

Spotlight on brimonidine topical gel 0.33% for facial erythema of rosacea: safety, efficacy, and patient acceptability

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Background: Brimonidine tartrate is a highly selective alpha 2 agonist that induces direct vasoconstriction of small arteries and veins, thereby reducing vasodilation and edema.

Objective: To review the current literature regarding the safety, efficacy, and patient acceptability of brimonidine 0.33% gel.

Methods: A PubMed search was performed using the terms brimonidine 0.33% gel, rosacea, safety, efficacy, and acceptability. Peer-reviewed clinical trials and case reports from 2012 to 2016 were screened for inclusion of safety, efficacy, and/or patient acceptability data.

Results: Brimonidine topical gel 0.33% is associated with mild, transient skin-related adverse reactions. Efficacy may be achieved within 30 minutes of administration with maximal reductions in erythema 3–6 hours after administration. Patient satisfaction with use of brimonidine topical gel is superior to vehicle gel for facial appearance, treatment effect, facial redness, and daily control of facial redness.

Limitations: Studies were typically limited to 1-year follow-up. Only one study has examined the use of brimonidine topical gel in combination with other rosacea and acne medications.

Discussion: Brimonidine topical gel 0.33% is a safe, effective, and patient-accepted treatment for facial erythema of rosacea.

Keywords: patient satisfaction, adverse reactions, side effects

Introduction

Rosacea is a chronic inflammatory skin disorder categorized into four types. These include erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PHY), and ocular rosacea (OR). ETR is characterized by flushing, erythema, and telangiectasias of the central face. PPR features papules and pustules of the central face. Patients with PHY have skin thickening and sebaceous gland hypertrophy leading to skin surface irregularity and disfigurement. OR symptoms include conjunctival hyperemia, anterior blepharitis, and keratitis. ETR is the most prevalent subtype, followed by PPR, OR, and PHY.¹ However, patients may have features of multiple subtypes of rosacea, complicating treatment regimens.²⁻⁴

Rosacea most commonly affects fair-skinned women aged >30 years.^{5,6} Ninety-six percent of patients with PPR are skin types I–II.⁷ Aggressive treatment is important as rosacea symptoms are frequently associated with lower self-esteem and fear of social stigma.⁸ The pathogenesis of rosacea is not completely understood, but innate immune dysfunction, inflammation, presence of microorganisms, UV damage, and

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neurovascular abnormalities in conjunction with various triggers may play a role in condition manifestation.⁷

Activation of the innate immune system in a susceptible individual may produce cathelicidin peptides that can induce vasodilation and inflammation.⁹ Levels of cathelicidin and kallikrein 5, a processing enzyme of cathelicidin, are elevated in the skin of patients with rosacea.¹⁰ *Demodex folliculorum* mites are present in greater concentrations in the sebaceous follicles of patients with rosacea.¹¹ *Bacillus oleronius*, a bacterium that may colonize *Demodex* mites, stimulates an inflammatory response at higher rates in patients with rosacea.¹² Given the distribution of rosacea in sun-exposed areas, ultraviolet radiation may play a role in rosacea pathogenesis. UVB radiation stimulates vascular endothelial growth factor and fibroblast growth factor from keratinocytes in mice.^{13–15} Reactive oxygen species produced by UV damage may also stimulate the innate immune system leading to the symptoms of rosacea.⁹ The transient receptor potential vanilloid (TRPV) ion channel is overexpressed in the sensory nerve endings in patients with rosacea.^{16–18} TRPV, a vasodilator, is activated in response to common triggers of rosacea such as heat, spicy food, and alcohol. It causes vasoactive peptides to be released, leading to vasodilation and flushing.^{19,20}

Treatment options for rosacea include topicals such as metronidazole, azelaic acid, ivermectin, brimonidine, oxymetazoline, and sulfacetamides. For PPR, oral metronidazole, doxycycline, or isotretinoin may be employed. Brimonidine and oxymetazoline are approved by the Food and Drug Administration (FDA) for the treatment of the facial erythema associated with rosacea.

Brimonidine is a highly selective alpha 2 agonist that binds alpha 2 receptors on the vasculature inducing direct vasoconstriction of both small arteries and veins, thereby reducing vasodilation and edema.²¹ We aim to summarize the safety, efficacy, and patient acceptability of brimonidine topical gel in the treatment of facial erythema associated with rosacea.

Methods

A PubMed search was performed using the terms brimonidine 0.33% gel, brimonidine and rosacea, brimonidine 0.33% gel and safety, brimonidine safety and rosacea, brimonidine 0.33% gel and efficacy, brimonidine efficacy and rosacea, and brimonidine acceptability and rosacea. Ten peer-reviewed clinical trials and case reports from 2012 to 2016 were screened for inclusion of safety, efficacy, and/or patient acceptability of brimonidine topical gel. Full text was

reviewed; all 10 articles were included as they contained pertinent research data or clinical reports. Review articles were excluded.

Results

The safety of topical brimonidine tartrate gel for moderate-to-severe facial erythema of rosacea was examined in two related Phase II studies (Table 1).²² The rates of adverse events were similarly low, ranging from 6% to 14%, between three different concentrations of brimonidine tartrate (0.5%, 0.18%, 0.07%) and vehicle gel after one-time application. When extended to once-daily application for 4 weeks with a 4-week follow-up period, adverse event rates ranged from 11% to 19% and were similar across all brimonidine tartrate concentrations. Adverse events were mild, transient, and limited to the skin. Irritation, flushing, worsened erythema, burning sensation, and pruritus were the most commonly reported side effects. Phase III studies of brimonidine tartrate 0.5% (equivalent to brimonidine topical gel 0.33%) noted adverse event rates ranging from 29.5% to 33.8% after 4 weeks of once-daily use. The rate of adverse reactions was slightly higher for brimonidine tartrate 0.5% than for vehicle gel, 29.5% vs 25.2% in the one-time treatment group and 33.8% vs 24.1% in the 4-week treatment group.²³ In a 1-year open-label study of brimonidine tartrate 0.5% applied once daily, adverse events were highest during 1–3 months of daily use with a rate of 41.9%. Rates decreased with longer duration of treatment; the adverse event rate was 19.5% at months 10 through 12 of treatment. Concomitant use of medications to address inflammatory lesions did not increase adverse reactions.²⁴ Since its commercial availability in 2013, multiple case reports have documented contact dermatitis and rebound erythema worse than baseline after initial improvement with brimonidine use.^{25–29}

Brimonidine topical gel 0.33% was efficacious compared to vehicle gel for moderate-to-severe persistent facial erythema of rosacea in Phase II, Phase III, and open-label studies (Table 2). There was a dose-dependent improvement in facial erythema with use of brimonidine tartrate as assessed by Clinician's Erythema Assessment (CEA) and Patient Self-Assessment (PSA) tools.²³ Concentrations of 0.07%, 0.18%, and 0.5% were compared against vehicle gel in both one-time and daily applications for 4 weeks. In the one-time dosing trial, improvement in facial erythema was correlated with increasing brimonidine tartrate concentration. After application of brimonidine tartrate 0.5% once daily for 4 weeks, there was superior improvement in erythema compared to lower concentrations and vehicle gel.²² When used once

Table 1 Safety of brimonidine topical gel for facial erythema of rosacea

PMID	References	Patient characteristics	Number of subjects	Intervention	Study design	Outcome measure	Results
27272086	Lowe and Lim ²⁵	– 41-year-old Caucasian female – ETR	1	0.33% brimonidine gel BID, metronidazole gel 1% nightly	Case report	Facial erythema	Effective blanching for 2 years followed by delayed paradoxical reaction with increased erythema and rash
26768997	Cookson et al ²⁶	– 24-year-old female – Rosacea erythema	1	0.33% brimonidine gel once daily	Case report	AEs	Developed facial dermatitis after 6 months use. Patch testing was positive for brimonidine
24742853	Ilkovich and Pomerantz ²⁷	– 29-year-old female – ETR	1	0.33% brimonidine gel once daily	Case report	Facial erythema	Effective blanching for 12 hours after application followed by rebound erythema worse than baseline lasting 12 hours
24438976	Rouff and Levitt ²⁸	– 26-, 38-, and 41-year-old females – Rosacea erythema	3	0.33% brimonidine gel once daily	Case report	Facial erythema	Erythema reduction for 1–6 hours after application followed by erythema and burning worse than baseline self-resolving > 12 hours
25219708	Swanson and Warshaw ²⁹	– 75-year-old female – Rosacea erythema	1	0.33% brimonidine gel once daily	Case report	AEs	Facial dermatitis days after beginning brimonidine gel. Patch test positive to brimonidine gel and eye drops confirming contact dermatitis to active ingredient
22050040	Fowler et al ²²	Studies A and B: – Age ≥ 18 years – Rosacea, moderate-to-severe erythema	A: 122 B: 269	A: BT 0.5%, 0.18%, 0.07% or vehicle once B: BT 0.5% once daily, 0.18% once daily, 0.18% twice daily, vehicle gel once daily, vehicle gel twice daily	Randomized, double-blind, vehicle controlled	CEA and PSA of erythema, AEs	A: AEs were similarly low across all treatment doses. The most common were irritation, erythema, burning sensation, and pruritus B: AEs were similarly low across all treatment doses. Vehicle gel twice daily had lower AE rate
23839181	Fowler et al ²³	– Age ≥ 18 years – Rosacea, moderate-to-severe erythema – Less than three facial inflammatory lesions	A: 260 B: 293	A and B: BT gel 0.5% vs vehicle gel once daily for 4 weeks with 4-week follow-up	Multicenter, randomized, double-blind, parallel-group, vehicle controlled	CEA and PSA of erythema, telangiectasia using 5-point scale, IGA of lesion severity, AEs	A: AE incidence 29.5% in BT group and 25.2% in vehicle group. Related AE incidence of 11.6% and 0.5%, respectively B: AE incidence of 33.8% in BT group and 24.1% in vehicle group. Related AE incidence of 9.5% and 9.7%, respectively
24385120	Moore et al ²⁴	– Age ≥ 18 years – Rosacea, moderate-to-severe erythema – No limit on inflammatory lesions present	449	BT gel 0.5% once daily for 1 year	Multicenter, open-label	CEA and PSA of erythema, telangiectasia using 5-point scale, AEs	AEs highest at months 1–3 (41.9% with at least one AE, 21.4% with at least one related AE) and decreases during treatment to 19.5% and 4.2%, respectively, for months 10–12 Concomitant use of other rosacea or acne therapies was not associated with increased AEs Most common AEs: flushing (9.1%), worsening erythema (6.5%), worsening rosacea (3.6%), skin burning (3.3%), skin irritation (3.1%), contact dermatitis (2.2%), and pruritus (2%)

Note: Clinical studies and case series evaluating the safety of brimonidine topical gel for facial erythema of rosacea.

Abbreviations: ETR, erythematotelangiectatic rosacea; AEs, adverse events; BT, brimonidine tartrate; CEA, Clinician's Erythema Assessment; PSA, Patient Self-Assessment; IGA, Investigator Global Assessment.

Table 2 Efficacy of brimonidine topical gel for facial erythema of rosacea

PMID	References	Patient characteristics	Number of subjects	Intervention	Study design	Outcome measure	Results
22050040	Fowler et al ²²	Studies A and B: – Age \geq 18 years – Rosacea, moderate-to-severe erythema	A: 122 B: 269	A: BT 0.5%, 0.18%, 0.07% or vehicle once B: BT 0.5% once daily, 0.18% once daily, vehicle gel once daily, vehicle gel twice daily	Randomized, double-blind, vehicle controlled	CEA and PSA of erythema	A: Reduced facial erythema after single application of BT in a dose-dependent fashion B: 0.5% BT once daily had significant improvement in erythema compared to vehicle on days 1, 15, and 29
23839181	Fowler et al ²³	– Age \geq 18 years – Rosacea, moderate-to-severe erythema – Less than three facial inflammatory lesions	A: 260 B: 293	A and B: BT gel 0.5% vs vehicle gel once daily for 4 weeks with 4-week follow-up	Multicenter, randomized, double-blind, parallel-group, vehicle controlled	CEA and PSA of erythema, telangiectasia using 5-point scale, IGA of lesion severity, adverse events	Studies A and B both demonstrated that BT gel has greater efficacy compared to vehicle across all measures. Maximum effect was observed from 3 to 6 hours after application
24385120	Moore et al ²⁴	– Age \geq 18 years – Rosacea, moderate-to-severe erythema – No limit on inflammatory lesions present	449	BT gel 0.5% once daily for 1 year	Multicenter, open-label	CEA and PSA of erythema, telangiectasia using 5-point scale, adverse events	CEA score improvement seen at hour 3 after each administration. Baseline CEA prior to BT gel administration also improved by month 3 and stayed stable until month 12. No evidence of tachyphylaxis
24918560	Jackson et al ³⁰	– Age \geq 18 years – Moderate-to-severe erythema – Less than three facial inflammatory lesions	A: 260 B: 293	A and B: BT gel 0.5% vs vehicle gel once daily for 4 weeks with 4-week follow-up	Subanalysis of previous multicenter, randomized, double-blind, parallel-group, vehicle controlled	CEA and PSA of erythema	Significantly higher percentage of subjects with I-grade improvement in CEA and PSA after 30 minutes for BT gel vs vehicle group on day 1 (A: 27.9% vs 6.9%; B: 28.4% vs 4.8%), day 15 (A: 55.9% vs 21.1%; B: 45.5% vs 28.4%), and day 29 (A: 58.3% vs 32%; B: 53.5% vs 34.5%)

Note: Clinical studies and case series evaluating the efficacy of brimonidine topical gel for facial erythema of rosacea.

Abbreviations: BT, brimonidine tartrate; CEA, Clinician's Erythema Assessment; PSA, Patient Self-Assessment; IGA, Investigator Global Assessment.

daily for 4 weeks as monotherapy in larger Phase III studies, brimonidine tartrate 0.5% had greater efficacy than vehicle gel in patients with less than three inflammatory lesions. Maximal effect was observed 3–6 hours after application of brimonidine tartrate 0.5%, with more patients experiencing at least a 2-grade improvement in CEA and PSA compared to vehicle.²³ Of the subjects treated with brimonidine tartrate 0.5% gel, 27.9% achieved a 1-grade improvement in both CEA and PSA scores 30 minutes after administration compared to vehicle gel (6.9% of subjects) on day 1. This end point was achieved by 55.9% of subjects in the brimonidine tartrate 0.5% group vs 21.1% of subjects in the vehicle group and 58.3% of subjects in the brimonidine tartrate 0.5% group vs 32% of subjects in the vehicle group on days 15 and 29, respectively.³⁰ A 1-year open-label study of brimonidine tartrate 0.5% gel daily evaluated the improvement in erythema based on CEA and PSA with no limit on inflammatory lesions and no restrictions on concomitant acne or rosacea medications. Reductions were continually observed in both CEA and PSA following application of brimonidine tartrate 0.5% gel throughout the course of the study, with maximal improvement 3 hours after administration. Baseline erythema scores prior to daily administration of brimonidine tartrate appeared to improve over time with continued brimonidine use. Mean PSA score prior to administration of brimonidine tartrate at day 1 of treatment was 3.1 and at month 3 of treatment was 2.3. Mean CEA score prior to administration of brimonidine tartrate decreased from 3.1 on day 1 to 2.4 at month 3. The baseline erythema improvement was maintained through the end of the 12-month study period.²⁴

Patient acceptability of brimonidine topical gel was demonstrated in Phase II, Phase III, and open-label studies (Table 3). Patient acceptability was best quantified by a randomized, double-blind, vehicle-controlled, and parallel-group study of 92 patients using 1 g brimonidine topical gel 0.33% or 1 g vehicle gel daily for 8 days. The study included patients with self-perceived severe facial erythema and measured patient-reported outcomes using a facial redness questionnaire, satisfaction questionnaire, and diary of facial redness. On comparing the treatment group vs the vehicle group, there was improved satisfaction with facial appearance (36.9% vs 21.5%), treatment effect (69.6% vs 40.4%), facial redness (67.4% vs 33.3%), and daily control of facial redness (83% vs 28.9%).³¹

Discussion

The safety of brimonidine topical gel 0.33% once-daily dosing is well characterized. Although there is a relatively

high rate of adverse reactions, up to 41.9% with daily use, the reactions are generally mild, transient, and limited to the skin.²⁴ The most common reactions are flushing, erythema worse (or at least perceived as worse) than baseline, worsening of rosacea, irritation, and pruritus.^{22–24} These side effects generally present shortly after application or as the effects of the medication are wearing off and resolve within hours without intervention. Side-effect incidence is typically highest from initial use through month 3 of use but decreases with longer duration of daily application. Early studies reported low incidence of contact dermatitis and rebound erythema with topical brimonidine tartrate, but recent case studies suggest that these are potentially significant reactions. Contact dermatitis to either vehicle ingredients or brimonidine occurred in multiple patients.^{24,26,29} Exaggerated rebound erythema ~12 hours after application of brimonidine topical gel has also been reported. The erythema may be worse than baseline but typically resolves within 6–12 hours.^{25,27,28} These adverse events should be considered when developing treatment regimens. However, given the mild and transient nature of these adverse reactions, a trial of brimonidine topical gel after side-effect counseling may be reasonable.

Brimonidine topical gel 0.33% is efficacious for moderate-to-severe facial erythema of rosacea, both as monotherapy and in conjunction with other acne and rosacea medications.^{22–24,30} Reduction in erythema is observed 30 minutes after administration, and patients can expect a peak benefit between 3 and 6 hours after administration. Due to the mechanism of action of brimonidine, redness will generally recur within 12 hours after application. Many patients may experience an overall reduction in baseline erythema after 3 months of daily use. Patient-reported outcomes after use of topical brimonidine 0.33% gel support patients' general acceptability of this treatment option.³¹

Data on efficacy, safety, and patient acceptability of topical brimonidine gel 0.33% for facial erythema of rosacea are limited to studies with <1 year follow-up and case reports. Case reports have been included to highlight several instances of contact dermatitis and rebound erythema in patients who used topical brimonidine gel, in contrast to the relatively low incidence of these adverse events in early studies. Only one study has evaluated the use of topical brimonidine gel with concomitant rosacea or acne medications or in patients with three or more inflammatory lesions.³² Although the current data establishes brimonidine topical gel as a safe and effective treatment for erythema associated with rosacea, further studies should aim to examine its long-term efficacy and safety in combination with other rosacea treatments.²⁴

Table 3 Patient acceptability of brimonidine topical gel for facial erythema of rosacea

PMID	References	Patient characteristics	Number of subjects	Intervention	Study design	Outcome measure	Results
26416164	Layton et al ³¹	<ul style="list-style-type: none"> – Average age 54.5 years (25–74 years) – Self-perceived severe facial erythema 	92	1 g 0.33% brimonidine gel once daily vs 1 g vehicle gel once daily for 8 days	Randomized, double-blind, vehicle-controlled, parallel group	Patient-reported outcomes via facial redness questionnaire, subject satisfaction questionnaire, and a patient diary of facial redness control	Improved satisfaction of facial appearance (36.9% vs 21.5%), overall treatment effect (69.6% vs 40.4%), facial redness (67.4% vs 33.3%) in BT vs vehicle control
23839181	Fowler et al ²³	<ul style="list-style-type: none"> – Age ≥ 18 years – Rosacea, moderate-to-severe erythema – Less than three facial inflammatory lesions 	A: 260 B: 293	A and B: BT gel 0.5% vs vehicle gel once daily for 4 weeks with 4-week follow-up	Multicenter, randomized, double-blind, parallel-group, vehicle controlled	CEA and PSA of erythema, telangiectasia using 5-point scale, IGA of lesion severity, adverse events	A and B both with significantly higher percentage of patients with 2-grade improvement on CEA and PSA over 12 hours in BT group. Maximum effect was observed from 3 to 6 hours after application
24385120	Moore et al ²⁴	<ul style="list-style-type: none"> – Age ≥ 18 years – Rosacea, moderate-to-severe erythema – No limit on inflammatory lesions present 	449	BT gel 0.5% once daily for 1 year	Multicenter, open label	CEA and PSA of erythema, telangiectasia using 5-point scale, adverse events	PSA score at hour 0 decreased from day 1 to month 3 and then stable (3.1–2.3)
24918560	Jackson et al ³⁰	<ul style="list-style-type: none"> – Age ≥ 18 years – Rosacea, moderate-to-severe erythema – Less than three facial inflammatory lesions 	A: 260 B: 293	A and B: BT gel 0.5% vs vehicle gel once daily for 4 weeks with 4-week follow-up	Subanalysis of previous multicenter, randomized, double-blind, parallel-group, vehicle controlled	CEA and PSA of erythema	PSA decreased from hour 0 to hour 3 after administration (3.1–2.1). Similar results maintained for all 12 months

Note: Clinical studies and case series evaluating the patient acceptability of brimonidine topical gel for facial erythema of rosacea.

Abbreviations: BT, brimonidine tartrate; CEA, Clinician's Erythema Assessment; PSA, Patient Self-Assessment; IGA, Investigator Global Assessment.

Rosacea treatment presents a unique challenge. Brimonidine topical gel 0.33% is a novel treatment agent for persistent erythema of rosacea. Though monotherapy may be beneficial in patients with ETR, combination therapy with other rosacea and acne medications may be necessary in patients with features of both ETR and PPR. The short-term and long-term erythema control offered by brimonidine tartrate gel has its advantages. Patients seeking short-term erythema control for specific events may benefit from as-needed use, whereas those seeking long-term erythema control may opt for daily use resulting in reduced baseline erythema. Controlling erythema in rosacea is a difficult task, but brimonidine topical gel 0.33% has proven to be a useful addition to the current treatment arsenal.

Disclosure

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