

## ONLINE FIRST

# Split-Face Double-blind Study Comparing the Onset of Action of OnabotulinumtoxinA and AbobotulinumtoxinA

Kenneth C. Y. Yu, MD; Kartik D. Nettar, MD; Sumit Bapna, MD; W. John Boscardin, PhD; Corey S. Maas, MD

**Objective:** To report and discuss the outcome of a prospective, internally controlled, randomized, double-blind, split-face study comparing the onset of action of 2 commercially available botulinum neuromodulators.

**Methods:** Ninety individuals with moderate-to-severe lateral orbital rhytids were treated with onabotulinumtoxinA, 10 U, and abobotulinumtoxinA, 30 U, for the treatment of lateral orbital rhytids. Participants were assessed live with a validated 5-point photographic scale before treatment and on days 2, 4, and 6 after treatment. Photographs were taken at each encounter. Statistical analysis was applied to evaluate for any significant difference in onset of action between the 2 products.

**Results:** AbobotulinumtoxinA and onabotulinumtoxinA demonstrated statistically significant change from baseline at day 2 in the treatment of lateral orbital rhytids at maximal contraction and rest when evaluated independently by investigator and participant ( $P < .001$ ). Also at day 2, the improvement with abobotulinumtoxinA was better than that with onabotulinumtoxinA for the pri-

mary end point of maximal contraction graded by the investigator, although this did not reach statistical significance ( $P = .21$ ); by day 4, the greater improvement achieved with abobotulinumtoxinA reached statistical significance ( $P = .02$ ) and remained superior at day 6 ( $P = .02$ ). The primary findings were strengthened by similar results in the secondary end points of patient self-grade at maximal contraction and at rest and of investigator grade at rest.

**Conclusions:** In conclusion, both abobotulinumtoxinA and onabotulinumtoxinA achieved statistically significant onset of action at day 2. This improvement was seen in all end points, with abobotulinumtoxinA demonstrating a trend toward greater improvement than onabotulinumtoxinA at day 2 and a statistically significant greater improvement at days 4 and 6 when looking at maximal contraction.

*Arch Facial Plast Surg.* 2012;14(3):198-204.

Published online December 19, 2011.

doi:10.1001/archfacial.2011.1142

**Author Affiliations:** The Maas Clinic, San Francisco, California (Drs Yu, Nettar, Bapna, and Maas); and Departments of Biostatistics and Medicine (Dr Boscardin) and Otolaryngology–Head and Neck Surgery (Drs Yu, Nettar, Bapna, and Maas), University of California, San Francisco.

**B**OTULINUM TOXIN IS A POTENT neuromodulator produced by the bacterium *Clostridium botulinum*.<sup>1</sup> It is a dichain polypeptide consisting of an approximately 100-kDa heavy chain linked by a disulfide bond to an approximately 50-kDa light chain associated with a single zinc atom. Botulinum toxin exerts its effect by blocking the action of acetylcholine, thus producing a state of functional denervation. It binds irreversibly to the presynaptic terminal of the neuromuscular junction. Although these naturally occurring proteins are widely known as toxins, they are better described, with respect to their current medical use, as neuromodulators. By selective weakening of certain hypertrophic muscle groups in the face and neck, unwanted lines and facial expressions can be suppressed or even eliminated.

Botulinum neuromodulator is found in nature in 7 serotypes (A through G). How-

ever, only the A serotype has demonstrated sustained benefit and efficacy in clinical applications. The B serotype (Myobloc; Solstice Neurosciences) offered favorable results in treating hyperfunctional frown lines. However, its clinical use has been limited by its shorter duration of action and pain associated with injection.<sup>2,3</sup>

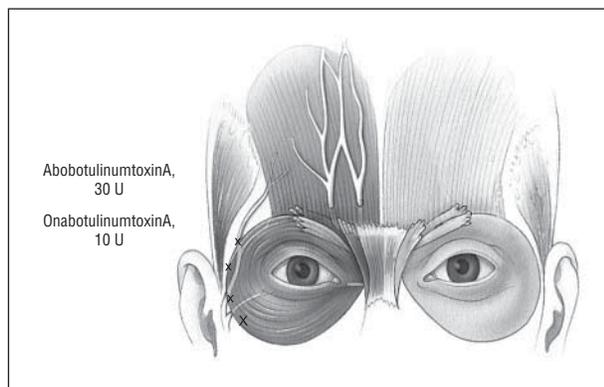
For years, the only botulinum product approved for cosmetic use in the United States was onabotulinumtoxinA (Botox Cosmetic; Allergan). In 2009, the US Food and Drug Administration approved the use of abobotulinumtoxinA (Dysport; Medicis) for cosmetic use. This product (previously known as Reloxin) had been used successfully for more than a decade in Europe to treat upper facial lines. It too is a formulation of *C botulinum* type A toxin-hemagglutinin complex.

Numerous studies have demonstrated the effect of botulinum toxin on facial rhytids produced by underlying muscle activity. Reports<sup>4-10</sup> of onabotulinumtoxinA and abobotulinumtoxinA established effec-

tive relaxation of glabellar rhytids after injection, and the efficacy and safety of both products have been proven in many studies. Studies<sup>11,12</sup> of each product in the treatment of glabellar lines have shown average onset of action to range from 1 to 3 days. However, there have been no double-blind, internally controlled studies comparing their onset of action. A split-face (internally controlled) paradigm can provide direct comparison of each product in the same patient. To minimize and/or eliminate any crossover effect or neuromodulator diffusion, the lateral orbital rhytids (crow's-feet) were chosen for study.

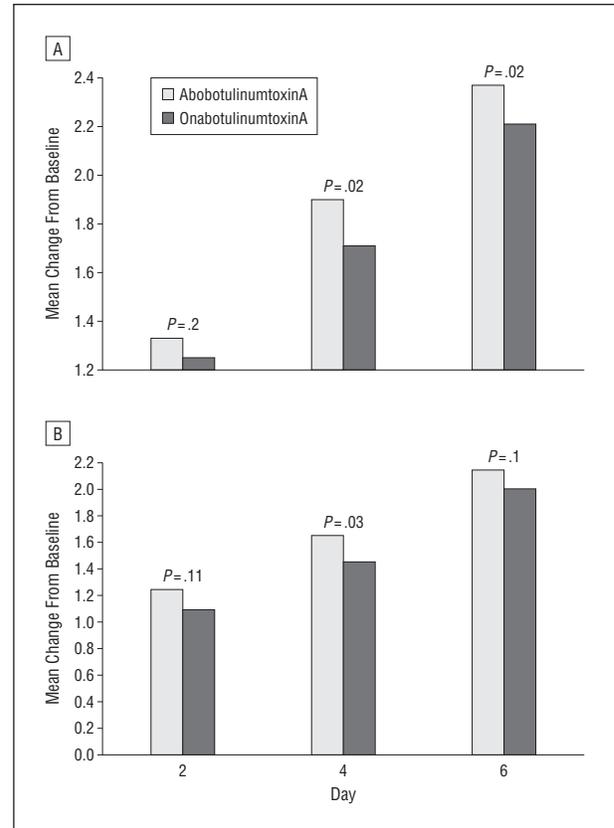
## METHODS

The study design and conduct were approved by an independent institutional review board (Aspire). From December 1, 2009, to August 30, 2010, 90 patients (77 women, 13 men) were enrolled in a randomized, double-blind study. Inclusion criteria were men or women aged 18 years or older with moderate-to-severe lateral orbital rhytids at maximal contraction. Exclusion criteria included botulinum neuromodulator treatment to the crow's-feet within 6 months, face-lift/brow-lift/blepharoplasty, periocular laser or chemical resurfacing, and adverse reactions associated with botulinum neuromodulator. In addition, individuals with a history of degenerative neuromuscular disorders were ineligible to participate in this study. Informed consent was obtained from each participant prior to enrollment.



**Figure 1.** AbobotulinumtoxinA, 30 U, or onabotulinumtoxinA, 10 U, divided into 4 aliquots (0.05 mL per injection site) was injected into lateral orbital rhytids.

Before treatment and at each follow-up visit, photographs were recorded for each patient, using commercial software (Mirror; Canfield Scientific, Inc) and a digital camera (Nikon D90; Nikon, Inc) in a dedicated photo lane. A standard 5-view photographic series was taken for each patient at rest and maximal contraction. In addition, the patient and investigator independently evaluated lateral orbital rhytids at rest and maximal contraction before treatment and at each follow-up visit. Live assessment of lateral orbital rhytids was made at rest and maximal contraction using



**Figure 2.** Grading of lateral orbital rhytids at maximal contraction. A, When graded by the investigator, abobotulinumtoxinA had clinically significant (confidence interval, 80%) greater improvement at day 2 and statistically significant greater improvement at days 4 and 6. B, When self-graded by the patient, abobotulinumtoxinA demonstrated clinically significant (CI, 95%) greater improvement than onabotulinumtoxinA at day 2. AbobotulinumtoxinA had statistically significant greater improvement at day 4.

**Table 1. Grade at Maximal Contraction<sup>a</sup>**

Time Point	Abo Mean (SD)	Abo Change From Baseline		Ona Mean (SD)	Ona Change From Baseline		P Value for Abo vs Ona
		Mean (SD)	95% CI		Mean (SD)	95% CI	
<b>Investigator's Grade</b>							
Baseline	3.64 (0.55)			3.68 (0.49)			
Day 2	2.31 (1.06)	1.33 (1.04)	1.11-1.55	2.43 (1.13)	1.25 (1.01)	1.03-1.46	.21
Day 4	1.75 (1.04)	1.90 (1.08)	1.67-2.13	1.97 (0.97)	1.71 (0.93)	1.52-1.91	.02
Day 6	1.28 (0.82)	2.31 (0.81)	2.20-2.55	1.49 (0.88)	2.21 (0.84)	2.03-2.39	.02
<b>Patient's Self-grade</b>							
Baseline	3.60 (0.56)			3.60 (0.58)			
Day 2	2.35 (1.06)	1.25 (1.05)	1.03-1.47	2.49 (1.09)	1.10 (0.97)	0.90-1.30	.11
Day 4	1.94 (1.12)	1.66 (1.11)	1.42-1.89	2.14 (1.06)	1.46 (0.96)	1.25-1.66	.03
Day 6	1.45 (0.92)	2.15 (0.86)	1.97-2.34	1.60 (0.99)	2.01 (0.89)	1.82-2.20	.10

Abbreviations: Abo, abobotulinumtoxinA (Dysport); Ona, onabotulinumtoxinA (Botox Cosmetic).

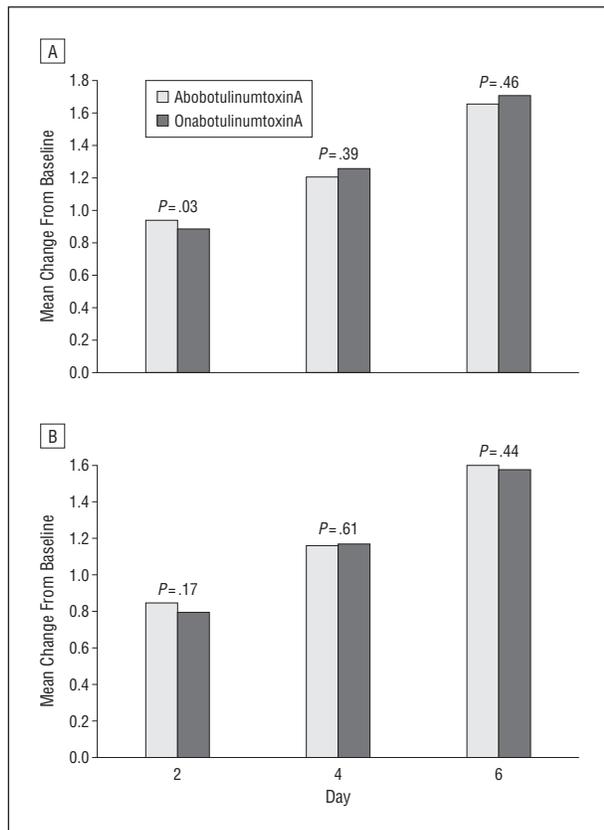
<sup>a</sup>(Grading explanation). For each product, the mean change from baseline was statistically significant ( $P < .001$ ) at days 2, 4, and 6.

**Table 2. Grade at Rest<sup>a</sup>**

Time Point	Abo, Mean (SD)	Abo Change From Baseline		Ona, Mean (SD)	Ona Change From Baseline		P Value for Abo vs Ona
		Mean (SD)	95% CI		Mean (SD)	95% CI	
<b>Investigator's Grade</b>							
Baseline	2.84 (0.86)			2.98 (0.78)			
Day 2	1.90 (0.95)	0.94 (0.86)	0.76-1.12	2.09 (1.00)	0.89 (0.78)	0.72-1.05	.03
Day 4	1.62 (0.91)	1.21 (0.84)	1.03-1.39	1.70 (1.00)	1.26 (0.80)	1.09-1.43	.39
Day 6	1.21 (0.83)	1.66 (0.79)	1.49-1.83	1.28 (0.92)	1.71 (0.84)	1.53-1.89	.46
<b>Patient's Self-grade</b>							
Baseline	2.86 (0.87)			2.91 (0.86)			
Day 2	2.00 (0.99)	0.85 (0.83)	0.68-1.03	2.11 (1.05)	0.80 (0.88)	0.61-0.98	.17
Day 4	1.68 (0.96)	1.16 (0.87)	0.97-1.35	1.72 (1.07)	1.17 (0.84)	0.99-1.35	.61
Day 6	1.27 (0.87)	1.60 (0.80)	1.43-1.78	1.34 (0.94)	1.58 (0.89)	1.39-1.77	.44

Abbreviations: Abo, abobotulinumtoxinA (Dysport); Ona, onabotulinumtoxinA (Botox Cosmetic).

<sup>a</sup>(Grading explanation.) For each product, the mean change from baseline was statistically significant ( $P < .001$ ) at days 2, 4, and 6.



**Figure 3.** Grading of lateral orbital rhytids at rest. A, When graded by the investigator, abobotulinumtoxinA achieved statistically significant greater improvement vs onabotulinumtoxinA at day 2. By days 4 and 6, there was significant difference between the 2 products. B, When self-graded by the patient, abobotulinumtoxinA had clinically significant (confidence interval, 80%) greater improvement at day 2. By days 4 and 6, there was no statistically significant difference between the 2 products.

a validated 5-point photographic scale (Merz Aesthetics, Inc).<sup>13</sup> A written description of each photograph was included to help standardize the application of the photographic scale.

The treatment consisted of injecting onabotulinumtoxinA, 10 U, on one side of the face and abobotulinumtoxinA, 30 U, on the contralateral side. This dose ratio was chosen on the basis of a preponderance of evidence<sup>14-18</sup> recommending a 3:1 ratio of abobotulinumtoxinA to onabotulinumtoxinA. Some studies<sup>19</sup> recommend an even higher ratio of 4:1 or 5:1; however,

recent studies<sup>8,16-18</sup> and the clinical experience of the senior author (C.S.M.) indicate a 3:1 ratio as being optimal.

Treatment sides of the face were randomized with computer-aided software. Preparation of the product was performed by an unblinded registered nurse, who was responsible for maintaining the investigator and participant blinding. AbobotulinumtoxinA is supplied as a 300-U vial, and onabotulinumtoxinA comes in 100-U or 50-U vials. In this study, a 100-U vial of onabotulinumtoxinA was reconstituted with 2 mL of normal saline without preservative, resulting in 5 U per 0.1 mL. A 300-U vial of abobotulinumtoxinA was reconstituted with 2 mL of normal saline without preservative, resulting in 15 U per 0.1 mL. Sterile tuberculin syringes were used to withdraw 0.2 mL of solution from the vials. This reconstitution protocol allowed identical volumes to be used, ensuring the blinding of the injector while delivering the selected 3:1 ratio. The injection area was cleansed with alcohol wipes, and patients were given the option of topical anesthetic. A dose of 0.05 mL of onabotulinumtoxinA or abobotulinumtoxinA was injected into the orbicularis oculi in the lateral orbital area in 4 separate injection points by the senior author (Figure 1). Patients were monitored for 30 minutes after injection to identify and record any adverse effects.

Patients were seen and the treatment sites evaluated on post-treatment days 2, 4, and 6. The time interval was designed to capture onset of action, known to occur by 1 week. The primary end point of the study was onset of action as defined by investigator assessment of maximal contraction. Secondary end points included onset of action measured by investigator assessment at rest, participant assessment of onset of action at rest, and maximal contraction.

Statistical analyses included the paired *t* test and McNemar test. Onset was defined as the time to improve by at least 1 scale point. A paired Wilcoxon signed rank test was used to compare the differences in onset of action for abobotulinumtoxinA and onabotulinumtoxinA.

## RESULTS

Ninety individuals (77 women, 13 men) met inclusion criteria and were enrolled. Ages ranged from 31 to 78 years (mean, 54.5 years). For the primary end point of investigator grade at maximal contraction, the abobotulinumtoxinA baseline mean grade was 3.64 and the onabotulinumtoxinA mean grade was 3.68. At day 2, abobotulinumtoxinA had a mean improvement of 1.33 and onabotulinumtoxinA had a mean improvement of 1.25. Both mean improvements



**Figure 4.** Participant received abobotulinumtoxinA, 30 U, on the right side and onabotulinumtoxinA, 10 U, on the left side. A, Maximal contraction on the right. B, Maximal contraction on the left. C, Rest on the right. D, Rest on the left. For all parts of the figure, upper left is day 0 (before treatment), upper right is day 2, lower left is day 4, and lower right is day 6 of treatment.

were statistically significant ( $P < .001$ ), but the superiority of abobotulinumtoxinA was only statistically suggestive ( $P = .21$ ). The statistically significant change for both products was maintained at days 4 and 6. At days 4 and 6, the amount of improvement for abobotulinumtoxinA was significantly superior to that for onabotulinumtoxinA ( $P = .02$  for both time points; **Table 1** and **Figure 2A**).

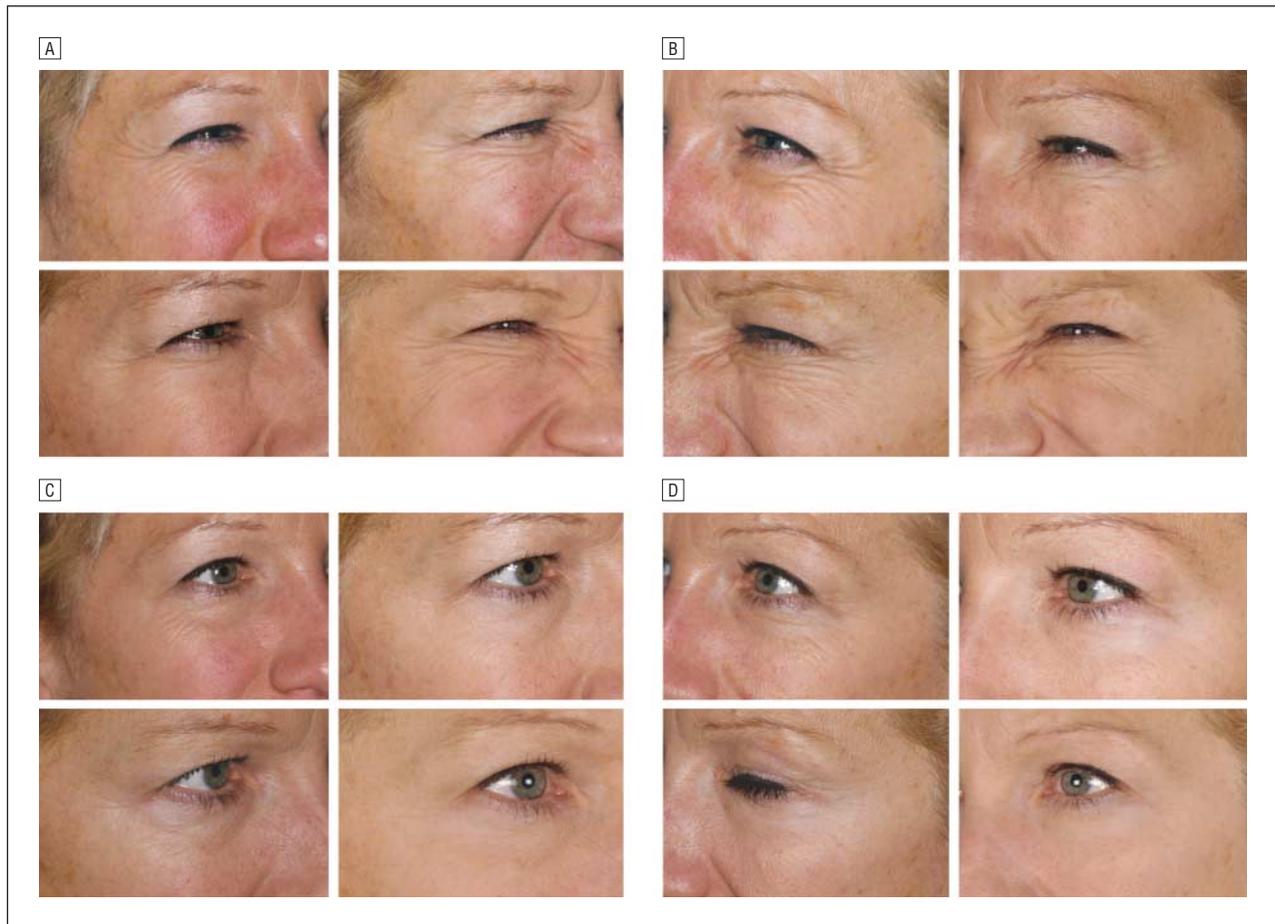
For the secondary end point of patient self-grade of crow's-feet at maximal contraction, both abobotulinumtoxinA and onabotulinumtoxinA had mean baseline grades of 3.60. At day 2, the mean grades were 2.35 and 2.49, respectively. Mean change from baseline for abobotulinumtoxinA was 1.25 and 1.10 for onabotulinumtoxinA. These findings were statistically significant ( $P < .001$ ) and continued at days 4 and 6. The greater change with abobotulinumtoxinA was clinically meaningful and trended toward statistical significance ( $P = .11$ ). AbobotulinumtoxinA demonstrated statistically significant greater improvement at day 4 ( $P = .03$ ) and clinically significant greater improvement at day 6 ( $P = .10$ ). Table 1 and Figure 2B summarize these results.

For investigator grade of crow's-feet at rest, the mean baseline grade was 2.84 for abobotulinumtoxinA and 2.98 for onabotulinumtoxinA. At day 2, abobotulinumtoxinA had a mean grade of 1.90 and onabotu-

linumtoxinA had a mean grade of 2.09; the mean change at day 2 was 0.94 and 0.89, respectively. These changes were statistically significant ( $P < .001$ ) and persisted at days 4 and 6. AbobotulinumtoxinA demonstrated statistically significant greater improvement than onabotulinumtoxinA at day 2 (mean, 0.94 vs 0.89,  $P = .03$ ). By days 4 and 6, there was no significant difference between the 2 products (**Table 2** and **Figure 3A**).

For patient self-grade at rest, the mean baseline grade was 2.86 for abobotulinumtoxinA and 2.91 for onabotulinumtoxinA. At day 2, there were statistically significant changes from baseline for both abobotulinumtoxinA and onabotulinumtoxinA (mean change, 0.85 vs 0.80,  $P < .001$ ). Statistically significant changes were maintained at days 4 and 6 for both products. AbobotulinumtoxinA demonstrated a trend toward greater improvement than onabotulinumtoxinA at day 2 (mean change, 0.85 vs 0.80,  $P = .17$ ). By days 4 and 6, there were no significant differences between the 2 products (Table 2, Figure 3B). Representative photographs are shown in **Figures 4, 5, and 6**.

No major adverse events were reported by any patient with either side of the face. One patient reported bruising at an injection site on the side treated with onabotulinumtoxinA, which resolved within 5 days.



**Figure 5.** Participant received onabotulinumtoxinA, 10 U, on the right side and abobotulinumtoxinA, 30 U, on the left side. A, Maximal contraction on the right. B, Maximal contraction on the left. C, Rest on the right. D, Rest on the left. For all parts of the figure, upper left is day 0 (before treatment), upper right is day 2, lower left is day 4, and lower right is day 6 of treatment.

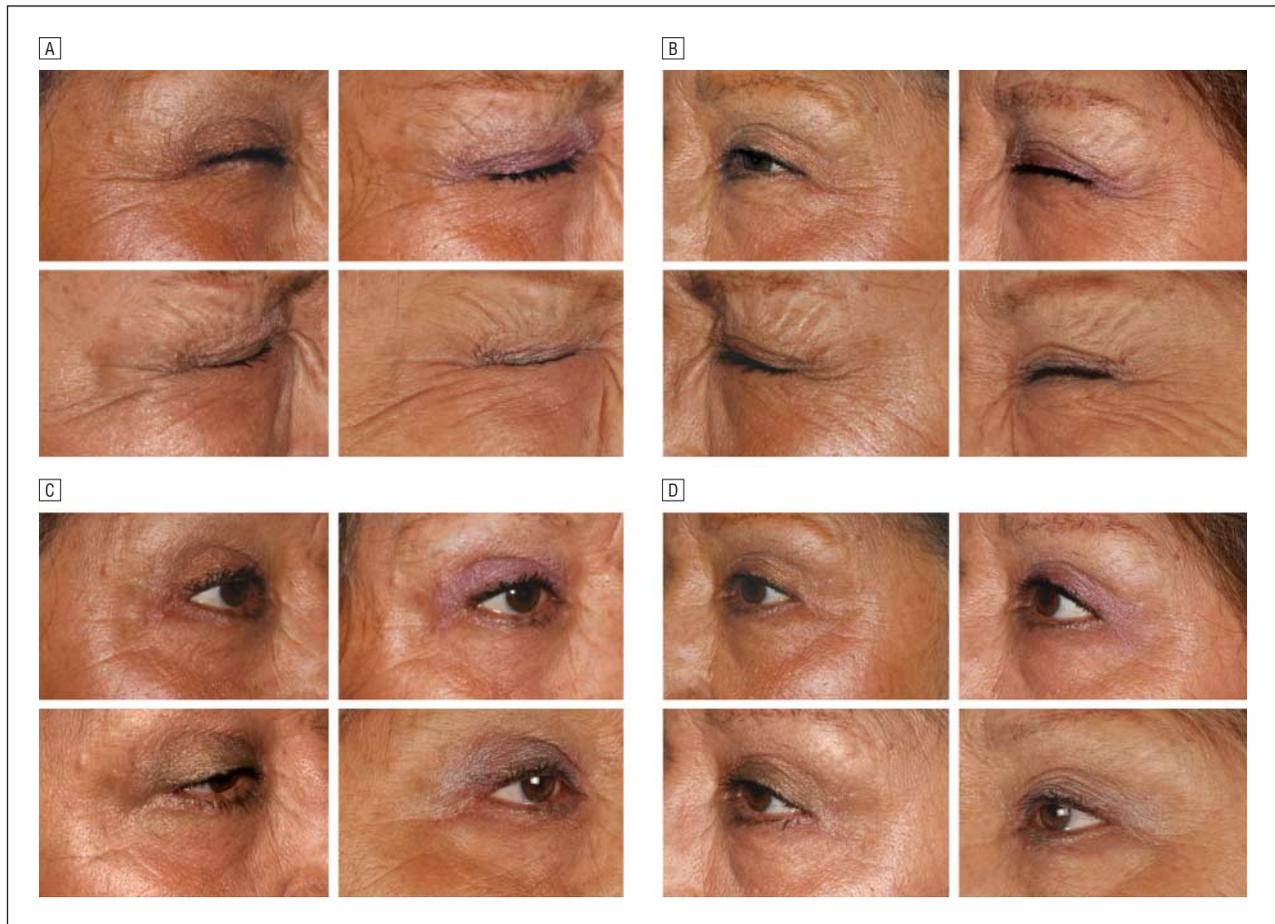
### COMMENT

AbobotulinumtoxinA and onabotulinumtoxinA are 2 botulinum neuromodulators approved for cosmetic use. Both formulations of neuromodulator serotype A act on the same substrate (synaptosomal-associated protein 25) but differ in clinical effects.<sup>20-23</sup> The purification processes are different for the neuromodulators and account for the differences in the complex size. The products also differ in the hemagglutinin and non-hemagglutinin proteins surrounding the active compound. These differences may play a role in the clinical profile observed with these neuromodulators. **Table 3** summarizes the differences between the 2 products. There have been anecdotal reports that abobotulinumtoxinA has a faster onset of action than onabotulinumtoxinA and has a greater diffusion effect. Unsurprisingly, because of the popularity of neuromodulator treatments, differences between the 2 products are topics of debate. However, there have not been any studies comparing their onset of action. This study sought to compare the onset of action of abobotulinumtoxinA and onabotulinumtoxinA in the treatment of lateral orbital rhytids in a double-blind fashion. The crow's-feet were selected as the target because it is the only location that allows a split-face study. Other facial

areas have potential for crossover effect, thereby interfering with an accurate interpretation of results.

In our study, we found that both abobotulinumtoxinA and onabotulinumtoxinA demonstrated onset characteristics by day 2 across all end points (Tables 1 and 2). Our findings correlate with those of other studies showing early onset of action for both neuromodulators.<sup>11,12</sup> For both maximal contraction and at rest (investigator grade and patient self-grade), mean improvement was statistically significant at day 2 and continued to day 6. Although both products achieved onset at day 2, clinically significant greater improvement was seen with abobotulinumtoxinA than with onabotulinumtoxinA for the primary end point of investigator grade at maximal contraction ( $P = .21$ ). At days 4 and 6, the greater improvement seen with abobotulinumtoxinA reached statistical significance ( $P = .02$ ). This observation of greater improvement was seen uniformly with all secondary end points as well.

This study revealed that there was no significant difference in onset of action between the 2 products; however, abobotulinumtoxinA clearly achieved greater improvement at each time point. The improved efficacy of abobotulinumtoxinA in treating crow's-feet was demonstrated in a separate arm of the study conducted at the senior author's research center.<sup>24</sup> The



**Figure 6.** Participant received onabotulinumtoxinA, 10 U, on the right side and abobotulinumtoxinA, 30 U, on the left side. A, Maximal contraction on the right. B, Maximal contraction on the left. C, Rest on the right. D, Rest on the left. For all parts of the figure, upper left is day 0 (before treatment), upper right is day 2, lower left is day 4, and lower right is day 6 of treatment.

**Table 3. Comparison of the Products Used**

Characteristic	Abo	Ona
Serotype	A	A
Strain	NCTC 2916	Hall
Receptor target	SV2/SNAP-25	SV2/SNAP-25
Purification process	Chromatography	Crystallization
Estimated complex size, kDa	500-900 <sup>16</sup>	900 <sup>17</sup>
Stabilization	Lysophilization	Vacuum drying
Solubilization	Normal saline	Normal saline
pH	-7	-7
Amount per vial, U	300	100
Protein per vial, ng	12.5	5
Year approved	1991	1989

Abbreviations: Abo, abobotulinumtoxinA (Dysport); Ona, onabotulinumtoxinA (Botox Cosmetic).

mechanism is unclear. The principal pharmacologic difference between onabotulinumtoxinA and abobotulinumtoxinA is the difference in the hemagglutinins and non-hemagglutinins that surround the core protein. This difference could result in a different penetration profile. Further studies are needed to decipher the roles of these substances.

It is also unclear whether our observations will translate to other sites, such as the glabella and forehead. The observed difference between abobotulinumtoxinA and

onabotulinumtoxinA may be related to the morphologic characteristics of the muscle being treated. The orbicularis oculi, a flat sheetlike muscle, may respond differently to abobotulinumtoxinA compared with a thick bulky muscle, such as the corrugator supercillii. Comparative studies between the 2 products in bulkier muscles would help answer this question.

Although we used a validated 5-point photographic scale to measure the crow's-feet, implementation revealed that the scale was a crude instrument to assess on-

set of action. To accurately capture onset as defined as any point change, unequivocal determination of change from one point to the next was challenging. We found that identifying a 2-point change was obvious and consistent across all participants. The difficulty in accurately determining initial onset of change with the current validated photographic scale was a limitation of the study. Conceptually, a more objective measuring system is needed, ideally a reproducible, standardized, computer photographic system.

Finally, there were no significant adverse effects or complications noted with either product during the study, confirming the safety of these neuromodulators.

In conclusion, both abobotulinumtoxinA and onabotulinumtoxinA achieved statistically significant onset of action at day 2. This improvement was seen in all end points. AbobotulinumtoxinA had a trend toward greater improvement than onabotulinumtoxinA at day 2 and a statistically significant greater improvement at days 4 and 6 when looking at maximal contraction.

**Accepted for Publication:** September 26, 2011.

**Published Online:** December 19, 2011. doi:10.1001/archfacial.2011.1142

**Correspondence:** Corey S. Maas, MD, The Maas Clinic, 2400 Clay St, San Francisco, CA 94115 (drmaas@maasclinic.com).

**Author Contributions:** *Study concept and design:* Nettare and Maas. *Acquisition of data:* Yu, Nettare, Bapna, and Maas. *Analysis and interpretation of data:* Yu, Nettare, Bapna, Boscardin, and Maas. *Drafting of the manuscript:* Yu, Nettare, and Bapna. *Critical revision of the manuscript for important intellectual content:* Yu, Nettare, Bapna, Boscardin, and Maas. *Statistical analysis:* Yu, Nettare, Bapna, and Boscardin. *Obtained funding:* Yu, Bapna, and Maas. *Administrative, technical, and material support:* Yu, Nettare, Bapna, and Maas. *Study supervision:* Yu, Bapna, and Maas.

**Financial Disclosure:** None reported.

## REFERENCES

- Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope*. 2001;111(2):218-226.
- Ramirez AL, Reeck J, Maas CS. Preliminary experience with botulinum toxin type B in hyperkinetic facial lines. *Plast Reconstr Surg*. 2002;109(6):2154-2155.
- Ramirez AL, Reeck J, Maas CS. Botulinum toxin type B (MyoBloc) in the management of hyperkinetic facial lines. *Otolaryngol Head Neck Surg*. 2002;126(5):459-467.
- Ascher B, Klap P, Marion MH, Chantelouf F. Botulinum toxin in the treatment of frontoglabellar and periorbital wrinkles: an initial study. *Ann Chir Plast Esthet*. 1995;40(1):67-76.
- Ascher B. Facial rejuvenation by non-endoscopic lifting and botulinum toxin injection. *Cah Ophthalmol*. 2000;45:25-31.
- Olver JM. Botulinum toxin A treatment of overactive corrugator supercilii in thyroid eye disease. *BMJ*. 1998;317:528-533.
- Erian A, Ionescu NE. Combination treatment of glabellar rhytids. *Int J Cosmetic Surg*. 1999;7(1):14-17.
- Feller G, Bayerl C, Jung E, Rzany B. Treatment of dynamic facial wrinkles with botulinum toxin type A (Dysport)—a pilot study. *Akt Dermatol*. 2000;26:65-69.
- Le Louarn C. Botulinum toxin and facial wrinkles: a new injection procedure. *Ann Chir Plast Esthet*. 1998;43(5):526-533.
- Rubin M, Dover J, Maas C, Nestor M. An analysis of safety data from five phase III clinical trials on the use of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J*. 2009;29(6)(suppl):S50-S56.
- Beer KR, Boyd C, Patel RK, Bowen B, James SP, Brin MF. Rapid onset of response and patient-reported outcomes after onabotulinumtoxinA treatment of moderate-to-severe glabellar lines. *J Drugs Dermatol*. 2011;10(1):39-44.
- Baumann L, Brandt FS, Kane MA, Donofrio LM. An analysis of efficacy data from four phase III studies of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J*. 2009;29(6)(suppl):S57-S65.
- Carruthers J, Carruthers A, Hardas B, et al. A validated grading scale for crow's feet. *Dermatol Surg*. 2008;34(suppl 2):S173-S178.
- Ascher B, Rzany BJ, Grover R. Efficacy and safety of botulinum toxin type A in the treatment of lateral crow's feet: double-blind, placebo-controlled, dose-ranging study. *Dermatol Surg*. 2009;35(10):1478-1486.
- Monheit G, Carruthers A, Brandt F, Rand R. A randomized, double-blind, placebo-controlled study of botulinum toxin type A for the treatment of glabellar lines: determination of optimal dose. *Dermatol Surg*. 2007;33(1, special issue):S51-S59.
- Pickett AM, Hambleton P. Dose standardisation of botulinum toxin. *Lancet*. 1994;344(8920):474-475.
- Hambleton P, Pickett AM. Potency equivalence of botulinum toxin preparations [letter]. *J R Soc Med*. 1994;87(11):719.
- Marion MH, Sheehy M, Sangla S, Soulayrol S. Dose standardisation of botulinum toxin. *J Neurol Neurosurg Psychiatry*. 1995;59(1):102-103.
- Brin MF, Blitzer A. Botulinum toxin: dangerous terminology errors. *J R Soc Med*. 1993;86(8):493-494.
- Breidenbach MA, Brunger AT. New insights into clostridial neurotoxin-SNARE interactions. *Trends Mol Med*. 2005;11(8):377-381.
- Pickett A. Dysport: pharmacological properties and factors that influence toxin action. *Toxicol*. 2009;54(5):683-689.
- Dysport [package insert]. Wrexham, UK: Ipsen Biopharm Ltd; 2009.
- Botox Cosmetic [package insert]. Irvine, CA: Allergan Inc; 2009.
- Nettare KD, Yu KCY, Bapna S, Boscardin J, Maas CS. An internally controlled, double-blind comparison of the efficacy of onabotulinumtoxinA and abobotulinumtoxinA. *Arch Facial Plast Surg*. 2011;13(6):380-386. doi:10.1001/archfacial.2011.37.