ORIGINAL ARTICLE

Impact of Intradermal AbobotulinumtoxinA on Facial Erythema of Rosacea

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BACKGROUND Facial erythema is a frequent and often distressing complaint of patients with rosacea. Treatment of facial erythema with botulinum toxin has previously been proposed and reported. However, the current literature has mixed results.

OBJECTIVE The primary objective of this study was to evaluate the safety and efficacy of intradermal abobotulinumtoxinA on facial erythema of rosacea.

MATERIALS AND METHODS Twenty-five subjects aged 35 to 70 years with Fitzpatrick skin Types I to IV and facial erythema of erythematotelangiectatic rosacea were enrolled in the trial. Subjects received 15 to 45 units of intradermal injections of abobotulinumtoxinA to the nasal tip, nasal bridge, and nasal alae. A nontreating investigator assessed the facial erythema of rosacea using a standardized grading system (0 = absent, 1 = mild erythema, 2 = moderate erythema, and 3 = severe erythema) to evaluate digital photographs at baseline, 1, 2, and 3 months after treatment. Statistical analysis of erythema grade included one-way repeated-measures analysis of variance and pairwise comparisons using SPSS (IBM Corporation) software.

RESULTS Fifteen of the 25 enrolled subjects completed all the appropriate follow-up visits. Only the 15 subjects with complete data were included in analysis. The subjects were of Fitzpatrick skin Types I to III, a mean age of 54 years, and 80% women. The mean baseline erythema grade was 1.80 (±0.56), and the mean erythema grade at 3 months after treatment was 1.00 (±0.38). The treatment resulted in statistically significant improvement in erythema grade at 1, 2, and 3 months after treatment when compared with baseline ($p < .05$, $p < .001$, and $p < .05$, respectively). Pairwise comparison to baseline showed a mean erythema grade improvement of 0.80 ($p < .001$) at 3-month follow-up.

CONCLUSION Intradermal injection of botulinum toxin for the treatment of facial erythema of rosacea seems both effective and safe. Larger, randomized, blinded, placebo-controlled studies are warranted. Additionally, further investigation is needed to elucidate the mechanism of action by which botulinum toxin improves facial flushing of rosacea.

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Rosacea is a common cutaneous condition characterized by centrofacial flushing (transient erythema), persistent erythema, visible blood vessels, and/or papules and pustules. However, the term rosacea likely refers to several separate clinical conditions, each with a predominant pathogenic mechanism.[1–3]

The National Rosacea Society Expert Committee on the Classification and Staging of Rosacea has established 4 rosacea subtypes. The erythematotelangiectatic subtype is the focus of the current trial and is characterized by flushing and persistent central facial erythema.[4,5]

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Erythema and flushing are a frequent complaint among patients with rosacea, and its severity can be graded from 0 to 3 based on intensity and frequency.[5] The Clinician's Erythema Assessment has also been used to evaluate erythema (0 = clear skin with no signs of erythema, 1 = almost clear with slight redness, 2 = mild erythema with definite redness, 3 = moderate erythema with marked redness, and 4 = severe erythema with fiery redness).[6] The episodes of flushing may occur unprovoked or in response to emotional stress, alcohol,[7] hot beverages,[8] spicy foods, exercise, cold or hot weather, or hot baths or showers.[1,9]

The exact pathogenesis of rosacea remains unclear, but mechanisms that have been proposed include aberrant innate immune response,[10] ultraviolet radiation exposure,[11,12] vascular changes,[12–14] epidermal barrier dysfunction,[15,16] neurogenic inflammation,[17,18] and microbes.[19–22] Flushing is likely the clinical manifestation of vascular dysfunction to a combination of the aforementioned pathogenic mechanisms.

There are only a limited number of current therapeutic strategies for the treatment of facial erythema and flushing of rosacea. Treatments include laser and intense pulsed light (IPL),[23,24] topical azelaic acid, topical metronidazole, systemic clonidine, and carvedilol.[25,26] In 2013, the FDA recently approved a topical alpha-2 adrenergic receptor agonist gel (brimonidine).[6,27] Intradermal botulinum toxin has recently been investigated as a novel treatment of facial erythema and flushing.[28–32] However, mixed results have been reported in the literature. Botulinum toxin blocks the release of the neurotransmitter acetylcholine from peripheral nerves. It has been proposed that acetylcholine plays a role in cutaneous vasodilatation.[33,34]

The primary end points of this pilot study were the safety and efficacy of intradermal abobotulinumtoxinA in the treatment of facial flushing of rosacea. The secondary end point was patient satisfaction. The authors hypothesize that intradermal abobotulinumtoxinA will be a safe and effective treatment of facial flushing of rosacea. AbobotulinumtoxinA was chosen among the FDA-approved Type A botulinum toxins because evidence suggests that abobotulinumtoxinA is associated with greater diffusion and migration, which is desirable when treating larger areas seen in facial flushing of rosacea.[35,36] The aforementioned study that failed to demonstrate benefit of botulinum toxin in facial flushing used onabotulinumtoxinA, which is associated with less diffusion and migration, which could explain the lack of efficacy in that case.

Materials and Methods

The authors performed a proof-of-concept non-controlled single-center pilot study. Men and women with facial erythema associated with mild-to-moderate erythematotelangiectatic rosacea were enrolled from the private practice of the author (D.J.G). Inclusion criteria were patients aged 35 to 70 years, Fitzpatrick skin Type I to IV, nonsmoker for ≥2 years, and a willingness to comply with all follow-up requirements. Subjects who had infection in the target area, previous botulinum toxin injections in the treatment area, history of poor wound healing, history of keloids, human immunodeficiency virus, hepatitis, immune compromise, pregnancy, lactation, known allergy to cow's milk protein, or known hypersensitivity to abobotulinumtoxinA or any of it ingredients were excluded. All subjects signed informed consent, and the independent Essex Institutional Review Board (Lebanon, NJ) approved the clinical study protocol (Protocol code DYSRDG10).

Each 300-unit vial of abobotulinumtoxinA (Dysport; Medicis, a Division of Valeant Pharmaceuticals, Inc., Scottsdale, AZ) was reconstituted with 3 mL of bacteriostatic 0.9% sodium chloride. Subjects underwent treatment with intradermal injection of 15 to 45 units of abobotulinumtoxinA (Dysport; Medicis, a Division of Valeant Pharmaceuticals, Inc.) through a 30-gauge half inch needle to the affected areas. The initial protocol was limited to treatment of the nasal bridge to nasal tip but was subsequently expanded to include treatment of the nose, cheeks, forehead, and chin (Figure 1, injection sites). The dose was limited to the aforementioned dosing range and determined based on the degree of erythema on clinical examination. Ice packs were immediately applied after treatment.

A nontreating investigator assessed the subjects' facial erythema using a standardized grading system

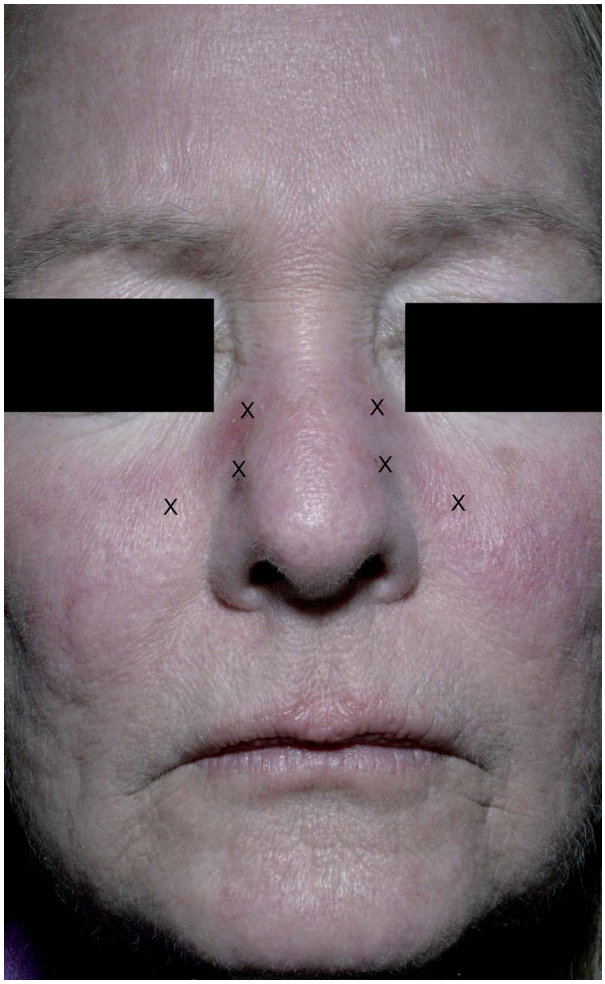

Figure 1. Example injection sites; x, injection site.

(0 = absent, 1 = mild erythema, 2 = moderate erythema, and 3 = severe erythema) to evaluate standardized digital photographs at baseline, 1, 2, and 3 months after treatment.[5] The nontreating investigator assessing the digital photographs was blinded to the chronological sequence of treatment and was thus unaware if any given photograph was in fact a baseline pretreatment photograph or a follow-up photograph. The presence and severity of the following side effects were specifically assessed in all subjects on clinical examination and written questionnaire: injection site pain, erythema, edema, muscle weakness, dysphagia, dry mouth, fatigue, headache, eye disorders, musculoskeletal pain, and dysphonia.

Statistical analysis was performed using SPSS software (version 21.0; IBM Corporation, Armonk, NY). The effect of treatment on erythema grade was evaluated using a one-way repeated-measures analysis of variance (ANOVA) and pairwise comparisons. A one-way repeated-measures ANOVA was used to determine whether the mean of subjects' rosacea score, at each time point, differed significantly.

Results

Twenty-five subjects were enrolled, one withdrew, and 15 completed all the appropriate follow-up visits. The 9 remaining patients had inconsistent follow-up visits and were thus excluded from analysis. The mean age was 54 years, 80% were women, and subjects were of Fitzpatrick skin Types I to III. Age, sex, skin type, and erythema grade were recorded for each patient visit and listed in Table 1. The mean dosage per patient was 25 units. A one-way repeated-measures ANOVA was conducted, with the factor being baseline erythema grade. The dependent variable was erythema grades analyzed at each follow-up visit. The mean baseline erythema grade was 1.80 ($\pm$0.56), and the mean erythema grade at 3 months after treatment was 1.00 ($\pm$0.38).

The treatment resulted in statistically significant improvement in erythema scores at 1, 2, and 3 months after treatment when compared with baseline. Subjects attained statistically significant improvement from baseline at 1 month after treatment ($p < .05$), 2 months after treatment ($p < .001$), and 3 months after treatment ($p < .05$).

Pairwise comparisons of erythema grades were conducted (Table 2). Pairwise comparison to baseline showed a mean erythema grade difference of 0.80 ($p < .001$) at 3-month follow-up. Pairwise comparison of erythema grades also showed statistically significant improvement from 1-month follow-up to 3-month follow-up ($p < .05$) and 2-month follow-up to 3-month follow-up ($p < .05$).

Evaluation of pre-treatment and post-treatment digital photography, blinded to chronological sequence of treatment, demonstrated appreciable improvement of rosacea-associated facial erythema (Figure 2). The majority of subjects (93%) were noted to have some

TABLE 1. Subject Characteristics and Clinician-Assessed Erythema Grades

				Erythema Grade			
Subject	*Sex*	*Age*	*Fitzpatrick Skin Type*	*Baseline*	*1-Month Follow-Up*	*2-Month Follow-Up*	*3-Month Follow-Up*
1	F	53	2	1	1	1	0
2	F	47	2	2	2	1	1
3	F	50	2	2	1	1	1
4	F	75	2	2	1	1	1
5	F	44	2	1	1	1	1
6	F	44	2	1	1	1	1
7	M	55	3	2	1	1	1
8	F	66	2	2	1	1	1
9	F	38	2	2	2	2	1
10	F	53	2	1	1	1	1
11	M	57	2	2	2	2	2
12	F	61	2	3	2	2	1
13	F	57	1	2	2	1	1
14	F	55	2	2	1	1	1
15	M	53	2	2	2	2	1

0, absent (no signs of erythema); 1, mild erythema; 2, moderate erythema; 3, severe erythema.

improvement with treatment. Larger treatment doses were not associated with superior results. No patients suffered from either worsening or "rebound" flaring of their rosacea; all patients either remained consistent in their erythema grade throughout the duration of the study or showed marked improvement. The one patient without improvement maintained a stable erythema grade throughout the study period. Subjects reported transitory minimal discomfort at the injection site. There were no other adverse effects or serious adverse effects reported. Specifically, there were no subjects that developed motor function deficits or drooping. All the patients with improved erythema grades had maintained improvement throughout the study period.

Discussion

This study demonstrates the successful and safe treatment of rosacea-associated facial erythema using intradermal botulinum toxin. The use of botulinum toxin is a rational approach if one assumes that neuron-mediated vascular dysfunction plays important pathogenic roles in rosacea.[12–14,37] This has been

TABLE 2. Clinician-Assessed Erythema Grades—Pairwise Comparisons

Erythema Grade (A)	*Erythema Grade (B)*	*Mean Difference (A − B)*	*SE*	*Significance (p)*
Baseline	1-month follow-up	0.400*	0.131	.009
Baseline	2-month follow-up	0.533*	0.133	.001
Baseline	3-month follow-up	0.800*	0.145	.000
1-month follow-up	2-month follow-up	0.133	0.091	.164
1-month follow-up	3-month follow-up	0.400*	0.131	.009
2-month follow-up	3-month follow-up	0.267*	0.118	.041

*Reaches statistical significance.

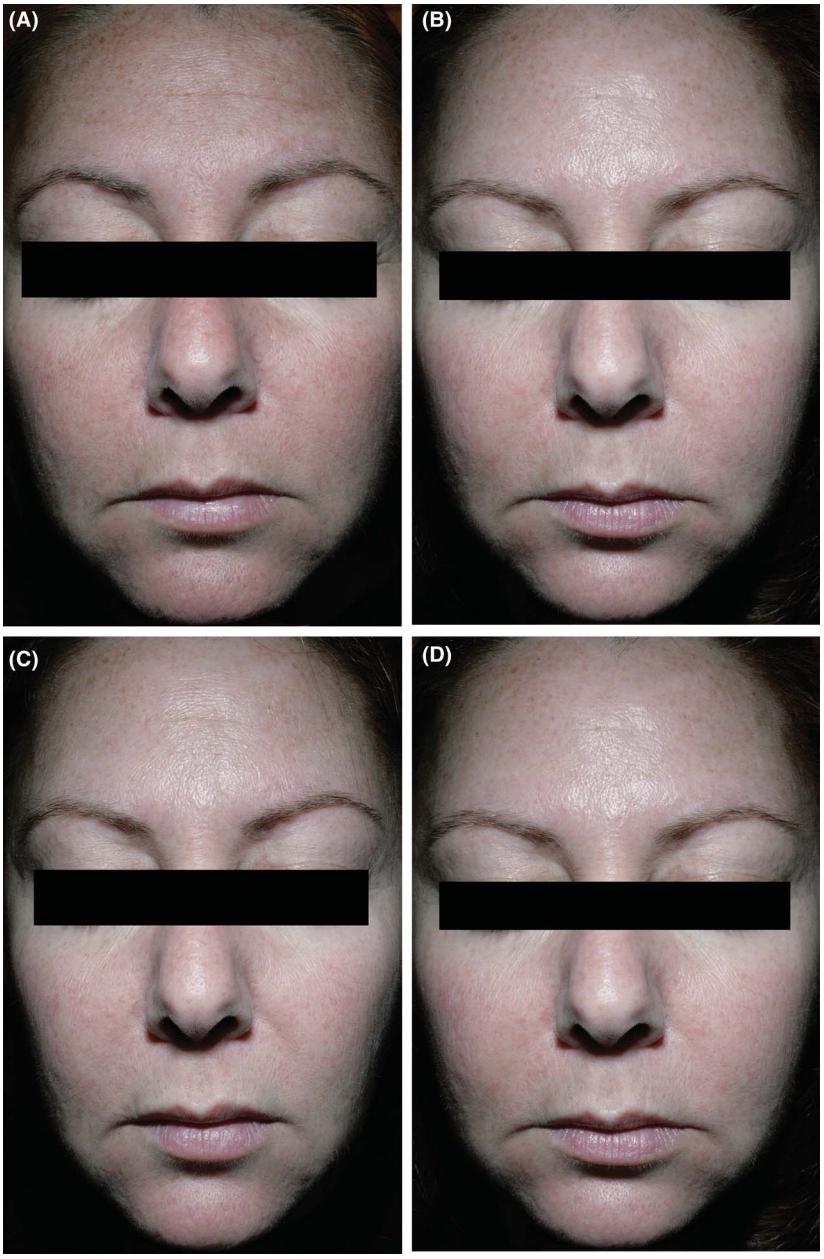

Figure 2. Pre-treatment and post-treatment digital photography for sample subject. (A) Baseline, (B) 1-month follow-up, (C) 2-month follow-up, (D) 3-month follow-up.

confirmed by recent morphological and molecular studies, which demonstrate the critical roles of neurovascular and neuroimmune networks in the development of rosacea.[37] It follows that drugs such as botulinum toxin, which function on neurovascular and/or neuroimmune communication, may be used in the treatment of rosacea.[37]

Enhanced cutaneous blood flow in lesional skin has been demonstrated in several studies investigating rosacea.[14,38] Additionally, autonomic nerve fibers are known to play an important role in vasomotor control and thus cutaneous blood flow.[34] In nonglabrous skin, 2 branches of the sympathetic nervous system are largely responsible for changes in cutaneous blood flow. The vasoconstrictor branch is noradrenergic and mediated by the neurotransmitter norepinephrine along with one or more cotransmitters (neuropeptide Y and/or adenosine triphosphate).[34,39,40] The vasodilator branch is cholinergic and mediated by the

neurotransmitter acetylcholine along with one or more cotransmitters (vasoactive intestinal peptide, pituitary adenylyl cyclase-activating polypeptide, and/or nitric oxide).[34,41,42]

Botulinum toxin type A inhibits the exocytosis of preformed vesicles in cholinergic nerves (motor and autonomic) and results in the blockade of acetylcholine release. One possible mechanism by which botulinum toxin improves flushing is this potent blockade of acetylcholine release from autonomic peripheral nerves of the aforementioned cutaneous vasodilatory system. However, based on studies in patients with Frey syndrome, it is likely that acetylcholine cotransmitters are also involved. These studies demonstrated that atropine blockade of acetylcholine prevents sweating but not flushing in Frey syndrome.[43,44]

Initial interest in the use of botulinum toxin for the treatment of facial erythema and flushing stemmed from its successful treatment of patients with Frey syndrome, also known as auriculotemporal syndrome that results from trauma or disease of the parotid gland and is characterized by gustatory sweating and flushing.[31,45] Sterodimas and colleagues later reported a case of successful treatment of anterior neck and anterior chest wall flushing with intracutaneous botulinum toxin type A. The patient was treated with 100 U of onabotulinumtoxinA injected intracutaneously at 3 visits each 2 weeks apart, and complete abolition of symptoms were noted 4 weeks after the final treatment.[30]

Yuraitis and Jacob[32] later reported a case of successful treatment with botulinum toxin of recalcitrant facial flushing. Each cheek was treated with a total of 10 U of intradermal onabotulinumtoxinA. Other authors have not been able to duplicate the benefits on facial flushing, and in one report, no improvement in flushing was seen despite the use of doses sufficient to cause facial drooping.[28,46] A more recent study showed that botulinum toxin B was ineffective in the treatment of facial flushing. However, these disparate results may simply be a reflection of the different underlying pathophysiologic mechanisms in various rosacea subtypes.

Dayan and colleagues[47] reported anecdotal evidence of successful treatment of 13 rosacea patients treated with intradermal microdroplet injections of onabotulinumtoxinA. The initial treatment regimen included IPL treatments with adjunctive onabotulinumtoxinA injections. However, Dayan and colleagues[47] subsequently abandoned the IPL and reported that 8 to 12 U per cheek of onabotulinumtoxinA injections was effective in decreasing flushing, erythema, and inflammation within 1 week of treatment and persisting for up to 3 months.

A recent case report of a woman who developed white patches on her forehead at sites of abobotulinumtoxinA injections provides further evidence that botulinum toxin interferes with neurovascular networks and may provide symptomatic relief to patients with flushing.[48]

The results of this study are promising and provide objective prospective data of improved facial erythema in patients with rosacea. Interestingly, no patients were noted to have cosmetic improvement of rhytides. This is likely a consequence of the relatively low dosing per area and the injection technique intradermally.

Limitations of this study include the small sample size, lack of a control group, and poor follow-up rates. An additional limitation of this study is the variable range of neurotoxin injected at the treatment sites (15–45 U). However, this was necessary as patients had different grades of erythema and the study was not designed to determine the optimal dosage. Just as in treating hyperkinetic muscle tone, different dosages were required for different patients. A larger, randomized, blinded, placebo-controlled dose–response trial is necessary to substantiate the findings that intradermal botulinum toxin is an effective treatment of rosacea-associated facial erythema.

Conclusion

Intradermal injection of botulinum toxin seems to be a safe and efficacious treatment of rosacea-associated facial erythema. The benefits may be enhanced if used in conjunction with current treatments of erythema including laser therapy. Larger, randomized, blinded, placebo-controlled studies are warranted. Further

study is needed to determine the optimal number of units and the duration of action of intradermal botulinum toxin when used for this indication. Additionally, further investigation is needed to elucidate the mechanism of action by which botulinum toxin improves facial flushing of rosacea.

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