

A New Treatment Regimen for Rosacea: OnabotulinumtoxinA

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ABSTRACT

Rosacea is a cutaneous condition with several clinical subtypes that are commonly seen in daily medical practice. There are many different treatment modalities for each of the physical findings associated with this disease, and all have varying results. As the use of onabotulinumtoxinA rises, its benefit in the treatment of a growing number of medical diseases increases. The authors report anecdotal evidence of patients with rosacea experiencing improved symptoms of erythema and flushing after treatment with intradermal, microdroplets of onabotulinumtoxinA. There were no adverse events reported for any of the treatments. The mechanism of action through a likely neurogenic component to vascular dysfunction, inflammation, and hypersebaceous activity is reviewed.

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INTRODUCTION

Worldwide, botulinum neuromodulators are now the most popular medical treatment for wrinkle reduction, but its storied history and broad-based applications for treating many noncosmetic medical conditions go back further. The Food and Drug Administration (FDA) initially approved it in 1989 for strabismus and soon after for cervical dystonia, and there have been six additional indications since then.[1,2] The advancement and evolution of additional indications seem consistently to outpace many other pharmaceuticals. It seems the quest for new uses for botulinum toxin is uncontained, and limited only by the imagination.

Interestingly, many of the newer indications, from migraines to hyperhidrosis, have been stumbled upon serendipitously while treating a recognized indication. In our own experience, we anecdotally noticed that, following a cosmetic treatment to the glabella and the forehead area with onabotulinumtoxinA, there was not only a reduction in wrinkle formation, but also a curious skin-quality change that appeared to be the result of light reflecting robustly off a smooth, homogenous skin surface. There also appeared to be a reduction in acneic lesions and peripustule erythema in treated areas. Recognizing that erythema, flushing, and inflammation had been reduced in our patients with acne vulgaris prompted us to use botulinum toxin empirically as a treatment for relieving symptoms associated with rosacea.

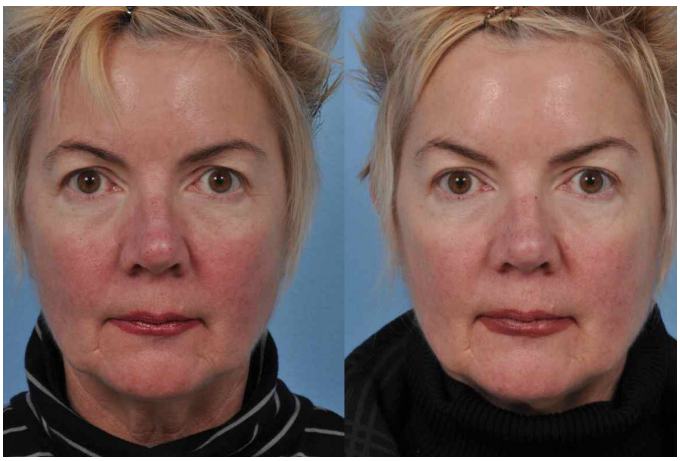
Rosacea, a common condition affecting 16 million Americans, has a variable presentation. The clinical diagnosis for rosacea can be difficult to identify at times, but its most important sign is erythema over the central face persisting for longer than three months. Flushing, papules, pustules, and telangiectasias are other common characteristic signs.[3] A 2004 article published by leading experts classified rosacea into four subtypes: erythematotelangiectactic, papulopustular, phymatous, and ocular.[4] Erythematotelangiectactic rosacea (ETR), characterized by flushing that persists for longer than 10 minutes, can be brought on by different triggers from emotional stress to foods to topical products. It is often associated with burning and stinging, but not with palpitation, light-headedness, or sweating. Papulopustular rosacea (PPR) is the classical rosacea characterized by a red central portion of the face with small papules that may be surmounted by pinpoint pustules. Flushing occurs but is not as marked as in ETR. Persistent or episodic inflammation is commonly seen, and the inflammation may lead to chronic edema and fibrous changes to the skin. Phymatous rosacea is characterized by marked skin thickening and irregular surface nodularities leading to rhinophyma (nose), gnathophyma (chin), and metophyma (forehead). The fourth type, ocular rosacea, centers around the eyes. Other clinical considerations for rosacea include glandular and granulomatous rosacea represented by nodularities that can lead to scarring but are not necessarily associated with flushing. Nonrosacea conditions such as chronic sun damage, topical steroid abuse, and adverse drug reactions may have similar symptoms to rosacea and should be ruled out prior to diagnosing rosacea.

MATERIALS AND METHODS

Over the past two years, we have treated 13 patients presenting with rosacea with intralesional microdroplet injections (0.05 cc) of onabotulinumtoxinA (Botox® Cosmetic; Allergan, Irvine, CA) in a dilution of 7 cc of saline solution per 100 units.

Multiple injections were performed intradermally and ranged on average from 8 to 12 units per affected cheek area. Decreased flushing, erythema, and inflammation were noted within one week and persisted for up to three months. When we first started using botulinum toxin for rosacea, we used it as

FIGURE 1. Substantial decrease in erythema of the bilateral cheeks.



an adjunct to intense pulsed light (IPL) treatments, which had been our treatment of choice. However, we have subsequently abandoned the IPL treatment, recognizing it as no longer necessary because the efficacy of botulinum toxin appears to be singularly adequate for a three-month period.

Case 1

A 59-year-old Caucasian female presented with focally increased telangiectasias, persistent erythema focused on the malar cheeks and nose, and facial flushing triggered by heat and/or stress. Her past medical history was noncontributory, her history of sun exposure was moderate, and she had not previously received any cosmetic treatments or prescription agents for these clinical concerns. Physical examination revealed prominent telangiectasias on the malar cheeks and nose overlying a background of ill-defined erythema, and the patient reported a burning sensation during facial flushing episodes. Also noted were fine rhytides of the forehead, glabella, and periocular areas.

Because the patient was concerned with both of these physical findings, possible treatment options were reviewed, and it was decided to use one treatment modality for both concerns, the injection of a neuromodulator, onabotulinumtoxinA. After informed written consent was obtained, the botulinum toxin A was diluted with 7 cc of isotonic saline to create a final dilution of 1.4 units per 0.1 cc. Using a 30-gauge needle, six units were injected into the right cheek and four units were injected into the left cheek in a microdroplet intradermal technique at 0.5 cm intervals. At a two-week follow-up appointment, the patient noted a substantial decrease in erythema of the bilateral cheeks (Figure 1). There were no side effects reported, including paralysis or asymmetry. Pleased with clinical results that had lasted approximately three months, the patient requested another treatment. At this treatment, 11.2 units total were injected into each cheek and 5 units into the nasal affected skin. Again, the patient reported a decrease in the amount of erythema at the affected area.

Case 2

A 50-year-old Caucasian female presented over many years with persistent erythema, intermittent flushing, and telangiectasias on her cheeks and glabella. She had previously been treated with microdermabrasion and over-the-counter topical treatments without success. Her medical history was noncontributory, and her history of sun exposure was moderate. Physical examination revealed generalized erythema of the bilateral cheeks and glabella areas, with increased telangiectasias on the malar cheeks. After discussing available treatment options, a series of IPL treatments (Harmony System; Alma Lasers Ltd, Caesarea, Israel) was initiated on the full face. The initial treatment parameters included a wavelength 530 nm to 950 nm, energy of 16 J/cm^2, 15 ms pulse duration, and one pass over the full face. A total of eight treatments was completed over a year and half, resulting in only mild improvement in the background erythema. Subsequently, an additional two IPL treatments were performed with the Lumenis M22 platform (Lumenis Ltd, Yokneam, Israel), using settings of a wavelength 590 nm to 1,200 nm, energy of 13 J/cm^2 to 18 J/cm^2, 4 ms triple pulse duration, with one pass over the cheeks, resulting in only mild improvement in the erythema.

> "Following a cosmetic treatment to the glabella and the forehead area with onabotulinumtoxinA, there was not only a reduction in wrinkle formation, but also a curious skin-quality change that appeared to be the result of light reflecting robustly off a smooth, homogenous skin surface."

Using the same microdroplet intradermal technique outlined in case 1, 11.2 units of onabotulinumtoxinA were injected evenly throughout the clinically affected area of the cheek and glabella at 0.5 cm intervals. The patient tolerated the procedure well. There were no side effects, and a marked improvement in the evident erythema was noted at her 10-day follow-up appointment. At this visit, the procedure was repeated again with the same treatment parameters. The patient reported a considerable reduction in the pore size, erythema, and flushing of the affected areas one month after treatment (Figure 2). No side effects were noted. As the patient was satisfied with the results, she returned for another treatment four months after the initial treatment with onabotulinumtoxinA.

DISCUSSION

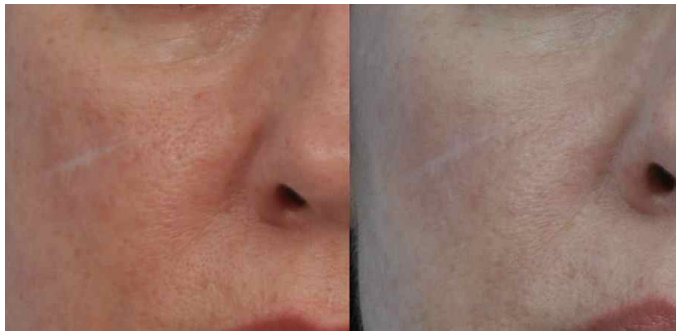
It is important to recognize the subtype of rosacea, because the pathophysiology, clinical course, and outcomes can vary among them. However, vascular abnormality is perhaps the

most consistent finding in all rosacea patients. Facial flushing, vasodilation, and increase in blood flow, whether pathological or not, are a result of both humoral and neural stimuli. Neuropeptides such as substance P (SP), vasoactive intestinal polypeptide (VIP), and acetylcholine (ACh) have all been implicated in increased vascular flow. Moreover, increased microvascular flow secondary to stress, heat, or irritants is common to the ETR and PPR rosacea subtypes. Over the past few years, a neurogenic component to rosacea is becoming increasingly clear. Although supporting evidence for SP seems to be waning,[5,6] the morphological and molecular evaluation using immunohistochemistry studies and gene array analysis have shown marked upregulation of the neuropeptide genes for VIP, pituitary adenylate cyclase-activating polypeptide (PACAP), 5-hydroxytryptamine (serotonin) 3A receptors, nerve growth factor beta, alpha1D-adrenergic receptors, adrenomedullin 2, and cathelicidin antimicrobial peptide in rosacea patients.[7] This all suggests that there is an important neurogenic component to vascular dysfunction in rosacea.

Chronic poor vascular hemostasis leads to leaky vessels, pooling, delayed removal of inflammatory mediators, and a prolonged perivascular inflammation. Inflammation is a common denominator in rosacea and, when prolonged, leads to tissue hypertrophy and fibroplasias, the likely mechanism behind rhinophyma. There is debate over the origin of the inflammation in rosacea, and controversy surrounds the theory of a perifollicular inflammatory process that is aggravated by microbial organisms. The bacteria *Propionibacterium acnes* and Demodex mites have been causatively linked to rosacea, with evidence that antibiotics targeting these organisms are helpful in treating the symptoms of rosacea; but these organisms are also found in high concentration in people without rosacea.[3] However, a neurogenic component to the inflammation in rosacea is strongly supported by histochemical evidence. Mast cells, a potent contributor to the release of inflammatory mediators, including histamine, are identified in increased quantity in rosacea patients, and receptors for histamine and serotonin, leading to vasodilatory effects, are upregulated in all forms of rosacea. Additionally, the neuropeptides VIP and PACAP are known activators of mast cells and may be important connectors from nerve to mast cell to histamine release, all affecting inflammation in rosacea. A neurogenic origin to the inflammatory component of rosacea, as well as the vascular component, can be well supported. Therefore, as eluded to by Schwab et al, drugs that affect neurovascular and neuroimmune communication may be advantageous in the treatment of rosacea.[7]

Botulinum toxin type A, as an inhibitor of ACh and VIP release, supports a mechanism of action which explains its benefits in reducing facial and neck flushing. When body temperature rises, cutaneous blood flow and vasodilatory effects are partially dependent on post ganglionic cholinergic ACh and VIP release.[8,9] OnabotulinumtoxinA as a potential modality for treating flushing

FIGURE 2. Reduction in the pore size, erythema, and flushing of the affected areas one month after treatment.



was described by Yuraitis and Jacob, who noted a decrease in facial flushing and extremely satisfying results two weeks after 10 units (2 U/0.1 cc) of onabotulinumtoxinA had been placed at 1 cm intervals into one cheek of a 26-year-old male.[10] Flushing is also common to gustatory sweating (Frey syndrome), a well-described sequelae following parotid surgery in which parasympathetic fibers intended for the parotid gland regenerate and reinnervate sweat glands. Upon eating, neurosignaling intended to stimulate parotid gland salivation instead triggers regional sweating. Tugnoli et al reported that 25 U to 55 U of onabotulinumtoxinA (100 U/5 cc) in 2 U increments and 100 U to 180 U of abobotulinumtoxinA (300 U/5 cc) in 6 U increments effectively reduced gustatory sweating, cutaneous blood flow, and flushing on the treated side for up to 18 months.[11]

Although botulinum toxin's potent effects on ACh release inhibition suggest it is the signaling neuropeptide behind the flushing, another peptide must also be involved because atropine blockade of ACh action in patients with Frey syndrome stops the sweating, but not the flushing.[12,13] Vasoactive intestinal peptide has been suggested as another parasympathetically released neuropeptide likely responsible for the flushing.[14] Sterodimas and colleagues in 2003 reported on treating a patient with neck flushing with a diluted version of onabotulinumtoxinA.[15] Three hundred units of onabotulinumtoxinA (1 U/0.1 cc) was injected into the anterior chest in three subsequent 100 U doses; each dose was separated by two weeks. Four weeks after the third treatment, the patient had complete abolition of her symptoms and no adverse events. Using the same concentrated version of onabotulinumtoxinA (4 U/ 0.1 cc) as Yuraitis and Jacobs,[10] Kranendonk et al injected eight units in four sites over the central cheek. They noted no reduction in erythema but were concerned at an alteration in mimetic activity of the cheek and upper lip during smiling one week after the injection.[16] However, others have been unable to duplicate the onabotulinumtoxinA antiflushing effects.[17] Alexandroff and colleagues, using 2 U/0.1 cc dilution, injected 10 units at 1 cm intervals to one cheek of two separate patients with a history of facial flushing, and they noted no improvement after six weeks. Although injection protocols may be similar in the few existing case reports, the dilution and dosing of the toxin seem to differ,

and this may have an effect on the outcome. Sample sizes are small, and no large, placebo-controlled trials have been conducted to date.

In addition to flushing, hypersebaceous activity is characteristic in many patients with rosacea, especially those with a glandular type.[3] Excess sebum production is also a frequently implicated component of acne vulgaris. In a large meta-analysis of patients treated with onabotulinumtoxinA for facial lines, acne was statistically significantly less common in the onabotulinumtoxinA-treated participants than in the placebo group,[18] suggesting that onabotulinumtoxinA may have a therapeutic effect on acne reduction. Although a mechanism of action has not been clearly identified in explaining the botulinum toxin type A effects on reducing acne, there is speculation that the neuropeptides ACh and SP may be a neurogenic origin of both sebaceous activity and inflammation.[19] Moreover, botulinum toxin type A at 2 U/0.1 cc dilution, a known inhibitor, has been reported to reduce oily skin and the appearance of pore size when injected intradermally into facial skin.[20] Other studies have also indicated that intradermal injections on onabotulinumtoxinA and abobotulinumtoxinA improve the aesthetic appearance of the skin.[21]

Similar to the technique used for hyperhidrosis and oily skin, the effectiveness in reducing symptoms of rosacea along with preventing adverse muscular dysfunction seems dependent on injecting the toxin intradermally. We selected a higher dilution (100 U/7 cc), recognizing that it allows for more spread[22] and, in theory, also reduces the potency of any product that penetrates past the dermal subcutis junction to reach a specific muscle group, thereby reducing the possibility of mimetic complication.

CONCLUSION

The ability to offer a treatment that takes just minutes and can be performed three to four times per year, obviating the need for multiple laser treatments, systemic medications, or daily topical treatments, would provide a desirable alternative for both the patient and the physician. Rosacea affecting the face can be a major disruption in one's professional, social, and family life. Surveys by the National Rosacea Society indicate that more than 76% of rosacea patients find that the condition lowers their self-confidence and self-esteem, with 41% reporting that it causes them to avoid public contact or cancel social engagements.[3] The proposed mechanisms of action responsible for botulinum toxin efficacy in reducing the symptoms of rosacea are logical, but still not clearly delineated. Perhaps by inhibiting release of VIP and ACh, botulinum toxin is inhibiting the effects of two of the known neurogenic peptides linked to inflammation and vasodilation in rosacea, or perhaps, the exact mechanisms are yet to be identified by which botulinum toxin prevents the release of one of the numerous other neuropeptides involved in sebaceous activity, vascular homeostasis, and inflammation. While our results are anecdotal, the curious nature of this product continues to expand serendipitously to new indications. A double-blind, randomized, placebo-controlled trial is in order and expected soon.

DISCLOSURES

Dr. Dayan has been a consultant, investigator, and speaker for Merz, Medicis, and Allergan.

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