammatory properties as other tetracyclines (e.g., doxycycline and minocycline) with a narrower antibacterial spectrum [19, 20].

Clinical Trial Findings

A prospective, multicenter parallel-group, investigator-blinded, controlled pilot study (n = 102) found that treatment with sarecycline resulted in a statistically significant greater percentage of participants achieving an IGA score of clear or almost clear at week 12 compared to a control multivitamin tablet (75% vs. 16%). In addition, sarecycline demonstrated a statistically significant greater percentage reduction in total inflammatory lesion counts (− 80% vs. − 60% at week 12, respectively) and Subject Global Assessment (SGA) improvement (44% better and 35% slightly better vs. 16% better and 16% slightly better, respectively). Significantly greater reductions in erythema, dryness, peeling, and burning were also noted (63% vs. 12% for erythema, 98% vs. 84% for dryness, 96% vs. 76% burning, 94% vs. 76% for

pruritus, respectively). Adverse events in the sarecycline group included nausea (2.6%), headache (2.6%), facial sunburn (2.6%), and gastroenteritis (2.6%). No adverse events for the control group were noted [21].

Role in Clinical Practice

Sarecycline is currently an off-label treatment option for rosacea. Because rosacea is a chronic condition, patients often need prolonged oral antibiotic therapy for continued benefit. Since sarecycline has a narrower spectrum of antibacterial activity, this might reduce the development of antibiotic resistance and reduce the incidence of other antibiotic-associated complications and disruption of the microbiome compared to other oral antibiotics [19, 22]. However, further in vivo studies are needed to examine the relative long-term effectiveness and safety of chronic sarecycline use in rosacea, particularly with respect to effects on the microbiome.

Ivermectin Cream

Background

Ivermectin 1% cream was approved by the FDA for the treatment of rosacea in December 2014 [23]. Although the exact mechanism of ivermectin in rosacea is unknown, its therapeutic effect is presumed to result from its dual mechanism of action with acaricidal activity against *Demodex spp*. as well as anti-inflammatory properties [24–26].

Clinical Trial Findings

In two phase III randomized vehicle-controlled studies (n = 683) in adults, ivermectin 1% cream resulted in a statistically significant greater proportion of participants achieving an IGA score of clear or almost clear at week 12 across both studies, compared to the vehicle (38.4% vs. 11.6% and 40.1% vs. 18.8%, respectively). In addition, ivermectin 1% demonstrated greater reduction in inflammatory lesion counts from baseline to 12 weeks (mean difference of − 8.1 and − 8.2 lesions). Patient-reported outcomes were significantly better in the ivermectin group, with more patients in that group rating their rosacea improvement as "excellent or "good" after 12 weeks (69.0% vs. 38.6% and 66.2% vs. 34.4%, respectively) [27]. The most common cutaneous adverse events included the sensation of skin burning (1.8% with ivermectin vs. 2.6% with vehicle) in study 1; and pruritis (0.7% vs. 0%) and dry skin (0.7% vs. 0.9%) in study 2 [27]. In a subsequent investigator-blinded 40-week extension (n = 840) ivermectin 1% cream resulted in a greater proportion of IGA success relative to the former vehicle group that was switched to azelaic acid 15% gel twice daily (71.1% vs. 59.4% and 76.0% vs. 57.9%, respectively) [28].

In a phase III randomized, parallel-group, single-blinded study (n = 962), ivermectin 1% cream demonstrated significantly greater efficacy in achieving IGA scores of clear or almost clear at week 16 than metronidazole 0.75% cream (84.9% vs. 75.4% respectively). Additionally, ivermectin demonstrated a significantly higher reduction in inflammatory lesion count from baseline at 16 weeks (83.0% vs. 73.7%). The ivermectin patients also rated their rosacea improvement as "excellent" or "good" at a significantly higher rate (85.5% vs. 74.8%) [29].

Role in Clinical Practice

In a 2016 network meta-analysis, ivermectin 1% cream was found to be the most efficacious treatment for inflammatory papules and pustules [30]. Ivermectin cream has multiple strengths including its anti-inflammatory properties, relatively low side effect profile, and ability to address antimicrobial resistance that may be present against other therapies [25], making it an excellent first line option for the management of inflammatory papules and pustules in rosacea.

Brimonidine Tartrate 0.33% Gel

Background

Brimonidine tartrate 0.33% gel was approved by the FDA for treatment of rosacea in August 2013. It is a topical selective alpha 2 agonist that binds to alpha 2 receptors inducing vasoconstriction of microvasculature, reducing

vasodilation which likely contributes to flushing in rosacea [31]. Brimonidine has also demonstrated anti-inflammatory properties [31].

Clinical Trial Findings

In two randomized, double-blind, vehicle-controlled clinical studies (n = 553), brimonidine tartrate 0.5% gel demonstrated a significantly greater proportion of success defined as a two-grade improvement on both Clinician's Erythema Assessment and Patient Self-Assessment at hours 3, 6, 9, and 12 on day 29 (study 1: 31%, 30%, 26%, 23% vs. 11%, 10%, 10%, 9% with vehicle; study 2: 25%, 25% 18%, 22% vs. 9%, 9%, 11%, 10% with vehicle) [32, 33]. The most common adverse events with brimonidine tartrate gel included erythema (4% brimonidine vs. 1% with vehicle); flushing (3% vs. 0%); sensation of skin burning (2% vs. 1%) [32].

Role in Clinical Practice

Brimonidine tartrate topical gel was the first topical approved for treatment of facial erythema associated with rosacea. Given the important effects of facial erythema on quality of life, [34], brimonidine represents a useful therapeutic option. However, rebound flushing is an important potential limitation.

Oxymetazoline 1% Cream

Background

Oxymetazoline hydrochloride 1% cream was approved by the FDA for the treatment of rosacea in January 2017 [35]. It is a topical selective alpha-1a agonist with potent vasoconstrictive properties as well as anti-inflammatory properties via the inhibition of neutrophils and the production of pro-inflammatory cytokines [36–38].

Clinical Trial Findings

In two phase III multicenter, double-blinded, randomized, vehicle-controlled studies (n = 885), the oxymetazoline group demonstrated a significantly greater proportion of success, defined as a 2-grade improvement in both the Clinician's Erythema Assessment Scale and the Subject-Self Assessment Scale, at hours 3, 6, 9, and 12 on day 29 across both studies (study 1: 11.9%, 15.5%, 17.7%, 14.8% vs. 5.5%, 8.3%, 6.0%, 6.0% with vehicle; study 2: 14.3%, 13.4%, 15.5%, 12.3% vs. 7.4%, 4.8%, 8.5%, 6.1% with vehicle) [39, 40]. The most frequent adverse events included application-site dermatitis (1.4%), application-site erythema (1.4%) in study 1 [39], and worsening of inflammatory lesions (3.1% vs. 0.5% with vehicle), application-site dermatitis (1.8% vs. 0%), and application-site pruritus (1.8% vs. 1.8%) in study 2 [40].

A randomized, controlled, two-arm prospective study (n = 34) found that compared to oxymetazoline alone, combination treatment with pulsed dye laser and oxymetazoline resulted in greater improvement in vessel size and investigator Global Aesthetic Improvement Scale (GAIS) assessment [41].

Role in Clinical Practice

Similar to brimonidine, oxymetazoline 1% cream is important as a treatment option for facial erythema [34]. It may have a lower risk of rebound than brimonidine and has demonstrated efficacy in combination with energy-based therapy [41–43].

Hydroxychloroquine

Background

Although initially utilized as an anti-malarial, hydroxychloroquine was subsequently found to have therapeutic efficacy in systemic autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus) [44, 45]. Notably, hydroxychloroquine also prevents mast cell infiltration and reduces long-term survival of mast cells in tissues [46–50]. Given the role of immune dysregulation and mast cells in rosacea pathogenesis, there has been interest in whether hydroxychloroquine might be a treatment option for rosacea.

Clinical Trial Findings

A phase IV prospective, multicenter parallel-group, double-blinded, controlled pilot study (n = 66) of patients with papulopustular rosacea demonstrated noninferior efficacy of

hydroxychloroquine 200 mg twice daily when compared to doxycycline 100 mg daily. Comparable IGA scores of clear or almost clear and Clinician's Erythema Assessment success was achieved by both groups at 8 weeks (IGA success of 82.1% hydroxychloroquine vs. 93.3% with doxycycline; Clinician's Erythema Assessment success 89.3% vs. 86.7%, respectively) [51]. The most common adverse events in the hydroxychloroquine group included dry skin, dry eye, and dizziness (14.3%, 7.1%, 7.1%, respectively), while adverse events in the doxycycline group included dry skin and flatulence (16.7% and 10.0%, respectively) [51].

Role in Clinical Practice

Although data are limited, hydroxychloroquine could be considered as an alternative systemic treatment option for patients who cannot achieve adequate improvement with topical therapies and would like to avoid other systemic options such as oral antibiotics or isotretinoin. It might also complement other systemic therapy options in those with recalcitrant rosacea.

Intradermal Botulinum Toxin Type A

Background

Botulinum toxin is an injectable neuromodulator that might block mast cell degranulation via cleavage of SNARE proteins and modulate vessel dilation by interfering with physiologic acetylcholine signaling of peripheral autonomic nerves, resulting in reduced vasodilation and blockade of substance P and calcitonin gene-related peptide [52, 53].

Clinical Trial Findings

In a prospective study, single-arm study among 16 patients with erythematotelangiectatic rosacea, intradermal botulinum toxin A injections spaced 1 cm apart and administered at 1, 3, and 6 months resulted in a statistically significant decrease in Clinician's Erythema Assessment scores from baseline to 1 month after treatment (2.9 vs. 1.0; $p < 0.001$). Mean flushing over the cheek also showed improvement (47.8 at baseline, 18.8, 20.2, and 26.5 at 1, 3, and 6 months, respectively). Improvements in Dermatology Life Quality Index (DLQI) scores were also observed (22.3 at baseline, 7.7, 7.1, 10.6 at 1, 3, and 6 months, respectively). Mild adverse effects reported included self-limited facial tightness (18.8%), and asymmetric facial expression (6.3%) which resolved within 1 month [54].

Role in Clinical Practice

While cost might be a limiting factor, intradermal botulinum toxin type A represents an additional potential therapeutic strategy for the management of recalcitrant redness and flushing due to rosacea.

SUMMARY OF POTENTIAL TREATMENTS IN CLINICAL PIPELINE

Topical 4% Cromolyn Sodium

As mast cells might play a role in rosacea pathogenesis, topical 4% cromolyn sodium ophthalmic solution has been explored as a rosacea treatment option due to its mast cell stabilization properties that inhibit mast cell mast cell degranulation and the subsequent release of inflammatory mediators [46]. A randomized, double-blind, placebo-controlled, two-arm phase II study among ten patients with papulopustular rosacea demonstrated improvement in facial erythema measured using the Clinician's Erythema Assessment scale in the topical 4% cromolyn sodium ophthalmic solution arm when compared with the 0.9% sodium chloride arm at 8 weeks (− 1.6 vs. − 0.8, respectively) [55]. However, the study did not include formal statistical hypothesis testing, and effects on inflammatory papules and pustules were not evaluated. No adverse events were reported in this trial; common side effects of topical 4% cromolyn sodium include local irritation and redness and burning at the site of application [46].

B244 Topical Spray

B244 is a topical formulation of a strain of *Nitrosomonas eutropha*, an ammonia-oxidizing

bacteria that produces nitrite and nitric oxide, which have antibacterial and immunoregulatory/vasodilatory effects, respectively. A phase II double-blinded, randomized, vehicle-controlled study ($n = 122$) among patients with mild-to-moderate rosacea found a greater proportion of participants with improvement in IGA relative to baseline in the B244 group than the control group after 8 weeks (69.9% vs. 56.7%). The proportion of patients with improvement in Clinician's Erythema Assessment was also greater in the B244 group (67.1% vs. 56.7%). Adverse events included pruritus (4.1%), rash (2.7%), hordeolum (2.7%), urinary tract infection (2.7%), and headache (2.7%) [56].

Spongilla Powder

DMT310 is a once-weekly topical powder derived from a freshwater sponge, *Spongilla lacustris,* reported to have efficacy due to anti-inflammatory and mechanically penetrative properties. A phase IIb double-blinded, randomized, vehicle-controlled study in 180 patients with moderate-to-severe papulopustular rosacea was completed December 2022. No study results are yet publicly available, but a press release from Dermata Therapeutics (San Diego, CA, USA) stated that while the DMT310 group had greater numerical rates of IGA success by week 12 (36% vs. 23%), these differences did not reach statistical significance [57, 58].

Rofumilast

Roflumilast is a topical selective phosphodiesterase 4 (PDE4) inhibitor approved by the FDA in July 2022 for the treatment of plaque psoriasis [59]. A phase II double-blinded, randomized, vehicle-controlled study in 40 patients with papulopustular rosacea was completed in February 2023. No study results available at this time [60].

TP-04 (Lotilaner Gel, 2%)

TP-04 is a novel topical gel formulation of lotilaner that has demonstrated anti-parasitic activity against *Demodex* mites by inhibiting parasite-specific γ-aminobutyric acid-gated chloride (GABA-Cl) channels [61, 62]. As *Demodex* mites are thought to have a role in the pathogenesis of rosacea, there has been interest in whether TP-04 might be a potential treatment option [63–66]. A phase II multicenter, double-blinded, randomized, vehicle-controlled study in 30 patients with moderate-to-severe papulopustular rosacea has been ongoing since 2023; the study results are not yet available at this time [67].

Low-Dose, Extended-Release Minocycline

DFD-29 is an extended-release preparation of minocycline. In a press release describing the results of two phase III randomized parallel-group trials ($n = 653$) among patients with moderate to severe papulopustular rosacea, minocycline hydrochloride was found to have greater treatment success rates by IGA compared to doxycycline and placebo by week 16 (65.0% and 60.1% with minocycline vs. 46.1% and 31.4% with doxycycline vs. 31.2% and 26.8% with the placebo) [68–70]. Minocycline hydrochloride also demonstrated improvement in total reduction in the number of inflammatory lesions relative to doxycycline and placebo (− 21.3 and − 18.4 with minocycline vs. − 15.9 and − 14.9 with doxycycline vs. − 12.2 and − 11.1 with placebo) [68–70].

Oral Rifaximin

Rifaximin is a nonabsorbed, broad-spectrum, oral antibiotic with anti-inflammatory properties [71]. In a study of 113 rosacea patients and 60 sex- and age-matched healthy controls, the prevalence of small intestinal bacterial overgrowth (SIBO) was higher in patients with rosacea (46.0% vs. 5.0%). In a follow-up trial among those with rosacea and SIBO who were randomized to receive either rifaximin or placebo, those treated with rifaximin demonstrated improved rates of clearance after 1 month (70.1% cleared and 21.4% greatly improved with rifaximin; 90.0% unchanged and 10.0% worsened with placebo) [72]. Adverse events were not noted in this study.

Table 1 Summary of novel treatments

Drug	Formulation	Mechanism of action	Phase completed (ClinicalTrials.gov identifier)	Results	Place in clinical practice
Encapsulated benzoyl peroxide 5%	Cream	Exact mechanism unknown, oxidizing agent with bactericidal and keratolytic effects	Phase III (NCT03564145, NCT03564119, NCT03448939)	Phase III: By week 12, 43.5% of treatment group achieved IGA success vs. 16.1% with vehicle. Treatment group demonstrated reduced inflammatory counts (− 17.4 vs. − 9.5 with vehicle) Most common cutaneous adverse events were application site pain, erythema, pruritis, and edema	Bactericidal agent complimentary to current standard of care for inflammatory papules and pustules (e.g., azaleic acid, metronidazole, ivermectin)
Minocycline 1.5%	Foam	Topical second-generation semi-synthetic tetracycline-derived antibacterial agent, which also has anti-inflammatory properties	Phase III (NCT03142451, NCT04608500)	Phase III: By week 12, 52.1% and 49.1% of treatment group reached IGA success vs. 43.0% and 39.0% with vehicle. Treatment group demonstrated reduced inflammatory and noninflammatory lesion counts (− 17.6 and − 18.5 vs. − 15.7 and − 14.9 with vehicle). Most common cutaneous adverse event was pruritis. No skin hyperpigmentation was observed	Alternative topical antimicrobial agent, although comparative effectiveness data is lacking
Sarecycline	Oral	Third-generation tetracycline antibacterial agent, which has anti-inflammatory properties	Prospective clinical study (NCT04555525)	Prospective clinical study: By week 12, 75% of treatment group reached IGA success vs. 16% with multivitamin control. Treatment group demonstrated greater percent decrease in inflammatory lesions (− 80% vs. − 60% with multivitamin). Most common adverse events in treatment group included nausea, headache, facial sunburn, and gastroenteritis. No adverse events in control group were noted	Narrow-spectrum oral antibiotic that might reduce risk of antibiotic resistance and disruption of the microbiome

Table 1 continued

Drug	Formulation	Mechanism of action	Phase completed (ClinicalTrials.gov identifier)	Results	Place in clinical practice
Ivermectin 1%	Cream	Exact mechanism unknown, acaricidal activity against *Demodex* spp., anti-inflammatory properties	Phase III (Study 1 N/A, Study 2 N/A; NCT01493947)	Phase III: By week 12, 38.4% and 40.1% of treatment groups reached IGA success vs. 11.6 and 18.8% with vehicle. Treatment group demonstrated greater reduction in inflammatory lesion counts (mean difference of − 8.13 and − 8.22 lesions) Phase III: By week 16, 84.9% of treatment groups reached IGA success vs. 75.4% with metronidazole 0.75% cream. Treatment group demonstrated greater percent decrease in inflammatory lesions (− 84.9% vs. − 75.4 with metronidazole)	Low side effect profile, superior efficacy to metronidazole in head-to-head studies; likely excellent first-line option for inflammatory papules and pustules
Brimonidine tartrate 0.33%	gel	Selective alpha 2 adrenergic agonist that improves erythema via vasoconstriction	Prospective clinical study (Study 1 N/A, Study 2 N/A)	Prospective clinical study: Treatment group reported greater proportion of success on CEA and PSA at hours 3, 6, 9, and 12 on day 29 (study 1: 31%, 30%, 26%, 23% vs. 11%, 10%, 10%, 9% with vehicle; study 2: 25%, 25% 18%, 22% vs. 9%, 9%, 11%, 10% with vehicle) Most common adverse events included erythema, flushing, and sensation of skin burning with once daily brimonidine	First topical approved for treatment of facial erythema associated with rosacea

Table 1 continued

Drug	Formulation	Mechanism of action	Phase completed (ClinicalTrials.gov identifier)	Results	Place in clinical practice
Oxymetazoline 1%	Cream	Selective alpha 1a adrenergic agonist that improves erythema via vasoconstriction, anti-inflammatory properties	Phase III (N/A, N/A), prospective clinical study (NCT04153188)	Phase III: Treatment group reported greater proportion of success on CEA and PSA at hours 3, 6, 9, and 12 on day 29 (study 1: 11.9%. 15.5%, 17.7%, 14.8% vs. 5.5%, 8.3%, 6.0%, 6.0% with vehicle; study 2: 14.3%, 13.4%, 15.5%, 12.3% vs. 7.4%, 4.8%, 8.5%, 6.1% with vehicle). Most common adverse events included application-site dermatitis, application-site erythema, worsening of inflammatory lesions, and application-site pruritus	Potentially lower risk for rebound than brimonidine, demonstrates efficacy in combination with energy-based therapy
Hydroxychloroquine	Oral	Mast cell suppression, reduction of mast cell survival and infiltration	Phase IV (N/A)	Phase IV: By week 8, 82.1% of treatment group reached IGA success vs. 93.3% with doxycycline. Treatment group demonstrated comparable CEA success (89.3% vs. 86.7% with doxycycline). Most common adverse events in treatment group were dry skin, dry eye, and dizziness	Potential alternative treatment option for patients who cannot achieve adequate improvement with topical therapies and would like to avoid oral antibiotics or isotretinoin
Intradermal botulinum toxin type A	Injectable	Cleavage of SNARE proteins blocking mast cell degranulation	Prospective clinical study	Prospective clinical study: By 1 month, CEA of treatment group was 2.9 vs. 1.0 at baseline. Treatment groups demonstrated improvement of mean flushing scores over the cheek (47.8 at baseline, 18.8, 20.2, and 26.5 at 1, 3, and 6 months respectively). Most common adverse events included self-limited facial tightness, and asymmetric facial expression which resolved within a month	Potential therapeutic strategy for recalcitrant erythematotelangiectatic rosacea

CEA Clinical Erythema Assessment, *IGA* Investigator Global Assessment, *N/A* not available, *PSA* Patient's Self-Assessment

Table 2 Summary of potential treatments in clinical pipeline

Clinical trial identifier	Drug	Formulation	Mechanism of action	Phase completed (ClinicalTrials.gov identifier)	Results
N/A	Topical 4% cromolyn sodium	Solution	Mast cell stabilizer, blockage of mast cell degranulation	Phase II completed (NCT01933464)	Phase II: By week 8, the treatment group demonstrated a change in CEA of -1.6 vs. -0.8 with normal saline. Common adverse events include local irritation, redness, and burning at site of application
B244	Ammonia-oxidizing bacteria *Nitrosomonas eutropha*	Spray	First-in-class topical formulation designed to repopulate the skin microbiome with beneficial bacteria that oxidize ammonia into nitrite (antibacterial) and nitric oxide (regulated inflammation and vasodilation)	Phase II completed (NCT03590366)	Phase II: By week 8, 69.9% of treatment group reached IGA success vs. 56.7% of vehicle group. 67.1% of treatment group reported improvement in CEA vs. 56.7% of vehicle group. The most common adverse events included pruritus, rash, hordeolum, urinary tract infection, and headache
DMT310	Spongilla	Powder	Topical powder derived from a freshwater sponge, *Spongilla lacustris*, with anti-inflammatory and mechanically penetrative properties	Phase IIb (NCT05108025)	Phase IIb: By week 12, 36% of treatment group reached IGA success vs. 23% of vehicle-control, but statistical significance was not reached
N/A	Rofumilast	Cream	Topical selective phosphodiesterase 4 (PDE4) inhibitor	(NCT05278624)	No results posted
TP-04	Lotilaner 2%	Gel	Inhibits parasite-specific GABA-Cl channels, resulting in activity against Demodex mites	(NCT05838170)	No results posted

Table 2 continued

Clinical trial identifier	Drug	Formulation	Mechanism of action	Phase completed (ClinicalTrials.gov identifier)	Results
DFD-29	Low-dose, extended-release minocycline	Oral	Second-generation semi-synthetic tetracycline-derived antibacterial agent, which has anti-inflammatory properties	Phase III (Study 1 NCT05343455, Study 2 NCT05296629)	Phase III: By week 16, 65.0% (study 1) and 60.1% (study 2) of treatment group reached IGA success vs. 46.1% and 31.4% with doxycycline vs. 31.2% and 26.8% with placebo. Treatment group demonstrated greater reduction in inflammatory lesion counts (− 21.3 and − 18.4 vs. − 15.9 and − 14.9 with doxycycline vs. − 12.2 and − 11.1 with placebo)
N/A	Rifaximin	Oral	Nonabsorbed broad spectrum oral antibiotic, which has anti-inflammatory properties	Prospective clinical study, Phase II (NCT03864978)	Prospective clinical study: By 1 month, 70.1% of patients with SIBO and rosacea cleared cutaneous lesions and 21.4% greatly improved with rifaximin, 90.0% were unchanged and 10.0% worsened with placebo. No AEs reported in study
N/A	Secukinumab	Injectable	Human monoclonal antibody which binds to IL-17A resulting in anti-inflammatory effect	Phase Ib (NCT03079531)	Phase Ib: By week 16, improvement noted with treatment in papules and pustule count (median reduction by 5 lesions), CEA (− 0.3), change in RosaQol (− 0.6). Most common AEs were skin or nail infection and pruritis

Table 2 continued

Clinical trial identifier	Drug	Formulation	Mechanism of action	Phase completed (ClinicalTrials.gov identifier)	Results
AMG 334	Erenumab	Injectable	Human monoclonal antibody which binds to the CGRP receptor which likely contributes to flushing via vasodilation	Phase II (NCT04419259)	No results posted

AEs Adverse events, *CEA* Clinical Erythema Assessment, *CGRP* calcitonin gene-related peptide, *GABA-Cl* γ-aminobutyric acid-gated chloride channels, *IGA* Investigator Global Assessment, *IL* interleukin, *N/A* not available, *RosaQol* Rosacea-specific Quality of Life Instrument, *SIBO* small intestinal bacterial overgrowth

A phase II double-blinded, randomized, placebo-controlled trial with rifaximin delayed-release tablets among patients with moderate-to-severe papulopustular rosacea began enrolling in 2018; however, no study results are yet publicly available [73].

Secukinumab

Secukinumab is a subcutaneous human monoclonal antibody which binds to interleukin 17A (IL-17A), resulting in an anti-inflammatory effect [74]. In a phase 1b, open-label, rater-blinded, single-arm study in 24 patients with moderate-to-severe papulopustular rosacea, secukinumab resulted in a significant reduction at 16 weeks in both papules (median reduction by 5 lesions) and Clinician's Erythema Assessment (− 0.3 points). Change in the Rosacea Quality of Life Index (RosaQoL) was also improved by a median value of − 0.6 from baseline. The most common adverse events were skin or nail infection (16.7%) and pruritus (12.5%) [66].

Erenumab

Erenumab is a subcutaneous human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor, resulting in reduced vasodilation of microvasculature that likely contributes to flushing in rosacea by vasodilation [75]. A phase II, open-label, single-arm study in 30 patients with moderate-to-severe erythematotelangiectatic rosacea has been completed [76]. No study results are yet publicly available.

CONCLUSIONS

Over the past decade, the number of available treatments for rosacea has expanded substantially (Table 1). There are now topical and systemic treatments for papules and pustules that encompass a variety of anti-inflammatory and antimicrobial mechanisms and likely can be used in combination for increased efficacy. In addition, the introduction of brimonidine and oxymetazoline has provided the first topical treatments for redness and flushing associated with rosacea. However, the clinical pipeline (Table 2) for rosacea appears to be limited, and there remain important unmet needs for patients with more recalcitrant rosacea or phymatous disease. In addition, there is a need for comparative effectiveness studies to identify the highest value treatment approaches for patients with rosacea.

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Declarations

Conflict of Interest. John S. Barbieri has received consulting fees from Dexcel Pharma for work unrelated to the present study. James Choe has nothing to disclose.

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.

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