Undesirable facial lines can result from repeated contrac-
tions of facial expression muscles and may eventually
remain present even when a person’s facial muscles are at
rest. Botulinum toxin type A inhibits neurotransmitter
release from the peripheral terminals of motor neurons
and, when applied focally to the facial muscles, can inhibit
muscular contractions to improve the appearance of facial
lines. Botulinum toxins have become a standard treatment
modality for such lines, and in most countries, 1 or more

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products are approved for the treatment of moderate or severe glabellar lines.1,3

In Argentina, onabotulinumtoxinA (BOTOX; Allergan, Inc, Irvine, California) has been available for the management of moderate to severe upper facial lines, including glabellar lines, since November 2001. In January 2007, another botulinum toxin type A product, incobotulinumtoxinA (Xeomin; Merz Pharma, GmbH, Frankfurt, Germany), was approved in Argentina for the treatment of moderate or severe glabellar lines.

Botulinum neurotoxins are biological products that are manufactured through a series of complex and highly controlled steps.4 The precise manufacturing process is different for each botulinum neurotoxin product, resulting in final formulations that are not identical. An important example is related to biological activity: as biological products, doses of botulinum neurotoxins are expressed in terms of units, which is shorthand for units of biological activity. These units are not interchangeable among products, in part because they are not standardized; instead, each manufacturer uses a proprietary method to determine the amount of its product that constitutes a unit. This disparity has been demonstrated in pharmacological studies that have found that incobotulinumtoxinA units have a different biological activity than onabotulinumtoxinA units when tested in the proprietary assay used to define Allergan units.5,6 Thus, although these 2 products were approved at similar unit doses for use in the glabella, we cannot infer comparable clinical efficacy or safety at those doses due to the underlying differences in biological activity. This noninterchangeability is underscored by guidelines within the Argentinean package inserts and by regulatory agencies worldwide stating that units are specific to each different botulinum neurotoxin product and cannot be converted between products using a dose ratio.7–11

The approval and use of different botulinum neurotoxins provides an opportunity to understand the physicians’ and recipients’ perceptions of the performance of these products in actual clinical use. This study was therefore designed to retrospectively evaluate real-world changes in facial aesthetic treatment patterns and subject satisfaction following the introduction of incobotulinumtoxinA in Argentina.

**METHODS**

**Study Design and Subjects**

This was a multicenter, observational, retrospective chart review of subjects treated with onabotulinumtoxinA (BOTOX) and incobotulinumtoxinA (Xeomin) for facial lines in Argentina. For the purpose of this study, “facial lines” included any line on the face that was treated with neurotoxin, such as glabellar lines, crow’s feet lines, perioral lines, or chin dimpling.

Eligible subjects included women 18 years or older at the time of first botulinum toxin A treatment who had received at least 1 treatment with incobotulinumtoxinA prior to November 1, 2009, and had been previously treated with onabotulinumtoxinA for at least 2 consecutive treatment cycles immediately prior to receiving treatment with incobotulinumtoxinA. Subjects could have had a second switch, from incobotulinumtoxinA back to onabotulinumtoxinA, to be included in additional analyses of the study. No exclusion criteria were specified, and the 4 treatment centers were asked to include data from as many eligible subjects as possible in the time available for data collection to provide a representative subject sample.

**Chart Review and Outcome Measures**

Study site staff reviewed medical records and entered data into case report forms. All charts at each site that met the inclusion/exclusion criteria were included in the study. All data were deidentified and compliant with Comité de Ética e Investigación (CECIC, Argentina) regulations.

The primary end points of this study were the mean and median total doses of onabotulinumtoxinA and incobotulinumtoxinA in the last treatment cycle per period. A period was defined as the interval during which subjects received only 1 brand of botulinum toxin type A (Figure 1). All subjects had data for at least 2 periods in this study, per the inclusion criteria: treatment period 1, in which they received onabotulinumtoxinA, and treatment period 2, in which they switched to incobotulinumtoxinA. Some subjects continued with incobotulinumtoxinA treatments and therefore stayed in period 2. Subjects who switched back to onabotulinumtoxinA had data for period 3.

Total dose per treatment cycle was defined as the sum of the doses given during the cycle, which included the initial treatment dose, the total follow-up dose, and the total touchup dose. Touchup treatments were those that occurred within 6 weeks of the new treatment cycle, included 1 or more facial regions treated in the initial treatment, had less than or equal to 50% of the original total dose, and/or had less than or equal to 50% of the original dose to an individual region. A follow-up treatment was a treatment occurring within 6 weeks of the start of a new treatment cycle in which new facial regions were treated (ie, injection sites/regions not included in the initial treatment).

Secondary efficacy variables investigated additional aspects of botulinum toxin A treatments, including mean and median dose ratios of the 2 products, treatment

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switches and reasons for switching, and mean/median interinjection intervals (start date of the next treatment cycle minus the start date of the current treatment cycle).

### Analyses

Descriptive summary statistics for continuous variables included the number of subjects, mean, median, range, and standard deviation (SD). Descriptive summary statistics for categorical variables included frequency counts and percentages. Comparisons of total doses were conducted between periods 1 and 2 and between periods 2 and 3 for facial lines and, separately, for glabellar lines. These analyses compared the total dose from the last treatment cycle in period 1 with the first treatment cycle in period 2 having an injection pattern matching that of period 1. If a treatment cycle could not be found in period 2 with an injection pattern matching that of period 1, total dose was counted as missing for the purpose of these analyses. Satisfaction with treatment responses was calculated for each patient per period as the mean of all satisfied and dissatisfied responses in a given period (ie, as 100 × [number of responses satisfied in a period divided by the number of responses satisfied or dissatisfied in period]). Between-group comparisons for dosing, injection intervals, and satisfaction data were conducted with either the paired t test or Wilcoxon signed rank test depending on data normality. Results were deemed statistically significant for P < .05.

#### RESULTS

### Subjects

A total of 110 subjects were recruited and enrolled at 4 study sites. All subjects were women, with a mean age of 54.5 years (range, 32-74 years; Table 1). Just over half were identified as white, and the race for the remaining subjects was unknown, since it was not documented. Thirty-four of 110 subjects (30.9%) had 1 or more additional facial treatments during the period of review: 12 (10.9%) had chemical peels, 10 (9.1%) had lasers, 8 (7.3%) had topical creams, 1 (0.9%) had facial plastic surgery, and 25 (22.7%) had other treatments (primarily hyaluronic acid).

### Doses and Treatment Cycles

The total number of treatment cycles for the 110 subjects was 662, with an average of 6 treatment cycles documented per subject. Subjects underwent a mean (SD) of 2.1 (0.3) treatment cycles during period 1, 1.6 (0.9) treatment cycles during period 2, and 2.8 (1.6) treatment cycles during period 3. The mean (SD) duration of follow-up for each treatment cycle was 201.3 (94.4) days for the 110 subjects in period 1, 178.3 (113.6) days for the 106 subjects in period 2, and 203.2 (91.4) days for the 76 subjects in period 3.

Table 2 shows the frequency of facial regions injected and mean doses per treatment cycle. Three-fourths of subjects received injections in both the glabellar and frontalis regions; 69% received injections in the glabellar, frontalis, and crow’s feet regions; and 7% received injections in the glabellar region only.

Due to the high variability between individual subject injection patterns from treatment to treatment, only a limited population of subjects had matching injection patterns between periods and were eligible for inclusion in the total dose comparison analysis. No significant differences were found in the total doses of onabotulinumtoxinA used to treat facial lines for the last treatment cycle in period 1 (mean [SD], 49.2 [12.8] U, n = 34) and incobotulinumtoxinA for the first treatment cycle in period 2 with an injection pattern matching that of period 1 (48.1 [15.2] U, n = 34; P = .47). The total dose of onabotulinumtoxinA for the last treatment cycle in period 3 (mean [SD], 45.8 [4.7] U, n = 16) was not significantly different from the incobotulinumtoxinA dose in period 2 (P = .12).

Similarly, no significant differences were found in the total doses of onabotulinumtoxinA used to treat glabellar lines for the last treatment cycle in period 1 (mean [SD],
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12.9 [4.1] U, n = 19) and incobotulinumtoxinA for the last treatment cycle in period 2 (11.6 [2.4] U, n = 19; \( P = .28 \)). The total dose of onabotulinumtoxinA for the last treatment cycle in period 3 (mean [SD], 12.8 [3.2] U, n = 16) was not significantly different from the incobotulinumtoxinA dose in period 2 (\( P = .22 \)).

Treatment Switching

Per the inclusion criteria, all subjects included in this study had at least 2 treatments with onabotulinumtoxinA (period 1) and then switched to incobotulinumtoxinA (period 2). Of these 110 subjects, 92 (84%) switched back to onabotulinumtoxinA (period 3; Figure 2). Of the 92 subjects who switched back to onabotulinumtoxinA, most switched after 1 treatment of incobotulinumtoxinA (63 of 92; 69%), and all had switched after 1 to 3 treatments of incobotulinumtoxinA.

The most common reason for switching from onabotulinumtoxinA in period 1 to incobotulinumtoxinA in period 2 was identified as product cost (92%; 101/110 subjects; Figure 3). One subject was switched due to insufficient duration of the treatment effect with onabotulinumtoxinA (1%), and the reasons for switching for the remaining 8 subjects (7%) were unknown, missing, or not available; none of the records specified lack of efficacy or adverse events as a reason for switching to incobotulinumtoxinA.

As stated previously, after receiving incobotulinumtoxinA in period 2, 84% of subjects switched back to onabotulinumtoxinA (period 3; Figure 3). Slightly more than half (56%; 61/110) switched back to onabotulinumtoxinA due to insufficient duration of incobotulinumtoxinA, 6% switched due to lack of efficacy, 16% (18/110) remained on incobotulinumtoxinA, and the reasons for switching back for the remaining 23% (25/110) of subjects were unknown or not documented in the charts. None of the charts specified adverse events as a reason for switching back.

Treatment Satisfaction: Subjects

At follow-up visits, physicians entered information in patient charts about satisfaction with treatment effects based on discussions with patients according to their usual clinical practice; in this retrospective study, no standard questions about satisfaction were specified. Subject satisfaction responses in patient charts were reviewed by study staff at each site and documented in the

<table>
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<th>Table 2. Frequency of Regions Injected and Mean Doses per Treatment Cyclea</th>
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<tr>
<td>Glabellar lines</td>
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<td>Frontalis</td>
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<td>Crow’s feet</td>
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<td>Platysma</td>
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<td>Masseter</td>
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<td>Other</td>
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Subjects may have received injections in more than 1 region. A total of 75% of subjects received injections in both the glabellar and frontalis regions; 69% in the glabellar, frontalis, and crow’s feet regions; and 7% in the glabellar region only. Abbreviations: DAO, depressor anguli oris.

aTreatment cycles included touchup and follow-up doses; onabotulinumtoxinA doses were averaged over periods 1 and 3, and incobotulinumtoxinA doses were averaged over period 2.

bNumber and % of treatment cycles were based on 673 treatment cycles, including 662 in periods 1 to 3 and 11 in periods 4 to 6.

Figure 2. Percentage of subjects who switched back to onabotulinumtoxinA or stayed on incobotulinumtoxinA.

Figure 3. Reasons for switching treatments: (A) reason for switching to incobotulinumtoxinA and (B) reason for switching back to onabotulinumtoxinA.
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database as yes, no, or unknown. The same procedure was followed for physician satisfaction.

Following treatment with onabotulinumtoxinA in period 1, the mean (SD) percentage of satisfied responses was 99% (6.7%) among 80 subjects with available data on the dichotomous variable of satisfied/not satisfied with treatment (Figure 4). Following treatment with incobotulinumtoxinA in period 2, the mean (SD) percentage of satisfied responses was 33.7% (39.3%) among 74 subjects with available data. Following onabotulinumtoxinA in period 3, the mean (SD) percentage of satisfied responses was 90.3% (17.6%) among the 67 subjects with available data (Figure 4). Subject-rated treatment satisfaction was significantly greater during periods 1 and 3 than during period 2 (P < .001).

**Treatment Satisfaction: Physicians**

Following treatment with onabotulinumtoxinA in period 1, the mean (SD) percentage of satisfied responses reported by physicians was 99% (6.7%) for the 80 subjects with available data. Following treatment with incobotulinumtoxinA in period 2, the mean (SD) percentage of satisfied responses reported by physicians was 29.2% (38.4%) for 72 subjects with available data. Following onabotulinumtoxinA in period 3, the mean (SD) percentage of satisfied responses reported by physicians was 90% (18.0%) for 67 subjects with available data. Physician-reported treatment satisfaction was significantly greater during periods 1 and 3 than during period 2 (P < .001).

**Interinjection Interval**

Interinjection intervals for periods 1 through 3 are shown in Figure 5. The median interinjection interval following onabotulinumtoxinA injections in period 1 was 180.3 days (n = 110). The median interval in period 2 was 144.3 days (n = 106), which was significantly shorter than the period 1 interval (P = .014). Following the switch back to onabotulinumtoxinA in period 3, the median interinjection interval was 176.9 days (n = 76), which was significantly different from incobotulinumtoxinA in period 2 (P < .001).

**Adverse Events**

As per usual documenting standards in Argentina, adverse events that were considered minor were not recorded in patient charts. Only major adverse events such as blepharoptosis or diplopia are recorded in patient charts in Argentina. In this study, no major adverse events were documented.

**DISCUSSION**

The present study demonstrates the impact of the introduction of a new botulinum toxin product on practice patterns in 4 aesthetic clinics in Argentina. These results indicate that nearly all (92%) subjects who switched to incobotulinumtoxinA after its introduction were switched because the product was available at a lower cost than onabotulinumtoxinA. As expected, subjects were switched from onabotulinumtoxinA to incobotulinumtoxinA at approximately the same number of units. However, this dose of incobotulinumtoxinA did not provide sufficient benefit to encourage continuation with the new product, as 84% of those who received incobotulinumtoxinA in this study population elected to return to onabotulinumtoxinA for subsequent treatment sessions.

Treatment satisfaction is a critical consideration in facial aesthetics. The present study found that subjects expressed treatment satisfaction at 99% of visits with onabotulinumtoxinA in period 1 and 92% in period 3. During treatment with incobotulinumtoxinA in period 2,
subjects reported satisfaction at 34% of visits. This suggests that subjects were less satisfied following incobotulinumtoxinA than onabotulinumtoxinA injections at the doses used. A number of other studies have evaluated subject satisfaction following botulinum toxin type A injections using a variety of different measurement scales.\(^\text{12}\) In a dose-ranging study of onabotulinumtoxinA, 66% to 79% of subjects indicated that they were satisfied or very satisfied with the treatment, and 84% to 95% indicated that they would have the treatment again.\(^\text{13}\) Although variables such as dose, facial area treated, method of assessment, and neurotoxin product likely affect the exact rating obtained, satisfaction with botulinum toxin type A in facial aesthetics is high and usually ranges from 65% to more than 90%.\(^\text{12}\)

The interinjection intervals documented in this study included both touchup and follow-up doses as defined in the protocol and outlined in the Methods section. Two of the sites in this multicenter study regularly schedule touchups as part of their routine clinical practice. Follow-up visits, usually accompanied by touchups, are common practice in Argentina. Touchups contribute to total doses given per injection cycle and may influence injection intervals. Injection intervals may also be influenced by patient-specific factors such as economics, practical considerations (eg, time spent traveling to and from the physician’s office, time off work for office visits), and the precise aesthetic result the patient desires.

The median interinjection intervals with onabotulinumtoxinA were 177 and 180 days or approximately 6 months for each of the 2 periods, whereas the median interinjection interval with incobotulinumtoxinA was 144 days or 4.8 months. Based on these results, it appears that retreatment was required less frequently with onabotulinumtoxinA than incobotulinumtoxinA when the products were used at numerically comparable unit doses. This is supported by the data on neurotoxin switching: of the 92 subjects who switched back to onabotulinumtoxinA, 61 (66%) cited insufficient duration and an additional 6 (7%) cited lack of efficacy with incobotulinumtoxinA. These results are also supported by a Brazilian study of 56 subjects treated with incobotulinumtoxinA for facial wrinkles.\(^\text{14}\) Of the 38 subjects who returned for follow-up 15 days after injection, 19 (50%) complained of low or no efficacy or short-lived effects of the toxin, despite 15 of the 19 subjects having experienced satisfaction with previous treatments of other botulinum toxin type A products.

Although interinjection interval is often taken as a surrogate for duration of clinical benefit, it must be cautioned that interinjection intervals may be influenced by patient scheduling practices, the use of touchup doses, and potential financial considerations for these nonreimbursed interventions.\(^\text{15}\) Other measures have been used to define duration of efficacy, including time to return to baseline glabellar line severity and percentage of responders over the duration of the study. A recent review concluded that each botulinum neurotoxin product is associated with a duration that ranges from 3 to 5 months based on a variety of factors.\(^\text{15}\) For instance, prospective clinical studies often include a predefined minimum injection interval of 3 or 4 months.\(^\text{16}\)

The differences in interinjection intervals and subject satisfaction in the present study, despite the receipt of numerically comparable unit doses, support the noninterchangeability among unit doses of botulinum neurotoxin products. Subjects were switched to incobotulinumtoxinA at doses similar to those of their previous onabotulinumtoxinA injections, although regulatory guidelines worldwide indicate that units of botulinum neurotoxins are specific to each product.\(^\text{9,10,17,18}\) These results are also consistent with preclinical data showing differences in the biological activity of the 2 products.\(^\text{5,6}\)

One limitation of the present study is the low number of subjects included in the dose comparison analyses for facial lines (n = 34) and glabellar lines (n = 19). The analysis plan prespecified that comparisons would be made between subjects with matching treatment patterns to avoid bias due to additional areas being injected at different treatment sessions. It was not possible to include all treated subjects in these analyses as there was high variability between individual subject injection patterns from treatment to treatment, as permitted by the study protocol. Consequently, only subjects who had matching injection patterns between periods were included in the total dose comparison analyses.

This study has several potential limitations common to all retrospective chart reviews, including lack of randomization and potential bias among subjects and investigators. Doses were not prespecified and were somewhat lower than those listed in the product labels for the management of glabellar lines. In addition, the touchup and follow-up doses used routinely in this study may be a regional anomaly and may not be representative of clinical practice globally. However, retrospective study designs capture actual clinical practice experience, often include a broader patient population than controlled trials, and represent outcomes gleaned using normal clinical procedures such as doses, injection patterns, and follow-up intervals that are not mandated by a clinical trial design.

An advantage of the present study was the within-subjects design, such that all subjects were their own controls and experienced treatment with both products. Inclusion of a group that switched back to onabotulinumtoxinA permitted a more reliable comparison between neurotoxins; that is, confidence in the results is increased because satisfaction and injection intervals returned to their previous levels when subjects switched back to onabotulinumtoxinA.

Regardless of the botulinum neurotoxin product injected, however, we agree with Lorenc and colleagues\(^\text{19}\) that it is desirable to manage patient expectations. Promoting realistic expectations may help retain patients and increase satisfaction.

**CONCLUSIONS**

This “real-world” clinical study found that most Argentinian patients who initially switched to incobotulinumtoxinA...
for the treatment of glabellar lines did so because of its introduction as a lower-cost alternative treatment. However, 84% of those who received incobotulinumtoxinA elected to return to onabotulinumtoxinA, with insufficient duration cited as the primary reason for switching back. These findings suggest that patients may not perceive the same facial aesthetic benefits from incobotulinumtoxinA when administered at doses numerically comparable to those of onabotulinumtoxinA. These findings support the labeling claims for botulinum toxin products, which state that units are not interchangeable among different products.

Acknowledgments

Participating investigators were Raúl A Banegas, MD, private practice, Buenos Aires, Argentina; Fernando Farache, MD, Clinica Milito, Buenos Aires, Argentina; Valeria López, MD, Bioaurea Gurruchaga, Buenos Aires, Argentina, Alberto Rancati, MD, private practice, Buenos Aires, Argentina; and Myriam Chain, Aisthetike Palermo, Buenos Aires, Argentina.

Disclosures

Drs Gallagher and Caulkins are employed by Allergan, MD, private practice, Buenos Aires, Argentina; Fernando Farache, MD, Clinica Milito, Buenos Aires, Argentina; Valeria López, MD, Bioaurea Gurruchaga, Buenos Aires, Argentina, Alberto Rancati, MD, private practice, Buenos Aires, Argentina; and Myriam Chain, Aisthetike Palermo, Buenos Aires, Argentina.

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