

Review Article

OnabotulinumtoxinA for Treatment of Moderate to Severe Crow's Feet Lines: A Review

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Alastair Carruthers, MD, BM, BCh, FRCPC, FRCP (Lon);
Suzanne Bruce, MD; Sue Ellen Cox, MD; Michael A.C. Kane, MD;
Elisabeth Lee, MPH; and Conor J. Gallagher, PhD

Abstract

Lateral canthal lines or crow's feet lines (CFL) may be treated with onabotulinumtoxinA. We identified several key concepts important to understanding the use of onabotulinumtoxinA for treatment of moderate-to-severe CFL. To contextualize and integrate data on the recommended dose and injection patterns of onabotulinumtoxinA for treatment of CFL, we summarized data from pivotal clinical studies in the development of onabotulinumtoxinA for treatment of CFL. Data from key studies of onabotulinumtoxinA for CFL are presented. The efficacy and safety of onabotulinumtoxinA treatment of moderate-to-severe CFL were evaluated in 2 randomized, controlled phase 3 studies comprising 1362 patients. The 24U total dose of onabotulinumtoxinA used in these studies was based on a phase 2 dose-ranging trial. Two injection patterns were available to investigators; each involved 3 injection sites per side in the lateral orbicularis oculi muscle. A cross-sectional analysis of photographs from the phase 3 trials provided detailed information on the frequency of 4 distinct CFL patterns. In the primary efficacy analysis for each phase 3 trial, CFL responder rates were significantly greater with onabotulinumtoxinA vs placebo at day 30 ($P < .001$). Eyelid edema (1%) was the only adverse event reported in $\geq 1\%$ of patients receiving onabotulinumtoxinA, occurring more frequently with onabotulinumtoxinA than with placebo. The studies showed that onabotulinumtoxinA is effective and generally well-tolerated for CFL treatment. Additionally, 2 different injection patterns allow physicians to tailor treatment based on a patient's CFL pattern.

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The use of onabotulinumtoxinA (Botox Cosmetic; Allergan, Inc., Irvine, CA) for aesthetic treatment of facial lines has expanded since its initial approval for temporary improvement in the appearance of moderate-to-severe glabellar lines (GL).¹ Lateral canthal lines, also known as crow's feet lines (CFL), are wrinkles that form around the eyes and are commonly treated with onabotulinumtoxinA. Dynamic CFL form as a result of repeated contraction of facial muscles involved in smiling, notably the orbicularis oculi muscles.^{2,3} Static lines may subsequently appear at rest, resulting from structural skin remodeling during aging, repeated facial muscle contraction, and damage from excessive sun exposure.⁴ Several different patterns of CFL have been described based on alignment of wrinkles in the lateral canthal area.^{5,6} In one trial of aesthetically oriented women between 30 and 65 years of age, 82% chose CFL as the facial feature most likely to be treated first.⁷ Additionally, the same cohort of women identified CFL as 1 of the facial features that bothered them the most.⁷

The efficacy and safety of onabotulinumtoxinA in CFL were demonstrated in 2 phase 3, randomized controlled trials comprising 1362 patients with moderate or severe CFL.^{8,9} Based on these trials, the Food and Drug Administration

Dr Carruthers is a Clinical Professor, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, British Columbia, Canada. Dr Bruce is a dermatologist in private practice in Houston, TX. Dr Cox is a Dermatologic Surgeon, Department of Dermatology, School of Medicine of the University of North Carolina, Chapel Hill, NC. Dr Kane is a Plastic Surgeon, Manhattan Eye, Ear and Throat Hospital, New York, NY. Dr Gallagher is Director of Facial Aesthetics and Medical Dermatology and Ms Lee is Director of Dermatology Research and Development, Allergan plc, Irvine, CA.

Corresponding Author:

Dr Alastair Carruthers, Carruthers Clinical Research, 943 West Broadway, Suite 820, Vancouver, British Columbia, Canada, V5Z 4E1.
E-mail: alastair@carruthers.net

(FDA) approved onabotulinumtoxinA in September 2013 for temporary improvement in the appearance of moderate to severe CFL associated with orbicularis oculi activity in adults.^{8,9} The purpose of this article is to contextualize and integrate the data supporting onabotulinumtoxinA treatment of CFL, including the rationale for selecting the 24U total dose and the basis for the 2 different recommended injection patterns.

METHODS

Through clinical experience, the authors identified several key concepts that are important to understanding the use of onabotulinumtoxinA for treatment of moderate-to-severe CFL. Support for these key concepts was derived from the dose-ranging data that form the basis for the recommended total dose of 24U of onabotulinumtoxinA, the cross-sectional analysis of untreated patients that illustrates the basis for offering 2 recommended injection patterns of onabotulinumtoxinA, and the clinical trials that studied the efficacy and safety of onabotulinumtoxinA at the recommended treatment dose. It should be noted that dose recommendations are not interchangeable among botulinum toxin products, and dosing cannot be converted using any dose ratio. To analyze these concepts and to place the dose and injection pattern into perspective, we summarized data from relevant dose-ranging studies; analyses of baseline clinical characteristics; and randomized, placebo-controlled safety and registration studies in the development of onabotulinumtoxinA for treatment of moderate-to-severe CFL.

RESULTS

Treatment of Crow's Feet Lines: Dose Selection Based on Phase 2 Clinical Trials

Although earlier studies of onabotulinumtoxinA treatment of CFL suggested a potential dose range that may be effective for treatment,^{10,11} a phase 2, dose-ranging trial was undertaken to further study the dose-response relationship. Patients (N = 162) with bilaterally symmetrical moderate or severe CFL were randomly assigned to receive treatment with 1 of several doses of onabotulinumtoxinA or placebo.¹² Study treatment was administered via intramuscular injection at 3 sites per side (total of 6 injections) in the lateral aspect of the orbicularis oculi muscle. Each injection was 0.1 mL in volume and contained onabotulinumtoxinA or placebo. Overall, the mean age was 47 years, 88.9% were women, and 98.8% were white. At baseline, 60.5% of patients had severe CFL, and 39.5% had moderate CFL. Of note, of patients randomized to receive a 24U total dose (n = 31), 74.2% had severe CFL and 25.8% had moderate CFL at baseline; of patients randomized to receive a 12U total dose (n = 33),

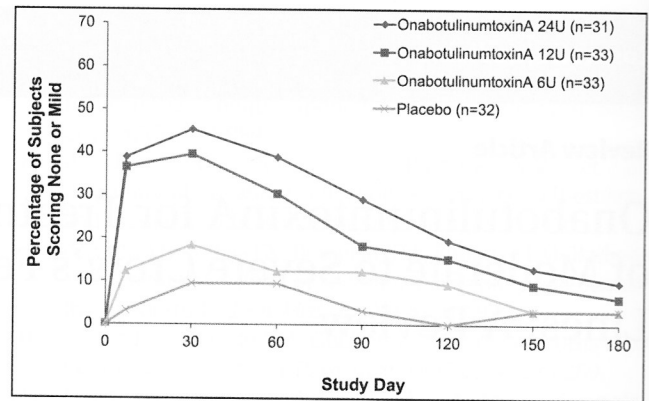


Figure 1. Responder rates (investigator rating of none or mild) over time in patients with at least moderate crow's feet lines. $P < .05$ for onabotulinumtoxinA 24U vs placebo at all time points through 120 days; $P < .05$ for onabotulinumtoxinA 12U vs placebo at days 7, 30, and 120.

60.6% had severe CFL and 39.4% had moderate CFL at baseline. The varied proportions of patients with baseline severity of severe vs moderate CFL may have affected the relative responder rates for the 24U and 12U total doses.

The primary efficacy analysis was based on the investigator's assessment of CFL severity at maximum smile using the Facial Wrinkle Scale (FWS) with photonic numeric guide.¹² The FWS is a validated 4-grade assessment tool (0 = none, 1 = mild, 2 = moderate, 3 = severe). At posttreatment day 30, the responder rate, defined as patients with an investigator rating of mild or none at postbaseline time points on the FWS at maximum smile, was significantly greater ($P < .05$) in onabotulinumtoxinA 12U and 24U groups compared with that in the placebo group (Figure 1). The responder rate was also greater for the 24U dose compared with lower doses. No dose-related safety signals were observed. Based on responder rates in this study, the 24U dose was selected as the treatment dose in the subsequent phase 3 development program.

Treatment of Crow's Feet Lines: Two Injection Patterns Based on 4 Crow's Feet Lines Patterns

An in-person evaluation of 100 patients identified 4 distinct CFL patterns: full fan, lower fan, central fan, and upper fan (Figure 2).⁵ The full-fan, lower-fan, and central-fan patterns were predominant (90%), and the upper-fan pattern was the least common (10%). Based on this observation, 2 injection patterns were available to investigators in the 2 phase 3 CFL trials (Figure 3).

The descriptive terminology for each of these 4 CFL patterns was recently modified to emphasize the orientation of lines in the lateral canthal area and adjacent facial regions.⁶

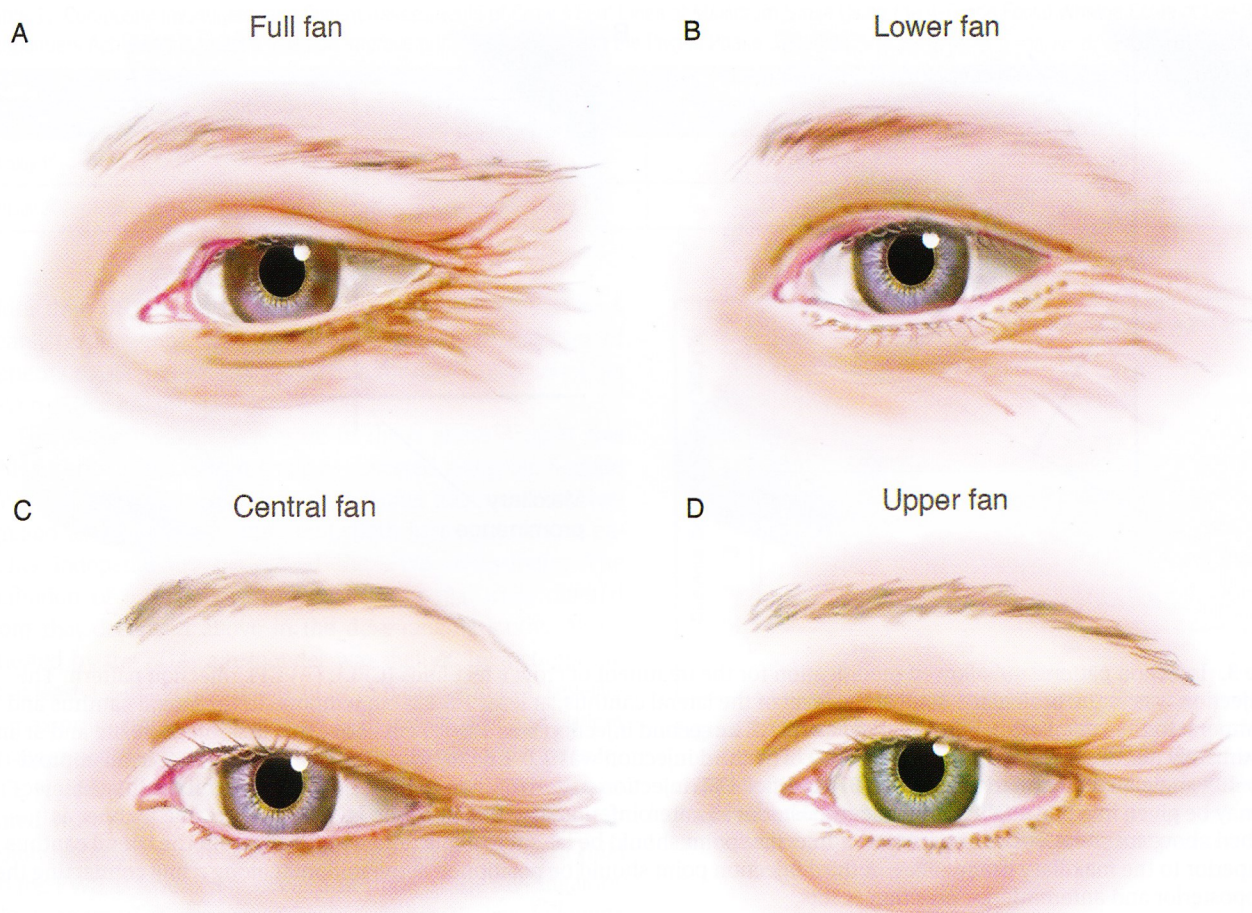


Figure 2. Classification of crow's feet lines patterns in untreated patients. In a full-fan pattern (A), lines project from the lateral canthal area and extend into both the superior malar area and the tail of the brow. In a lower-fan pattern (B), lines are predominantly confined to the lateral canthal area and the superior malar area. In a central-fan pattern (C), lines are predominantly confined to the lateral canthal area and do not extend into the superior malar area or lateral third of the brow. An upper-fan pattern (D) has lines predominantly confined to the lateral canthal area and extend toward or into the lateral third of the brow.

Their distribution was then characterized in a cross-sectional analysis of patients with moderate-to-severe CFL who participated in 3 separate onabotulinumtoxinA clinical trials, including the 2 CFL pivotal trials.⁶ Baseline photographs of each patient's CFL areas were taken using standardized equipment while the patient was at rest and while the patient was maximally smiling. Two investigators independently reviewed left-sided oblique photographs and classified each patient's CFL pattern according to the scheme shown in Figure 2. Consensus was reached between investigators whenever initial case assessments differed.

The cross-sectional analysis included 1392 untreated patients (2699 photographs at baseline).⁶ In the study cohort, mean age was 48.8 years, 85.9% were women, and 85.5% were white. At maximum smile, lower fan (34.7%) and central fan (32.8%) were the most common CFL patterns, followed by full fan (28.4%), then upper fan (4.2%).⁶

These results were consistent with findings from the prior analysis of 100 patients for which the lower-fan, central-fan, and full-fan patterns were commonly seen, whereas the upper-fan pattern was seen relatively infrequently. At rest, full fan (33.9%) and lower fan (32.0%) were the most common patterns, followed by central fan (27.7%), then upper fan (6.4%). In patients with both dynamic and static lines, 52.8% had the same CFL patterns at maximum smile and at rest.

The distribution of CFL patterns was found to vary according to baseline CFL severity and the patient's age and gender.⁶ The central-fan pattern predominated at maximum smile in patients with moderate CFL, whereas the lower-fan and full-fan patterns were most common in patients with severe CFL. The central-fan pattern also predominated at maximum smile in younger patients (aged ≤ 40 years), whereas the full-fan pattern was most frequently seen in

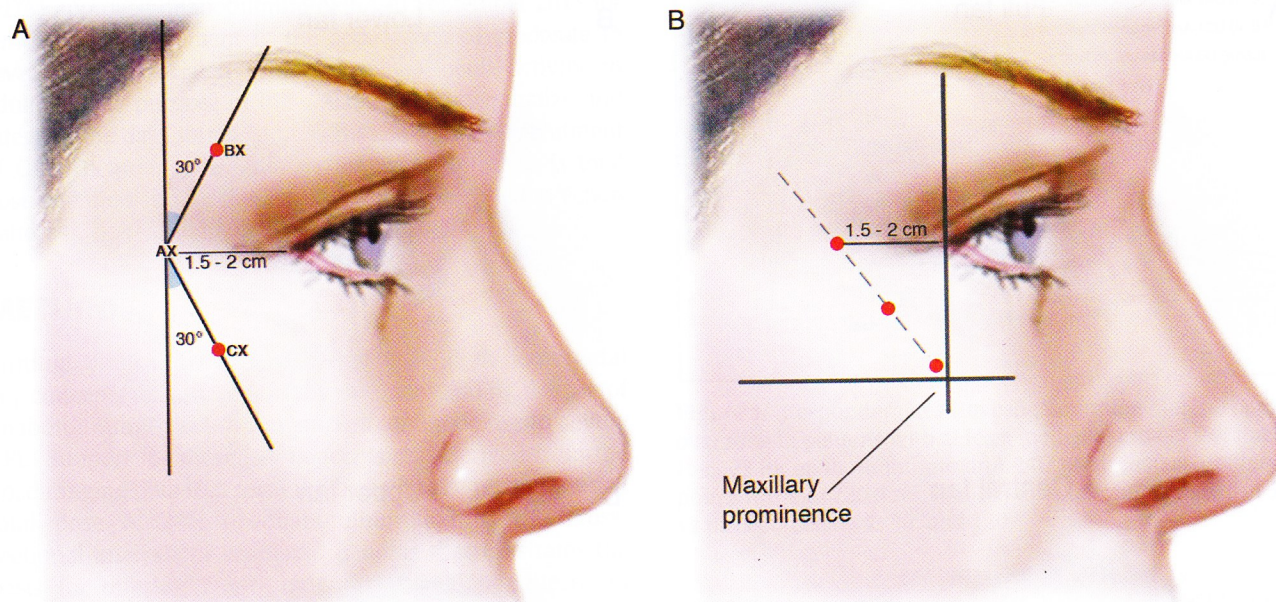


Figure 3. Injection pattern and allowed modification for the treatment of crow's feet lines (CFL). (A) CFL injection pattern. The first injection was in the orbicularis oculi at the level of the lateral canthus, at least 1.5-2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim (marked as AX). The second injection was 1.0-1.5 cm above this first injection site and at an approximately 30° angle medially (marked as BX). The third injection was 1.0-1.5 cm below the first injection site at an approximately 30° angle medially (marked as CX). (B) Modified CFL injection pattern. When CFL are below the lateral canthus, 3 injections may be given in a line angling from superoposterior to anteroinferior. The first injection is made in the same manner as described above for site AX. The anteroinferior injection point should be lateral to a line drawn vertically from the lateral canthus and superior to the maxillary prominence. A third injection point should be positioned at the midpoint along a line connecting the superoposterior and anteroinferior injection points.

older patients. These data suggest that the CFL pattern at maximum smile may progress from central or lower fan to full fan in older patients and with greater CFL severity.⁶ However, it should be noted that the cross-sectional nature of this analysis did not allow for definitive conclusions regarding progression over time from 1 fan pattern to another.

In terms of gender, the lower-fan pattern was predominant in men (53.6% at maximum smile; 52.4% at rest), whereas the central-fan, lower-fan, and full-fan patterns were each seen in about 30% of women at maximum smile and at rest. The upper-fan pattern was seen rarely in men (1.5% at maximum smile) and infrequently in women (4.6%). The differing frequency in CFL patterns by gender may reflect differences in how men and women smile, with men having greater recruitment of cheek elevators.

Efficacy of OnabotulinumtoxinA in Phase 3 Clinical Trials

The phase 3 program evaluated the efficacy and safety of onabotulinumtoxinA in the treatment of moderate to severe CFL in 2 pivotal, double-blind, placebo-controlled, randomized, multicenter trials.^{8,9} Together, these pivotal phase 3 studies randomized 833 patients to receive onabotulinumtoxinA

and 529 patients to receive placebo. Study 1⁸ evaluated onabotulinumtoxinA in the treatment of CFL alone, whereas study 2⁹ also assessed simultaneous treatment of CFL and GL. Both studies enrolled adults with bilaterally symmetrical moderate-to-severe CFL at maximum smile, whereas study 2 also required patients to have moderate-to-severe GL at maximum frown, which resulted in an older cohort with more severe CFL at baseline. In study 1, patients were randomly assigned in a 1:1 ratio to receive a single blinded treatment of onabotulinumtoxinA 24U or placebo.⁸ In study 2, patients were randomly assigned 1:1:1 to receive onabotulinumtoxinA 24U for CFL and placebo for GL, onabotulinumtoxinA 24U for CFL and an additional 20U for GL, or placebo for both CFL and GL.⁹

The treatment for CFL was the same in both studies and was delivered via injections into 3 sites of each orbicularis oculi muscle with the choice of injection pattern based on each patient's CFL characteristics and the investigator's discretion. Patients received a single treatment on day 1 in study 1 and were then followed for 5 months.⁸ In comparison, patients received their assigned treatments on days 1 and 120 in study 2 and were followed for a total of 7 months.⁹ The treatment arms in each study were well balanced with respect to demographic and baseline characteristics. However, the cohort in study 2 was somewhat

Table 1. Composite Investigator and Patient Assessments of Crow's Feet Lines at Maximum Smile Using the 4-Grade Facial Wrinkle Scale at Day 30 for Responders Achieving at Least a 2-Grade Improvement From Baseline in the Pivotal Phase 3 Studies

Study	OnabotulinumtoxinA 24U for CFL	OnabotulinumtoxinA 24U for CFL + 20U for GL	Placebo
Study 1 ⁸	26.1% (58/222)	—	1.3% (3/223)
Study 2 ⁹	20.3% (62/306)	21.3% (65/305)	0% (0/306)

older than the cohort in study 1 (mean ages: 49.5 and 46.4 years, respectively) and contained a greater proportion of patients with baseline CFL at maximum smile rated as severe (63.2% and 50.2%, respectively).

The primary efficacy measure in these phase 3 trials was CFL severity at maximum smile as assessed using the 4-grade FWS with photonic guide; day 30 after treatment was designated as the primary time point. Both investigators and patients independently performed the FWS assessment. The definition of a responder used for the pivotal trials differed from that described above in the dose-ranging study. As requested by the FDA, a responder was defined by a composite of at least a 2-grade improvement from baseline in CFL severity at maximum smile as assessed by both investigator and patient on a per-patient basis.^{8,9} In both studies, the responder rates for CFL were significantly greater with onabotulinumtoxinA compared with placebo at day 30 (Table 1). As a secondary endpoint, responders were also defined by a grade of none or mild on the FWS as assessed at maximum smile by the investigators. The proportion of responders peaked within 30 days following onabotulinumtoxinA treatment then declined slowly over time ($P < .001$) in study 1 (Figure 4).

Safety of OnabotulinumtoxinA in Phase 3 Clinical Trials

General Safety

Adverse events occur within the first week following injection of onabotulinumtoxinA and, while usually transient, may have a duration of several months or longer.¹³ Adverse events that may be associated with injection of onabotulinumtoxinA include localized pain, infection, inflammation, tenderness, swelling, erythema, and bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses that may include, for example, syncope or hypotension and may require appropriate medical therapy. Local weakness of the injected muscle represents the expected pharmacologic action of botulinum toxin. However, weakness of nearby muscles may also occur due to the spread of onabotulinumtoxinA.

Safety in Crow's Feet Lines

Eyelid edema was reported by 5 of 526 patients (1%) who were treated with onabotulinumtoxinA for CFL in the phase 3 trials.^{8,9} In comparison, none of the 530 patients who received placebo experienced eyelid edema. No other

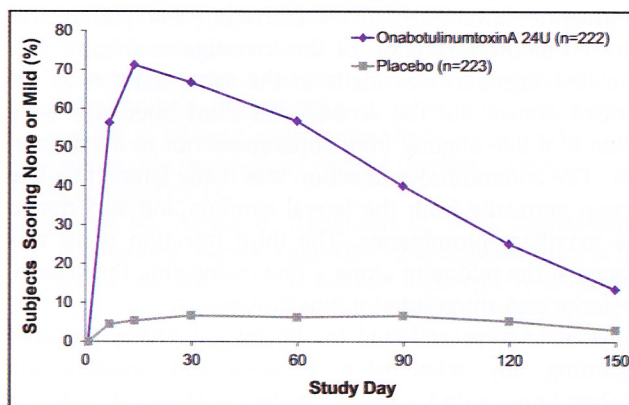


Figure 4. The percentage of patients who achieved grades of none or mild on the investigator's assessment of the severity of Crow's feet lines as assessed at maximum smile using the Facial Wrinkle Scale in study 1. $P < .001$ for onabotulinumtoxinA 24U vs placebo at all time points.

adverse event was reported within 90 days following treatment with onabotulinumtoxinA at an incidence of 1% or greater and more frequently than in placebo-treated patients.

DISCUSSION

Crow's Feet Lines Dose and Injection Patterns: Tailoring Treatment

The approval of onabotulinumtoxinA at the 24U dose based on the phase 3 clinical trials provides a well-founded framework for clinical use. The presence of different CFL patterns suggests that it may be possible to customize treatment administration with the 24U dose based on the patient's CFL pattern. In the pivotal phase 3 trials, 2 injection patterns were offered as options to the treating physician. Patients received injections into 3 sites per side (total of 6 injections) in the lateral orbicularis oculi muscle.^{8,9} The injections were made with the needle bevel tip pointed up and oriented away from the eye. Each injection was 0.1 mL in volume and contained 4U onabotulinumtoxinA, for a total dose of 24U.

The first injection was made approximately 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to

the orbital rim (Figure 3A). For patients with CFL above and below the lateral canthus (ie, central fan and full fan), the second injection was made 1.0 to 1.5 cm above the first injection site and at an approximate 30° angle medially, and the third injection was made 1.0 to 1.5 cm below the first injection site and at an approximate 30° angle medially. This injection pattern was also used for patients with an upper-fan pattern.

For patients with CFL primarily below the lateral canthus (ie, lower fan), an alternative injection pattern was allowed at the discretion of the investigator (Figure 3B). The first injection was made in the same manner as described above, but the second and third injections were given in a line angling from superoposterior to anteroinferior. The anteroinferior injection was made lateral to a line drawn vertically from the lateral canthus and superior to the maxillary prominence. The third injection point was placed at the midpoint along a line connecting the superoposterior and anteroinferior injection points.

No data were collected in the pivotal phase 3 studies regarding any relationship between CFL pattern and onabotulinumtoxinA dosing pattern. Thus, it remains to be determined whether the efficacy and safety of onabotulinumtoxinA are affected by either the CFL pattern or the injection pattern. Moreover, it is not known whether a dosing pattern that focuses on the area above the lateral canthus would be more appropriate for the small number of patients with an upper-fan pattern. However, the efficacy and safety results in the pivotal trials indicate that the 2 injection patterns would be appropriate for more than 95% of individuals with moderate or severe dynamic CFL. Based on the authors' combined clinical experience, the majority of patients with CFL are treated using the conventional injection pattern described in Figure 3A. It should be noted that the clinical trials described in this summary enrolled patients with moderate-to-severe CFL. As with many clinical trials for facial aesthetic treatment, most patients were white. Thus, extrapolation of findings to individuals from other ethnic groups should be made with caution.

CONCLUSIONS

The recommended 24U onabotulinumtoxinA dose and 2 injection patterns in the treatment of CFL were developed using a rational scientific approach and are supported by several large clinical trials. OnabotulinumtoxinA used as suggested has proven to be safe and effective for treatment of moderate or severe dynamic CFLs. Additionally, several CFL patterns have been identified, with gender and age-related differences in the frequency of patterns. The customization permitted by the two injection patterns allows physicians to tailor treatment of CFL based on clinical presentation, their clinical expertise, and the patients' preferences.

Disclosures

Dr Carruthers is a consultant for and has received research grants from Allergan plc (Dublin, Ireland). Dr Bruce is a consultant for Allergan plc, Lithera (name changed to Neothetics, Inc., San Diego, CA), Lumenis (Yokneam, Israel), and Ulthera, Inc. (Mesa, AZ). She also serves as an investigator for AbGenomics (Los Altos, CA); Actavis, Inc. (Parsippany-Troy Hills, NJ); Allergan plc; Anacor Pharmaceuticals, Inc. (Palo Alto, CA); Braintree Laboratories, Inc. (Braintree, MA); Cipher Pharmaceuticals, Inc. (Charleston, SC); DUSA Pharmaceuticals, Inc. (Wilmington, MA); Galderma R&D Inc. (Cranbury, NJ); G & E Herbal Biotechnology Co. Ltd. (Tainan City, Taiwan); G & W Laboratories, Inc. (South Plainfield, NJ); Health Outcomes Solutions (Winter Park, FL); LEO Pharma, Inc. (Ballerup, Denmark); Lithera; Maruho Co. Ltd. (Osaka, Japan); Novartis Pharmaceuticals Corp. (Basel, Switzerland); Obagi Medical Products, Inc. (Irvine, CA); Pfizer (New York, NY); Promius Pharma, LLC (Princeton, NJ); Ranbaxy Laboratories, Ltd. (Gurgaon, India); Revance Therapeutics, Inc. (Newark, CA); Stiefel Laboratories, Inc. (Middlesex, UK); Suneva Medical, Inc. (Santa Barbara, CA); Taro Pharmaceutical Industries, Ltd. (Hawthorne, NY); Tigercat Industries Inc. (Brantford, Ontario, Canada); Tolmar, Inc. (Fort Collins, CO); and Watson Pharmaceuticals, Inc. (Parsippany, NJ). Dr Cox is a consultant for Allergan plc and Medicis (Scottsdale, AZ) and serves on speakers' bureaus for and has received honoraria from Allergan plc, Medicis, and Merz (Frankfurt, Germany). Dr Kane has served as an investigator for Medicis; Revance Therapeutics, Inc.; Coapt (Chicago, IL); Teoxane (Genève, Switzerland); and Kythera (Dublin, Ireland). He is a consultant for Allergan plc; Mentor (Santa Barbara, CA); Medicis; Sanofi-Aventis (Paris, France); Revance Therapeutics, Inc.; Galderma (Lausanne, Switzerland); Johnson & Johnson (New Brunswick, NJ); QMed (Santa Monica, CA); Canfield (Fairfield, NJ); Coapt; Merz; Kythera; Beiersdorf (Hamburg, Germany); and Lithera, and serves on speakers' bureaus for Allergan plc; Mentor; Medicis; Sanofi-Aventis; Revance Therapeutics, Inc.; QMed; and Merz. Dr Kane also serves on advisory boards for Allergan plc; Mentor; Medicis; Sanofi-Aventis; Stiefel; and Revance Therapeutics, Inc.; has received honoraria from Allergan plc; Medicis; and QMed; and owns stock in Allergan plc and Medicis. Ms Lee and Dr Gallagher are employees of Allergan plc and may own stock or stock options in that company. The authors received no honorarium/fee or other form of financial support related to the development of this article. The opinions expressed in this article are those of the authors, and the authors made the final decision to submit this article for publication.

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