OnabotulinumtoxinA Treatment of Mild Glabellar Lines in Repose

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BACKGROUND OnabotulinumtoxinA is an established treatment for glabellar frown lines, but its effects on lines at repose are less well documented.

OBJECTIVE To assess the effect of onabotulinumtoxinA on elimination of mild lines at repose.

METHODS Data from two randomized, double-blind, placebo-controlled studies were included. Elimination of mild lines at repose was defined as change from mild to none on the Facial Wrinkle Scale.

RESULTS Analysis included 183 participants who received 20 U of onabotulinumtoxinA and 64 participants who received placebo, all with mild lines at repose at baseline. Participants were evaluated 7, 30, 60, 90, and 120 days posttreatment. Compared to placebo, onabotulinumtoxinA-treated participants were significantly more likely to have their lines at repose eliminated at each study day; [odds ratios ranged from 42.7 (95% confidence interval (CI) = 12.9–141.9) at day 30 to 4.9 (95% CI = 2.2–10.8) at day 120 ($p < .0001$ at each day)]. The highest response rate was observed at day 30 (68%).

CONCLUSION OnabotulinumtoxinA has demonstrated the ability to eliminate mild glabellar lines at repose for a significant number of patients. This effect, albeit more subtle than the effect on dynamic or more severe glabellar lines, may be an important treatment goal for patients who seek a smoother appearance at repose.

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Intramuscularly injected onabotulinumtoxinA has a well-defined mechanism of action that results in a long-lasting but reversible relaxation of targeted muscles. In addition to its therapeutic use in a wide variety of conditions, onabotulinumtoxinA is also now well established in cosmetic use to treat glabellar frown lines. When injected into the corrugator and procerus muscles, onabotulinumtoxinA limits the ability to frown actively, resulting in reduced visibility of glabellar frown lines during animation; this effect has been the focus of the bulk of the literature describing this indication.

The focus of onabotulinumtoxinA treatment has been the predictable reduction in dynamic glabellar lines. A less-well-described benefit of treatment is a reduction in the appearance of resting glabellar frown lines when patients are not actively animating (i.e., at facial repose).[1,2] This effect has also been demonstrated quantitatively using scanning electron microscope image analysis of silicon replicas of the glabellar region after onabotulinumtoxinA treatment. Using the skin surface topography parameters developed by Takahasi,[3] Dessy and colleagues reported a statistically significant reduction in

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superficial skin texture, including average skin roughness, after onabotulinumtoxinA treatment and suggested that this decrease in roughness clinically correlates with the observed "smoother and lighter" appearance of the skin after treatment.[4]

We further assessed the concept of potential "smoothing" effect by evaluating whether intramuscular injections of onabotulinumtoxinA can eliminate ("smooth") glabellar lines that are mild in severity at facial repose, albeit temporarily.

Materials and Methods

Data were extracted from two randomized, double-blind, placebo-controlled clinical studies; methods have been published previously.[1,2] The two studies followed identical protocols and enrolled similar populations. Patients were eligible if they were aged 18 to 75 with glabellar lines of at least moderate severity at maximum frown. There was no minimum severity requirement at repose, although only patients with mild severity at repose were included in this analysis. Both studies complied with the Declaration of Helsinki guidelines on human biomedical research, including written informed consent, and were institutional review board approved before study initiation.

Participants received five injections of placebo or 4 U of onabotulinumtoxinA (BOTOX Cosmetic, Allergan, Inc., Irvine, CA) per injection, two injections in each corrugator and one in the procerus, for a total of 20 U. Seven, 30, 60, 90, and 120 days after treatment, physicians assessed the appearance of glabellar lines at repose using the 4-point (none, mild, moderate, severe) photoguide-assisted Facial Wrinkle Scale (FWS).

The efficacy outcome for this analysis was "response," defined as elimination of glabellar lines at facial repose (i.e., going from mild to none according to the FWS). The analysis population was intent to treat, which consisted of all randomized participants with nonmissing baseline FWS ratings, analyzed in the treatment group to which they were randomized. Missing postbaseline data at a specific visit were imputed with the overall mean (regardless of treatment group) for that visit; means were rounded to the nearest integer to maintain consistency with the original FWS scale. Response was compared between treatment groups and over study days using generalized estimating equations using the SAS procedure GENMOD (SAS Institute, Inc., Cary, NC). Study homogeneity was evaluated by modeling the interactions between study, treatment, and study day. After careful consideration of the results of the interaction analyses and considering that both studies operated on identical protocols and enrolled similar patient populations, data from both studies were pooled for analysis of response, and the interaction results were noted. Demographic data were compared between treatment groups using chi-square, Fisher exact, *t*, or Wilcoxon rank sum tests, as appropriate. All statistical tests were two-sided with .05 significance levels.

Results

Of 494 enrolled participants, 247 (50%) had mild glabellar lines in repose at the time of enrollment and were thus included in this analysis. Of these, 183 received onabotulinumtoxinA treatment, and 64 received placebo. There were no significant treatment group differences in demographic characteristics. Median age was 44 (range 23–72); 86% of participants were female, and 87% were Caucasian.

At every posttreatment study day, participants in the onabotulinumtoxinA group were significantly more likely than placebo participants to be responders (i.e., demonstrate glabellar line elimination at facial repose) (Figure 1); odds ratios (ORs) ranged from 42.7 (95% confidence interval (CI) = 12.9–141.9) at day 30 to 4.9 (95% CI = 2.2–10.8) at day 120 ($p <$ .0001 for each day). The proportion of onabotulinumtoxinA responders was significantly higher at study day 30 (68%) than at any other study day except at day 60 (66%) (i.e., the effect plateaued in the 30- to 60-day range); ORs ranged from 3.0 (95%

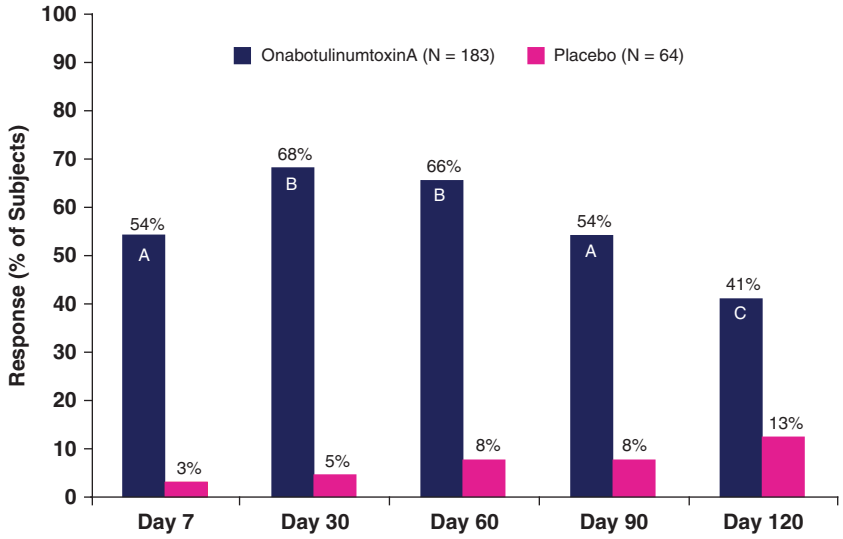

Figure 1. Response rates in subjects with mild baseline Facial Wrinkle Scale ratings at repose (pooled studies). OnabotulinumtoxinA response rate was significantly higher than placebo regardless of study day ($p < .0001$). Bars containing the same letters are not significantly different from each other. Within the onabotulinumtoxinA group, the time response profile differed significantly according to study; specifically: (A) Carruthers and colleagues[2] had a higher response rate than Carruthers and colleagues[1] at all study days except Day 7, and (B) in Carruthers and colleagues,[2] response rate at Day 120 returned to the Day 7 level, whereas in Carruthers and colleagues,[1] response at Day 120 was significantly lower than at Day 7.

CI = 2.2–4.1) for day 30 versus day 120 ($p < .001$) to 1.1 (95% CI = 0.9–1.4) for day 30 versus day 60 ($p = .39$). At each study day other than day 30, the proportion of onabotulinumtoxinA responders differed significantly from every other study day except for days 7 and 90, which were not statistically different from each other. Baseline severity of glabellar lines at maximum frown, as assessed according to physician-reported FWS, was not a significant predictor of response in onabotulinumtoxinA participants (OR = 1.0, 95% CI = 0.6–1.5, $p = .87$).

Discussion

In this study, nearly 70% of onabotulinumtoxinA-treated participants who had baseline mild glabellar frown lines at facial repose transitioned from mild to none (i.e., had no visible glabellar lines at repose after treatment), which was significantly greater than the response in placebo-treated participants. This study included only patients with a very specific severity level of facial lines (those with moderate or severe glabellar lines at maximum frown that persisted at only mild severity at facial repose). These conclusions may therefore not be generalizable to other severity levels, at animation or repose. Findings are further limited to a single treatment with a fixed dose in a single facial region. Of interest would be to determine whether the effects demonstrated in this study persist over repeated treatments. Furthermore, these results are specific to the formulation of botulinum toxin type A used (onabotulinumtoxinA).

The results of this study are compelling, because this smoothing effect, although subtler and less frequently studied than the treatment of dynamic and more severe glabellar lines, may be an important treatment goal of patients with resting lines of any severity. Glabellar lines that remain prominent at facial repose can contribute to facial miscues that create frustration and anxiety as a result of inaccurate societal interpretation of facial expression.[5] For instance, patients frequently seek treatment for their frown lines because others mistake them to be constantly angry or annoyed.[5,6] Furthermore, patients with mild lines at repose may gravitate to the appeal of a smoother, and potentially more youthful, appearance.[7]

The superficial skin smoothing effect of onabotulinumtoxinA treatment (its effect on glabellar lines at facial repose) is less well understood than its effect on dynamic glabellar lines, which is intuitive, given its known muscle-relaxing mechanism of action. It is possible that the smoothing effect is a simple edematous response to intramuscular injection, although there is rarely visible edema in the direct region of injection. In addition, a short-term edematous response to injection would not account for the long-term durable smoothing effect observed (41% of patients still showed elimination of glabellar lines at facial repose 120 days after treatment).

To account for the early onset and long-lasting effect, it is likely that the result is due to local relaxation of transverse muscle cells, tissue remodeling in response to reduced muscle activity, or both. Piérard and Lapière proposed that glabellar frown lines that persist in repose are the consequence of progressive extracellular remodeling of the hypodermal connective tissue.[8] Their research suggests that repetitive traction movements and mechanical stimuli by muscle cells result in increased fibrocyte activity with thickening and shortening of the hypodermal septae. When such stimulus is removed using onabotulinumtoxinA treatment, the remodeling process could be reversed, resulting in a smoothing effect.

Regardless of the mechanism of action, the results of this study provide promising evidence of a potential for elimination of glabellar lines at repose.

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