OnabotulinumtoxinA improves oral aperture in patients with scleroderma: A small clinical trial

Cristian D. Gonzalez, MD,[a] Jarod John Pamatmat, MD,[b] Kevin M. Burningham, MD,[b] Michelle Yang, MD,[a] and Heather W. Goff, MD, MPH[a]

Background: Reduced oral aperture (ROA), resulting from systemic sclerosis (SSc), is a debilitating condition with limited treatment options. Improvement in oral function has been reported with perioral administration of botulinum toxin type A.

Objective: To prospectively evaluate the efficacy of onabotulinumtoxinA (onabotA) injection in improving oral opening and quality of life in SSc patients with ROA.

Methods: Seventeen women with SSc and ROA were treated with 16 units of onabotA in 8 different sites around the cutaneous lips. Measurements of maximum mouth opening were taken before treatment, at 2 weeks posttreatment, and at 3 months posttreatment. Function and quality of life were also assessed via surveys.

Results: Interincisor and interlabial distances were significantly increased 2 weeks after treatment with onabotA ($P < .001$) but not 3 months after. Subjective improvement in quality of life was noted.

Limitations: This single-institution study enrolled 17 patients and did not have a placebo control group.

Conclusion: OnabotA appears to have a strong short-term symptomatic benefit in patients with ROA due to SSc, with possible benefit to quality of life. (J Am Acad Dermatol 2023;89:952-8.)

Key words: diffuse scleroderma; limited mouth opening; microstomia; neuromodulator; onabotulinumtoxinA; reduced oral aperture; scleroderma; systemic sclerosis.

INTRODUCTION

Scleroderma/systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by excessive extracellular matrix production and fibrosis due to an uncontrolled inflammatory reaction to endothelial injury, which increases differentiation of fibroblasts to myofibroblasts, the primary cells responsible for extracellular matrix production.[1] Widespread extracellular matrix production and fibrosis leads to a variety of severe complications, including pulmonary arterial hypertension, cardiomyopathy, and scleroderma renal crisis.[1,2] Microstomia or reduced oral aperture (ROA) is one such complication that is often understated despite its debilitating effects on physical appearance, phonation, mastication, dental hygiene, and overall quality of life.[3,4] Gastroesophageal reflux disease and xerostomia also contribute to poor oral health in these patients.[3] ROA may contribute to malnutrition, which is responsible for 4% of SSc deaths.[5] Current treatment options for ROA, including physical therapy, surgery, topical steroids, phototherapy, and

From the Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas[a]; and University of Texas Southwestern Medical School, Dallas, Texas.[b]

Funding sources: Supported by Department of Dermatology, University of Texas Southwestern.

IRB approval status: Reviewed and approved by University of Texas Southwestern institutional review board (STU-2020-0169).

Accepted for publication April 29, 2023.

Correspondence to: Heather W. Goff, MD, Department of Dermatology, University of Texas Southwestern, 5939 Harry Hines Blvd, Dallas, Texas, 75390-8570. E-mail: heather.goff@utsouthwestern.edu.

Published online June 8, 2023.

0190-9622

https://doi.org/10.1016/j.jaad.2023.04.069

immunosuppressive agents, have limited efficacy.[3,6,7] Although some case reports have suggested that hyaluronidase injections can relieve symptoms of ROA, no clinical trials of its effect have been performed.[7,8,9] More research into this possibility is warranted. Consent for publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal, stating that all patients gave consent for their photographs and medical information to be published in print and online, with the understanding that this information may be publicly available.

CAPSULE SUMMARY

- Botulinum toxin type A has a beneficial effect on microstomia in scleroderma, according to 1 case series. We present a clinical trial evaluating this claim.
- This study suggests that onabotulinumtoxinA is an efficacious short-term treatment for microstomia in scleroderma, and physicians should consider it to improve symptoms.

Botulinum toxin type A is another promising alternative therapy for ROA in SSc. Botulinum toxin type A is a group of neurotoxins that function as paralytics by preventing the release of acetylcholine to inhibit muscle contracture.[10] Botulinum toxin type A is also thought to decrease conversion of fibroblasts to myofibroblasts and increase matrix metalloproteinase.[11,12] It has been used effectively to treat a wide range of conditions such as rhytids, cervical dystonia, migraine, and chronic musculoskeletal pain.[13-16] The study of its therapeutic benefit in patients with SSc has so far been limited to treatment of Raynaud's phenomenon.[17-20] The use of botulinum toxin type A to treat ROA in SSc was described in a case series of 5 patients. Most of these patients were diagnosed with limited SSc, whereas skin fibrosis is commonly associated with diffuse SSc. In this series, patients received 20 units of botulinum toxin type A, injected into either 4 or 8 perioral sites. Two patients returned for multiple treatments over periods of 12 and 27 months, respectively. Oral apertures increased between 5 mm and 20 mm, with subjective improvements in quality of life due to increased confidence, greater enjoyment of meals, and more comfort during oral procedures.[21]

Our clinical trial intends to further elucidate the safety and efficacy of botulinum toxin type A in treating SSc-induced ROA. We hypothesized that at least short-term improvement would be observed in oral measurements of patients diagnosed with ROA in SSc following a single treatment of injections with onabotulinumtoxinA (onabotA) to perioral sites together with objective increases in functionality and quality of life as measured using standardized Mouth Handicap in Systemic Sclerosis Scale (MHISS) and Visual Analogic Scale (VAS).[22,23]

METHODS

We performed a pilot prospective cohort study of 17 women with a diagnosis of scleroderma (defined by the 2013 Classification Criteria for Systemic Sclerosis), treated at the University of Texas Southwestern Medical Center, who also have ROA (defined as an interincisal distance less than 50 mm).[24-27] Patients under 18 years of age were excluded.

Additional exclusion criteria included patients with a known history of hypersensitivity to any botulinum toxin formulation or to any of the components in the formulation, active skin infection at the proposed injection site, and concomitant neuromuscular disorder and patients who were pregnant or lactating, had missing incisors, or were on treatment with cyclophosphamide, UV A-1 therapy, or topical calcitriol. A maximum of 30 patients could have been enrolled with available grant funds. At the initial visit, all patients completed forms with demographic information in addition to the MHISS. The maximum interlabial distance (between the vermillion edge of the upper lip and lower lip), interincisal distance (between upper and lower incisor), and intercommissural distance of each patient were measured, using digital calipers, by the same operator. Participants were requested to open their mouth as wide as possible and photographs were taken. Injections were administered by the same physician to prevent interphysician variation. Due to the limited available subjects, all patients were included in the treatment group and no placebo control group was formed. Botox 100 U vials were each diluted with 2.5 mL saline, making for a 4 U/0.1 mL dilution. In 1 session, 0.05 mL (2 U) was injected per site into 8 different injection points (16 U in total) around the lips. The treatment was performed at no cost to the patients, with funding for the study supplied by the Dermatology Department, University of Texas Southwestern via an educational grant.

Follow-up after treatment was performed at 2 weeks and 3 months with repeat oral measurements. Additionally, the MHISS was repeated and VAS and satisfaction surveys were completed at first follow-up visit. The VAS asked patients to record the observed improvement from previous visit on a scale

Abbreviations used:

MHISS:	Mouth Handicap in Systemic Sclerosis Scale
onabotA:	onabotulinumtoxinA
ROA:	reduced oral aperture
SSc:	systemic sclerosis
VAS:	Visual Analogic Scale

of 1 to 10, with 10 representing "the best possible improvement." The satisfaction survey asked patients to rank their satisfaction with the treatment on a scale of 1 to 5, with 5 representing "very satisfied." Patients' experiences with the treatment were recorded qualitatively via exploratory questions regarding its impact on their daily life.

Patients' skin status was determined to be either "stable/quiescent," if no progression in dermal sclerosis was noted in the previous year, or "progressive," if any progression was noted. For both interincisor and interlabial distances, patients who experienced 1 mm or greater improvement between injection and follow-up at 2 weeks were categorized as "responders" and the remainder were classified as "nonresponders." Within the responders' designations, patients were further subdivided, by degree of improvement, into "significant" (>9 mm), "moderate" (4.1-9 mm), and "minimal" (1-4 mm). Outcome data were collected on MHISS and VAS. An appropriate intention-to-treat analysis approach was used to cf the mean interlabial, interincisal, and intercommissural distance changes at baseline, 2 weeks, and 3 months. Student 2-sided *t* test was used to determine the significance of changes in measurements, whereas Fisher's exact test was used to evaluate the correlation between skin involvement status (stable/quiescent or progressive) and responder status for interincisor and interlabial distances. A P value $<.05$ was considered statistically significant.

RESULTS

All 17 patients received a single treatment with onabotA as described above. Mean age was 54 years (IQR, 49-59 years). Fifteen patients were diagnosed with diffuse SSc and the remaining 2 with limited SSc. Twelve of the patients' skin disease was stable/quiescent, whereas 5 had progressive disease. The median time since SSc diagnosis was 9 years (IQR, 5-18 years). Patient demographic and clinical characteristics are summarized in Table I. All patients returned for the first follow-up appointment at 2 weeks posttreatment. Subjects 4, 6, 10, 14, and 15 were either lost to follow-up or did not return for the final assessment at 3 months.

Intercommissural distance was not significantly changed from baseline at either 2 weeks or 3 months. Significant improvement in interincisor distance was observed at 2 weeks (mean difference, 4.39 ± 4.3 mm in total cohort and 5.8 ± 4.0 mm in responders; both $P < .001$). However, this improvement did not persist at 3 months and had reduced to a mean difference of 1.4 ± 5.3 mm in total cohort ($P = .365$) and 2.4 ± 4.8 mm in responders ($P = .146$). Interincisor distance results are represented in Fig 1. The same trend was observed with interlabial distance; significant improvement was noted at follow-up at 2 weeks (mean difference, 7.8 ± 5.9 mm in total cohort and 10.7 ± 4.3 mm in responders; both $P < .001$) but did not persist at 3 months (mean difference, 1.5 ± 6.1 mm in total cohort; $P = .410$ and mean difference, 1.8 ± 6.4 mm in responders; $P = .389$). Interlabial distance results are represented in Fig 2. Thirteen patients (76%) and 7 patients (41%) had an improvement of at least 4.1 mm in interlabial and interincisor distance, respectively, at 2 weeks posttreatment.

There was no significant change in MHISS survey scores between baseline and 2 weeks among all patients ($P = .856$). However, VAS and satisfaction scores were positive, with 76% of subjects reporting that they were highly satisfied, satisfied, or moderately satisfied and 53% of subjects scoring their observed improvement in symptoms as "moderate-significant." The most commonly reported adverse effects of the treatment were difficulty drinking ($n = 5$, 29%), drooling ($n = 3$, 18%), mild speech impairment ($n = 2$, 12%), and difficulty puckering the lips ($n = 2$, 12%). These events were short-lived, with all lasting between 3 days and 2 weeks, except in the case of 1 patient whose reported complaint lasted approximately 2 to 3 months until the effect of the treatment had worn off entirely. No major complications due to the treatment were reported. When asked what they were pleased with, 4 patients reported increased lip eversion, 4 patients reported decreased perioral rhytids, 4 patients reported having an easier time flossing or seeing the dentist, 2 patients reported smiling was easier, and 1 patient reported having an easier time drinking.

There was no significant correlation between skin status of disease or responder status and changes in interincisor ($P = .538$) or interlabial ($P = .117$) distances.

DISCUSSION

Our study results suggest that a single treatment of onabotA injections to perioral sites had a short-term but considerable benefit for oral aperture in patients with ROA due to SSc, with an acceptably mild side-

Table I. Subject demographics and clinical characteristics

	Age (y)	Race	Ethnicity	Duration (y)	SSc subtype	Antibody profile	Skin involvement
Subject 1	54	B	N	10	Diffuse	ANA 1:2560, Scl 70 6.5	Stable/quiescent
Subject 2	45	W	N	5	Diffuse	ANA$^+$ 1:640 speckled, anti—RNA polymerase III$^+$ 126.2, SA $>$ 8.0	Stable/quiescent
Subject 3	61	W	N	36	Limited	ANA$^+$, anticentromere	Stable/quiescent
Subject 4	49	W	N	4	Diffuse	Ribonucleoprotein 5.9, ANA$^+$	Stable/quiescent
Subject 5	54	W	N	2	Diffuse	RNA polymerase III Ab$^+$	Progressive
Subject 6	58	W	N	6	Diffuse	PM-SCL antibody$^+$, ANA 1:2560	Progressive
Subject 7	57	B	N	12	Diffuse	SCL-70$^+$, ANA 1:2560	Stable/quiescent
Subject 8	38	W	H	22	Diffuse	ANA 30 equivalent to 1:160-640, anti-DNA$^+$, anti-Scl70$^+$, SSA$^+$	Stable/quiescent
Subject 9	45	D	H	5	Diffuse	ANA 1:1280, SCL-70$^+$	Stable/quiescent
Subject 10	25	D	H	18	Diffuse	scl 70$^+$	Stable/quiescent
Subject 11	50	W	N	6	Diffuse	ANA 1:640, Scl70$^+$, SSA$^+$, CCP$^+$	Stable/quiescent
Subject 12	63	W	N	3	Diffuse	RNA 3 polymerase, ANA$^+$ 1: 320 with a speckled pattern	Stable/quiescent
Subject 13	49	W	H	5	Diffuse	SCL 70$^+$, ANA$^+$	Progressive
Subject 14	59	W	N	13	Diffuse	ANA 1: 640 speckled pattern, SCL 70$^+$	Stable/quiescent
Subject 15	66	W	N	35	Limited	ANA$^+$ $>$1:2560	Progressive
Subject 16	59	W	N	26	Diffuse	ANA, RNP, PR3	Progressive
Subject 17	73	W	N	9	Diffuse	ANA, Scl-70	Stable/quiescent
Median	54			9			
IQR	49-59			5-18			
Min/max	25/73			2/36			

B, Black/African American; *D*, declined to respond; *H*, Hispanic/Latino; *Min/max*, minimum value/maximum value; *N*, non-Hispanic/Latino; *SSc*, systemic sclerosis; *W*, White.

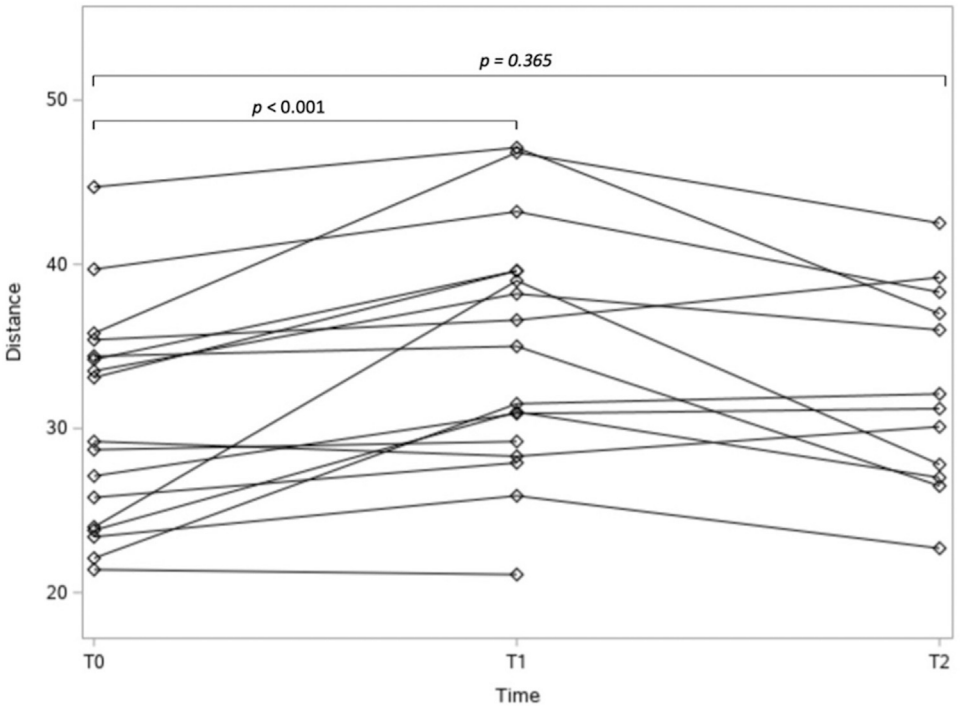

Fig 1. Reduced oral aperture in scleroderma. Plot of interincisor distance change over time for all subjects.

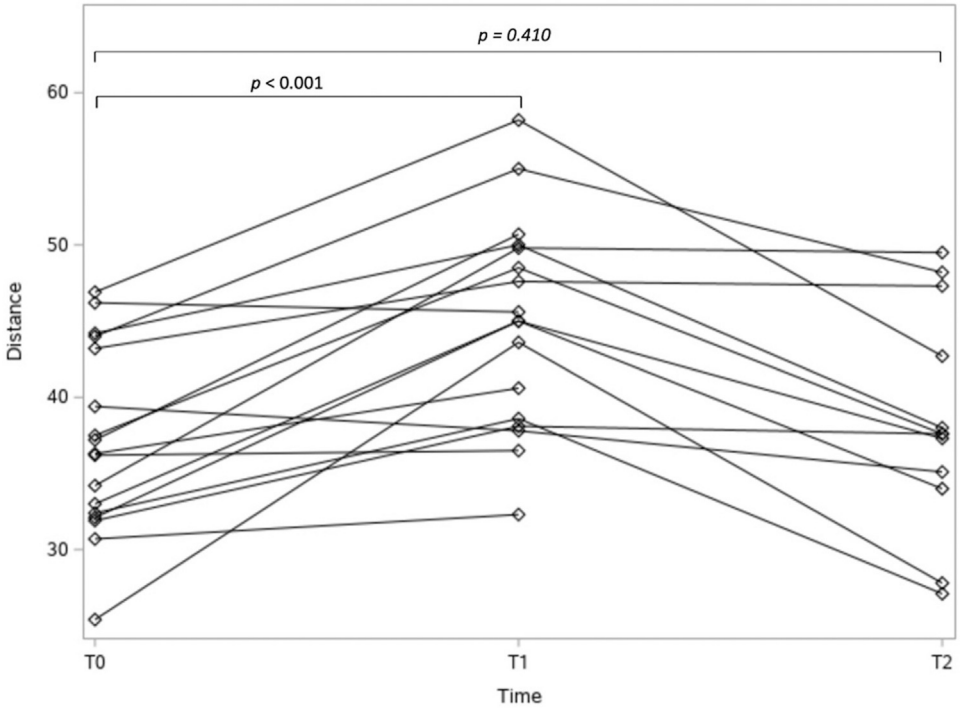

Fig 2. Reduced oral aperture in scleroderma. Plot of interlabial distance change over time for all subjects.

effect profile. Although the effect was not prolonged, this was expected and consistent with the known course of a single application of onabotA. The improvement appeared to be more pronounced with interlabial distance compared with interincisor distance (Figs 3 and 4). This was likely due to the perioral selection of onabotA injection, which primarily targets the orbicularis oris and, thus, should have a greater impact on the lips than on the teeth. OnabotA injections to the masseter and other muscles of the temporomandibular joint could improve interincisor distance to a larger degree and could be a promising area for further investigation. Intercommissural distance did not appear to be significantly affected by onabotA administration. As this distance is chiefly determined by the zygomaticus, buccinator, and risorius muscles, which were not targeted, this lack of change serves as therapy control for our study.

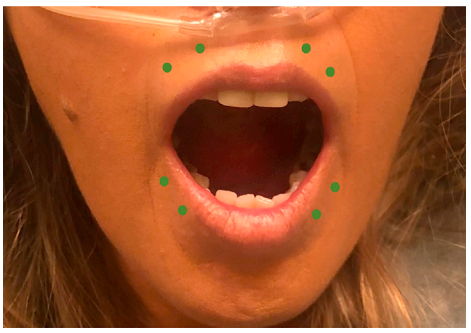

Fig 3. Reduced oral aperture in scleroderma. Pretreatment with injection sites indicated (green).

The MHISS, VAS, and satisfaction results are more difficult to reconcile. The results of the VAS and satisfaction surveys demonstrate that most of the 17 patients were satisfied with the treatment and experienced subjective improvement in their quality of life, as do the qualitative assessments recorded at the time of survey administration. After conclusion of the study, 8 of the 17 subjects returned for repeated treatments at their own expense. However, MHISS did not have individual correlation to patients' perceived improvement. There are potential explanations for this discrepancy. Several of the MHISS questions pertain to symptoms stemming from Sicca syndrome rather than microstomia. Also, some of the MHISS questions include medical terminology, such as "dentition," that may be difficult for patients to understand.[20] Qualitative data on patient satisfaction with in-depth interviews on the effects of the therapy and impact of oral aperture on quality of life may prove more useful.

Limitations to this study include its small sample size and resultant lack of a placebo control group.

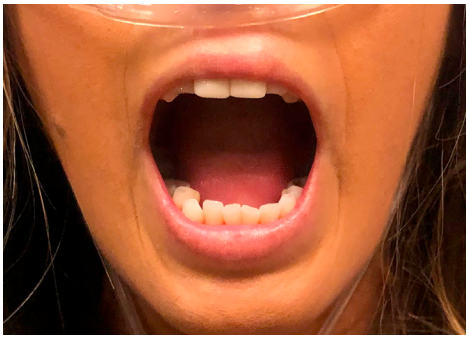

Fig 4. Reduced oral aperture in scleroderma. Two weeks posttreatment.

Uncontrolled studies are vulnerable to inherent bias, which limits the validity of our results. Looking forward, engaging multiple sites to generate a larger pool of data on more patients with placebo controls will yield more generalizable conclusions on the effects of onabotA as a tool for management of ROA in SSc. In particular, the antimyofibroblast and prometalloproteinase effects of onabotA may become more apparent with longitudinal therapy and repeated treatments. Further investigations regarding onabotA administration into the masseter at the mandibular angle may also prove useful for improvement of interincisor distance and jaw opening.

CONCLUSION

OnabotA injection appears to offer substantial short-term improvement in oral aperture in patients with systemic sclerosis. Patients also reported improvement in quality of life and high satisfaction with the treatment. Clinicians can consider use of onabotA when discussing therapeutic options to treat perioral aperture in patients with SSc.

Conflicts of interest

None disclosed.

REFERENCES

1. Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. *Nat Rev Dis Primers*. 2015;1:15002.
2. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest*. 2007;117(3):557-567.
3. Albilia JB, Lam DK, Blanas N, Clokie CM, Sándor GK. Small mouths ... big problems? A review of scleroderma and its oral health implications. *J Can Dent Assoc*. 2007;73(9):831-836.
4. Smirani R, Truchetet ME, Poursac N, Naveau A, Schaeverbeke T, Devillard R. Impact of systemic sclerosis oral manifestations on patients' health-related quality of life: a systematic review. *J Oral Pathol Med*. 2018;47(9):808-815.
5. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis*. 2007;66(7):940-944.
6. Pirrello R, Verro B, Grasso G, et al. Hyaluronic acid and platelet-rich plasma, a new therapeutic alternative for scleroderma patients: a prospective open-label study. *Arthritis Res Ther*. 2019;21(1):286.
7. Abbas LF, Coias J, Jacobe HT, Nijhawan RI. Hyaluronidase injections for treatment of symptomatic pansclerotic morphea-induced microstomia. *JAAD Case Rep*. 2019;5(10):871-873.
8. Melvin OG, Hunt KM, Jacobson ES. Hyaluronidase treatment of scleroderma-induced microstomia. *JAMA Dermatol*. 2019;155(7):857-859.
9. ClinicalTrials.gov identifier: NCT04656704. Accessed April 1, 2020. https://www.clinicaltrials.gov/study/NCT0465670
10. Guyuron B, Huddleston SW. Aesthetic indications for botulinum toxin injection. *Plast Reconstr Surg*. 1994;93(5):913-918.
11. Kim S, Ahn M, Piao Y, et al. Effect of botulinum toxin type A on TGF-β/Smad pathway signaling: implications for silicone-induced capsule formation. *Plast Reconstr Surg*. 2016;138(5):821e-829e.
12. Jeong HS, Lee BH, Sung HM, et al. Effect of botulinum toxin type A on differentiation of fibroblasts derived from scar tissue. *Plast Reconstr Surg*. 2015;136(2):171e-178e.
13. Carruthers J, Fournier N, Kerscher M, Ruiz-Avila J, Trindade de Almeida AR, Kaeuper G. The convergence of medicine and neurotoxins: a focus on botulinum toxin type A and its application in aesthetic medicine—a global, evidence-based botulinum toxin consensus education initiative: part II: incorporating botulinum toxin into aesthetic clinical practice. *Dermatol Surg*. 2013;39(3 Pt 2):510-525.
14. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818-1826.
15. Zhang T, Adatia A, Zarin W, et al. The efficacy of botulinum toxin type A in managing chronic musculoskeletal pain: a systematic review and meta analysis. *Inflammopharmacology*. 2011;19(1):21-34.
16. Cavallini M, Cirillo P, Fundarò SP, et al. Safety of botulinum toxin A in aesthetic treatments: a systematic review of clinical studies. *Dermatol Surg*. 2014;40(5):525-536.
17. Asad U, Austin B, Tarbox M, Paulger B. Botulinum toxin in the long-term treatment of refractory Raynaud's phenomenon. *J Drugs Dermatol*. 2019;18(9):943-945.
18. Dhaliwal K, Griffin M, Denton CP, Butler PEM. The novel use of botulinum toxin A for the treatment of Raynaud's phenomenon in the toes. *BMJ Case Rep*. 2018;2018.
19. Bello RJ, Cooney CM, Melamed E, et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: A randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol*. 2017;69(8):1661-1669.
20. Motegi S, Yamada K, Toki S, et al. Beneficial effect of botulinum toxin A on Raynaud's phenomenon in Japanese patients with systemic sclerosis: a prospective, case series study. *J Dermatol*. 2016;43(1):56-62.
21. Hoverson K, Love T, Lam TK, Marquart JD. A novel treatment for limited mouth opening due to facial fibrosis: a case series. *J Am Acad Dermatol*. 2018;78(1):190-192.
22. BOTOX (onabotulinumtoxinA) [package insert]. Allergan Pharmaceuticals Ireland. Accessed February 27, 2020. https://

www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf

23. Mouthon L, Rannou F, Bérezné A, et al. Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. *Ann Rheum Dis*. 2007;66(12):1651-1655.
24. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2013;65(11):2737-2747.
25. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72(11):1747-1755.
26. Naylor WP, Douglass CW, Mix E. The nonsurgical treatment of microstomia in scleroderma: a pilot study. *Oral Surg Oral Med Oral Pathol*. 1984;57(5):508-511.
27. Serrano-Martínez MC, Bagán JV, Silvestre FJ, Viguer MT. Oral lesions in recessive dystrophic epidermolysis bullosa. *Oral Dis*. 2003;9(5):264-268.