Injection of botulinum toxin type A (BoNTA) for the aesthetic correction of glabellar lines and other facial enhancements is the most common cosmetic procedure in the United States. In 2010, more than 2.4 million BoNTA procedures were performed, according to statistics from the American Society for Aesthetic Plastic Surgery. As the first BoNTA product available in the United States, onabotulinumtoxinA (Botox; Allergan, Irvine, California; Vistabel outside of the United States) was approved by the US Food and Drug Administration (FDA) in 2002 for aesthetic applications. It is officially indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults 65 years and younger, although it is also used widely in an off-label fashion for horizontal forehead lines, “crow’s feet,” and many other areas. This review article summarizes key efficacy and safety studies. Consideration is given to variable dosing strategies, and a discussion summarizes practical considerations related to onabotulinumtoxinA, including product handling.

**EFFICACY**

In 2002 and 2003, articles were published reporting on a total of 537 patients who were enrolled in 2 phase 3, randomized, multicenter, double-blind, placebo-controlled studies of identical design to evaluate the efficacy and safety of onabotulinumtoxinA for temporary improvement of the appearance of moderate to severe glabellar facial lines. Of those enrolled, 405 patients received onabotulinumtoxinA and 132 patients received placebo. For patients receiving onabotulinumtoxinA, total dosage was 20 U, equally divided into 5 injection points. Glabellar line severity was evaluated at maximum frown on day 30 by
the investigators’ assessment and the subjects’ global assessment of change. A validated 4-point grading scale (0 = none, 3 = severe) was used by the investigators. The patients’ global assessment of change was rated on a scale of +4 (complete improvement) to −4 (very marked worsening). Responders were defined as those having a grade of at least +2 (moderate improvement); these patients would have had an initial severity grade of 0 or 1.

Patients in the onabotulinumtoxinA group experienced significantly greater improvement in glabellar line severity than patients in the placebo group in both investigator and patient assessments. By investigator assessment, 80% of patients receiving onabotulinumtoxinA were considered responders versus 3% of those receiving placebo at the primary efficacy time point of day 30 (P < .001). By patient assessment of change, 89% in the onabotulinumtoxinA group were responders vs 7% in the placebo group (P < .001).4,5

The studies also evaluated the efficacy of onabotulinumtoxinA versus placebo in patients older than 65 years; a total of 32 patients (6%) in the studies fell into this group. Among these patients, there was a lower treatment-associated response compared with those patients younger than 65 years. Using investigators’ assessments, only 39% of older patients in the onabotulinumtoxinA group (vs 22% placebo) were responders, although, by patient assessment, 70% were responders (vs 11% placebo).5 This age-related discrepancy is multifactorial, encompassing elements such as the degree of skin’s intrinsic elasticity and the patient’s muscle mass.

ONSET AND DURATION OF EFFECT

Onset of onabotulinumtoxinA occurs within 7 days. In the 2 clinical trials previously described, the degree of response by both investigator and patient assessment was similar at day 7 and day 30.4,5 Peak effect was observed at day 30 in both studies. The studies were not designed to test specifically for duration of effect, but the results did suggest that onabotulinumtoxinA’s duration in treatment of glabellar lines is similar to the 3 to 6 months reported for other indications.6 Other studies of onabotulinumtoxinA for treatment of glabellar lines suggest injection intervals of as long as 3 to 7 months.7-10 Durations longer than 4 months, however, are more typical of patients who have received a series of treatments over the course of at least 1 year and may be dose dependent.4

VARIABLE DOsing

Because of variations in the size and strength of glabellar complex muscles, a range of dosages can be administered to achieve optimal effect. A variable dosing study has been published that evaluated doses of 20, 40, 60, or 80 U for treatment of glabellar lines in men.11 Higher doses were found to be safe and effective and, in many cases, more effective than 20 U for those patients with strong glabellar features. Many clinicians today start with dosages of 15 to 20 U and then administer higher dosages depending on the muscle mass and/or sex of the patient. Note that common dosages for off-label applications such as crow’s feet are covered in the consensus article found elsewhere in this supplement.

LONG-TERM SAFETY

As with other BoNTA products, onabotulinumtoxinA is generally well tolerated. The most frequent adverse events reported by more than 5% of patients in clinical trials included headache, respiratory tract infection, blepharoptosis, back pain, and acne. A significant adverse event for any BoNTA product is ptosis, which can manifest as either brow or eyelid ptosis (blepharoptosis). In an early clinical trial, blepharoptosis was reported in 5.4% of patients. Studies of the second BoNTA product (Dysport; Medicis Aesthetics, Scottsdale, Arizona) suggest that rates of ptosis generally decrease with increased clinician experience.2

The long-term safety of onabotulinumtoxinA after repeat administrations has been established based on years of clinical experience as well as a meta-analysis of the number and frequency of adverse events from 36 studies involving 2309 subjects.12 No study reported any serious adverse events. Focal weakness was the only adverse event to occur more often among the onabotulinumtoxinA group compared with the control group. Long-term onabotulinumtoxinA administration has been assessed in various treatment settings, with the level and duration of onabotulinumtoxinA efficacy response being maintained over repeated rounds of injection with no major safety concerns.13

DISCUSSION: ONABOTULINUMTOXIN-A IN CLINICAL PRACTICE

Product labeling advises that each BoNTA product is unique and its unit of measure is not interchangeable; formulations of each BoNTA product differ from one another, mostly based on the proprietary manufacturing process unique to each product. However, many physicians attempt to describe relative differences in the unit ratios of the different approved toxins. Caution must always be exercised to ensure appropriate dosing.

A box warning on the onabotulinumtoxinA package insert and on the inserts of the 2 other BoNTA products available in the United States alerts physicians to potential for distant spread of toxin beyond the injection site. Spread of onabotulinumtoxinA is dependent on the volume injected and the injection technique, with higher volume of product leading to increased physical distribution as the fluid is pushed from the injection point through the tissues.14

Handling and Preparation

OnabotulinumtoxinA and diluent do not contain preservatives. Once opened and reconstituted, the product should be refrigerated at 2°C to 8°C (36°F to 46°F). OnabotulinumtoxinA is always be exercised to ensure appropriate dosing.
is supplied in single-use vials of 50 U and 100 U. Dilution with 1.25 mL 0.9% sterile, preservative-free saline (for the 50-U vial) into a syringe to obtain a reconstituted solution at a concentration of 4 U/0.1 mL is recommended by the package insert, with a total treatment dose of 20 U in 0.5 mL. Product labeling advises that, once opened, any remaining solution should be discarded. Many clinicians, in an off-label fashion, do use a reconstituted vial more than once, provided that the same needle and syringe is not reinserted into the vial. This recommendation, however, is beyond the scope of official product labeling, and not all clinicians are in agreement because the product does not contain any antimicrobial agent.

**OnabotulinumtoxinA With Other Aesthetic Procedures**

BoNTA products may be used in conjunction with other aesthetic procedures, such as injectable dermal fillers and volumizing agents. There is no consensus about the order in which the two should be injected or whether the injections should be performed on the same day. However, there may be practical reasons for separating injections. A patient injected with BoNTA on one visit may return after approximately 1 week and be satisfied with the neuromodulator effect alone, deciding to forego administration of the dermal filler.

Combination therapy with neuromodulators and fillers/volumizing agents for facial rejuvenation has been a widespread practice for close to a decade. However, until recently, systematic studies of BoNTA therapy in conjunction with hyaluronic acid (HA) for use in the lower face had not been conducted. Carruthers and colleagues evaluated the safety and efficacy of combination treatment using onabotulinumtoxinA with a 24-mg/mL smooth, cohesive HA gel filler. Patients treated with onabotulinumtoxinA plus HA had greater improvement from baseline than subjects treated with either onabotulinumtoxinA alone or HA alone by both investigator and patient assessments. The authors concluded that combination therapy is superior to either modality used alone to rejuvenate the lower face. These findings support what has been routinely observed in clinical practice.

**OnabotulinumtoxinA for Treatment of Glabellar Lines in Repose**

Although the efficacy of BoNTA has been established for the treatment of glabellar frown lines, its effect for lines at repose are less clear. To assess the effect of onabotulinumtoxinA on the elimination of mild lines at rest, Carruthers and colleagues analyzed 183 participants with mild lines at repose who received 20 U of onabotulinumtoxinA and 64 participants, also with mild lines at repose, who received placebo. These participants were evaluated at days 7, 30, 60, 90, and 120. Compared with placebo, the patients treated with onabotulinumtoxinA were more likely to have their lines at repose eliminated for each point of evaluation. The highest response rate was observed at day 30 (68%).

On the basis of clinical experience and this study, the supplement authors believe that these results can be extrapolated to the other 2 BoNTA products and that patients most likely to benefit from BoNTA treatment of lines at rest are younger than 50 years, with mild lines at repose. Patients with more severe wrinkle rating will likely require a combination of approaches, including administration of BoNTA, dermal filler/volumizing agents, resurfacing procedures, and possibly surgical intervention.

**CONCLUSIONS**

The treatment of facial lines with onabotulinumtoxinA is effective and well tolerated with a safety profile comparable to placebo. Adverse events were mild or moderate in clinical trials. Variable dosing based on sex and muscle mass resulted in improved efficacy in many patients and did not increase the risk of adverse events.

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**REFERENCES**


