

Remodeling of periorbital, temporal, glabellar, and crow's feet areas with hyaluronic acid and botulinum toxin

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Summary

Botulinum toxins are currently used to reduce facial muscle activity, and hyaluronic acid is used to correct volume loss. This study evaluates the combination of abobotulinumtoxinA (Dysport) and hyaluronic acid 20 mg/mL (Perlane) for rejuvenating specific areas of the upper face. Subjects ($n = 20$) with mild to moderate temporal volume loss as well as glabellar and/or periorbital rhytids were enrolled in this single-center, open-label, nonrandomized pilot study. Subjects were randomly assigned a number and treated with hyaluronic acid, divided between temporal and glabellar region, and abobotulinumtoxinA in the periorbital and glabellar region. A 1-month touch-up was given if needed. Subjects were evaluated by the investigator, and each subject completed a questionnaire at baseline and at 3, 6, and 9 months after treatment. For glabellar lines and crow's feet, median grades decreased from baseline at 1 month and at 3 months, but returned to baseline values at 6 months. For temporal assessments, the median grade decreased from baseline at 1, 3, and 6 months and returned to baseline at 9 months. Similar trends were observed in subjects' perceived age, perceived social and professional limitations, and desire to alter their facial appearance. Among subjects previously treated with botulinum toxin alone, 64% rated the combination treatment said "superior." Adverse effects were mild and transient. The combination of abobotulinumtoxinA and hyaluronic acid appears to rejuvenate the periorbital, temporal, glabellar, and crow's feet areas with minimal adverse effects.

Keywords: abobotulinumtoxinA, filler, upper face, rejuvenation

Introduction

Rejuvenation of the periorbital area has traditionally been limited to injections with botulinum toxins to reduce the activity of the orbicularis oculi muscle and the use of lasers to decrease the periorbital rhytids and

tighten the skin. These modalities do not, however, treat loss of soft tissue associated with aging and do nothing to remediate volume loss of upper facial areas such as the temporal. To address global aging of these areas, researchers have advocated the use of hyaluronic acid (HA) in conjunction with botulinum toxin.^{1–3}

As a soft tissue filler, HA offers important advantages. Cross-linked HA binds water, forming a viscous material that helps in hydration and tissue turgor, even as the filler is broken down. Because HA is chemically identical across species and tissues,⁴ immunogenicity and implant rejection are unlikely.^{1,5} Another

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Clinical Trial Registration. <http://clinicaltrials.gov/ct2/show/NCT01354743?term=upper+face+remodeling&rank=1>

Upper Facial Remodeling with Perlane-L and Dysport (DPL-2010)

Accepted for publication November 17, 2013

advantage is that HA has been shown to stimulate collagen synthesis.⁶ Finally, thicker HA molecules with high G' (a measure of gel hardness) have the potential to lift and sculpt areas of the upper face that lose volume and sag with age.

The purpose of this pilot study was to evaluate the combination of ABO and HA for upper face rejuvenation. In this report, the upper face refers only to the periorbital, temporal, glabellar, and crow's feet areas; it does not include the forehead.

Materials and methods

Subjects

Women ($n = 20$, aged 40–99 years [median 52.5], skin types 2–5) with mild to moderate temporal atrophy with glabellar or periorbital rhytids were enrolled in the single-center, open-label, nonrandomized, IRB-approved study in which all subjects provided signed informed consent. Because this was a pilot study, a formal justification for the sample size was not provided. Subjects of childbearing potential had a negative urine pregnancy test result at baseline and practiced a reliable method of contraception throughout the study. Exclusion criteria were injection(s) of botulinum toxin of any serotype during the previous 6 months; injection of semipermanent fillers in the glabella, periorbital area, or temporal area within the previous 12 months; injection of permanent fillers at any time; planned a facial cosmetic procedure during the study period or had prior cosmetic procedures that may affect the evaluation of response; facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or an inability to substantially lessen upper facial rhytids even by physically spreading them apart; previous cosmetic surgery of the upper face; laser resurfacing or soft tissue augmentation in the periocular areas 12 months before visit 1; medical condition or medications that might interfere with neuromuscular function; profound atrophy/excessive weakness of muscles in target areas of injection; history of facial nerve palsy; autoimmune disease or compromised immune system; infection; allergy to any component of the injected materials of study; or recent exposure to an investigational drug study.

Procedure

At the first (baseline) visit, subjects were randomly assigned a number and treated with 20 mg/mL HA filler (Perlane-L[®]; Mediscs Pharmaceutical Corporation,

Scottsdale, AZ, USA), up to 4 mL per subject, divided between temporal and glabellar regions, and abobotulinumtoxinA (ABO, Dysport[™]; Mediscs), 40–60 units in the periorbital and 50–80 units in the glabellar region. Injections into the glabellar region were performed using low-pressure, low-flow techniques to avoid superficial necrosis resulting from damage to blood vessels.⁷ According to the manufacturer, each syringe of filler was a sterile gel of HA generated by *Streptococcus* species of bacteria, chemically cross-linked with butanediol diglycidyl ether (BDDE), stabilized and suspended in phosphate-buffered saline at pH = 7 and concentration of 20 mg/mL with 0.3% lidocaine. The median particle size was between 750 and 1000 μm . As stated by the manufacturer, each vial of botulinum toxin contained 300 units (U) of freeze-dried ABO. Product was supplied in a single-use, sterile 300-unit vial for reconstitution with 0.9% sodium chloride injection USP (without preservative). Each vial was diluted with 1.5 mL nonpreserved normal saline to yield a solution of 10 units per 0.05 mL.

On the second visit, a 1-month touch-up was given if deemed necessary by the investigator, subject, or both. Subjects received only the amount remaining after initial injection (i.e., no more than 4 mL of HA between initial treatment and touch-up to temporal fossa/glabella and no more than 60 units of ABO to the periorbital and no more than 80 units to the glabellar region). If subject received touch-up treatment, he or she returned for 1-month follow-up visit. Subjects were evaluated at 3, 6, and 9 months and completed an author-developed questionnaire (Table 1) at each visit, including baseline. Photographs were taken under standardized conditions of position and lighting just before treatment and touch-up and at each follow-up visit. Investigator assessments were conducted at each visit, using the Rao-Goldman 5-Point Facial Wrinkle Scale (1 = wrinkle absent, 2 = shallow but visible, 3 = moderately deep, 4 = deep with well-defined edges, and 5 = very deep with redundant folds) and 4-Point Temporal Atrophy Scale (0 = no temporal atrophy, 1 = mild temporal atrophy, 2 = moderate temporal atrophy, and 3 = severe temporal atrophy). Adverse events were monitored and recorded at each visit.

Data analysis

The distributions of grades were tabulated at baseline, 1, 3, 6, and 9 months. Differences between proportions were tested for significance by Pearson's chi-square test. The initial comparisons included all five groups

Table 1 Subject questions

How well do you like the appearance of your face?*
How much does your current facial appearance bother you?*
Do you think your current facial appearance makes you look older in other's eyes?*
Do you think your current facial appearance limits your social or professional activities?*
How confident are you that your facial appearance is the best it can be?*
Would you like to alter the appearance of your upper face?*
My upper face area (temple and forehead) makes me look my age, years younger, or years older.
Would you recommend this treatment to a friend? (yes, no)
Would you do this treatment again? (yes, no)
Have you had treatment with botulinum toxin in the past? (yes, no)
If yes, did you think that this treatment was superior, equal, or inferior to treatment with botulinum toxins used alone?
Where did you receive botulinum toxin (location on face or other?)

*0 = not at all; 1 = somewhat; 2 = moderately; 3 = very much; 4 = completely.

(baseline, 1, 3, 6, and 9 months). Proportions at 1, 3, 6, and 9 months were then compared individually with baseline for each parameter. Because multiple comparisons were made, the Bonferroni correction was applied to the traditional $P = 0.05$ cutoff level. For example, glabellar scores of four groups were compared individually with baseline for a total of four nonindependent comparisons (i.e., all included baseline). The significance level was therefore adjusted by dividing 0.05 by 4 to arrive at $P = 0.0125$, the corrected cutoff level for significance.

Results

Eighteen subjects completed the study, and two were lost to follow up. Eight subjects required a touch-up procedure at the 1-month visit. In the following analyses, the 1-month data included scores of subjects not requiring a touch-up and the post-touch-up scores of subjects who received a touch-up treatment.

Investigator assessments

The median scores at each time point are presented in Figs 1–3.

Glabellar lines

The median grade (Fig. 1) decreased from baseline at 1 month and 3 months, but returned to its baseline value at 6 months and increased to 4.0 at 9 months. When proportions among grades for each time point were compared to baseline, the decrease was signifi-

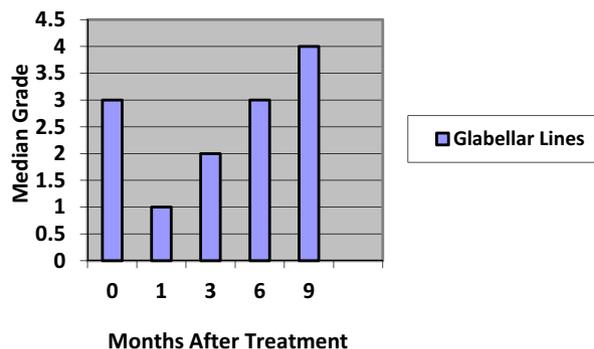


Figure 1 The median scores for glabellar lines at baseline (0 months) and follow-up visits.

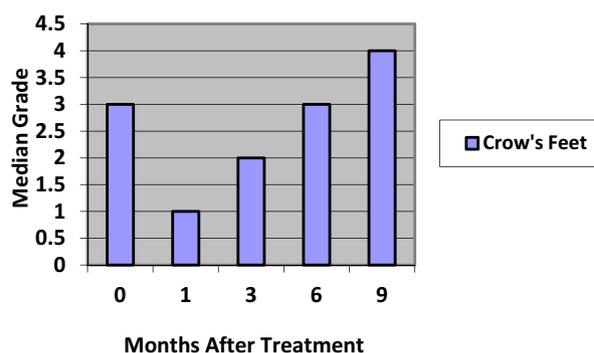


Figure 2 The median grade values for crow's feet at baseline (0 months) and follow-up visits.

cant at 1 month ($P < 0.0001$) and 3 months ($P = 0.0002$). These data suggest that improvement appears optimum at approximately 1 month and persists (although to a lesser degree) for an additional several months.

Crow's feet

The median grades (Fig. 2) decreased from baseline at 1 month and at 3 months, but returned to baseline at 6 months and increased to 4.0 at 9 months. When proportions among grades for each time point were compared to baseline, the decrease was significant at 1 month ($P = 0.0001$) and 3 months ($P = 0.0027$). These data suggest that improvement appears optimum at approximately 1 month and persists (although to a lesser degree) for an additional several months.

Temporal assessment score

The median grades (Fig. 3) decreased from baseline at 1, 3, and 6 months and returned to baseline at

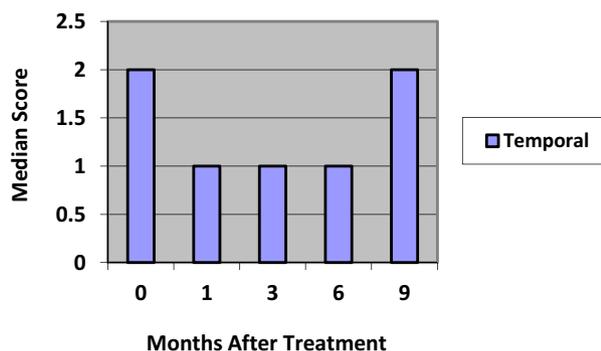


Figure 3 The median scores for temporal scores at baseline (0 months) and follow-up visits.

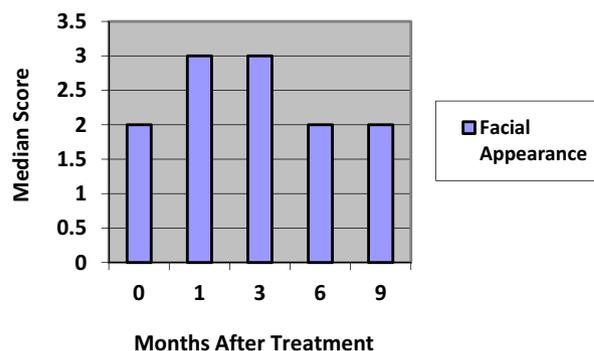


Figure 4 The median scores for how well subjects like their facial appearance at baseline (0 months) and follow-up visits.

9 months. When proportions among grades for each time point were compared to baseline, the decrease was significant at 1 month ($P < 0.0001$), 3 months ($P < 0.0001$), 6 months ($P < 0.0001$), and 9 months ($P = 0.0020$). These data suggest that improvement reached its maximum by approximately 1 month, persisted for at least 5 months and, for some subjects, persisted for up to 9 months. The significant difference at 9 months (when the median score returned to baseline) is due to a difference among the proportions of grades among the 18 subjects. At baseline, the grade was 2.0 for all subjects, while at 9 months seven subjects were graded at 1.0 and 11 subjects were graded at 2.0. At both baseline and 9 months, the median score was 2.0, a reflection of the low sensitivity of the median calculation.

Subject questionnaire responses

Responses to questions at each time point are shown in Figs 4–9.

When subjects were asked whether they liked their facial appearance, the median grade (Fig. 4) increased from baseline at 1 month and at 3 months, but returned to baseline at 6 months and did not change at 9 months. When proportions among grades for each time point were compared to baseline, the decrease was significant only at 1 month ($P = 0.0004$) and 3 months ($P = 0.0036$). These data suggest that improvement in facial appearance was optimum at approximately 1 month and persisted for two additional months.

Regarding how much subjects' current facial appearance bothered them, the median grade (Fig. 5) decreased slightly (2.0–1.0) from baseline at 1 month ($P = 0.0238$) and returned to its baseline value for the

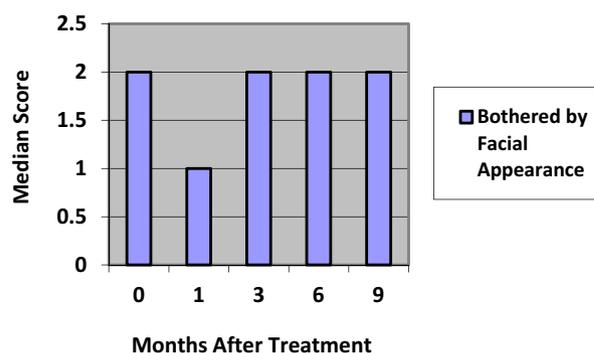


Figure 5 The median scores for how well subjects are bothered by their facial appearance at baseline (0 months) and follow-up visits.

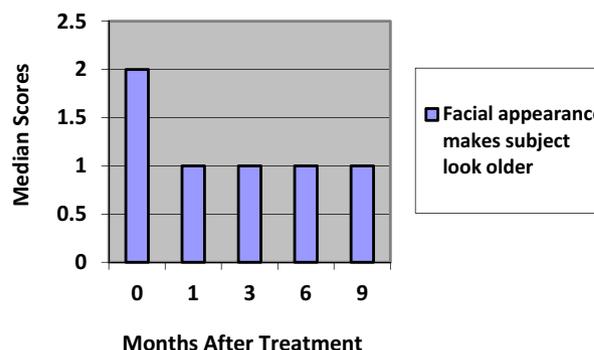


Figure 6 The median scores for how subjects' facial appearance makes subject look older in the eyes of others at baseline (0 months) and follow-up visits.

remainder of the study period. When proportions among grades for each time point were compared to baseline, the decrease was not significant at any time point. This suggests that facial appearance bothered

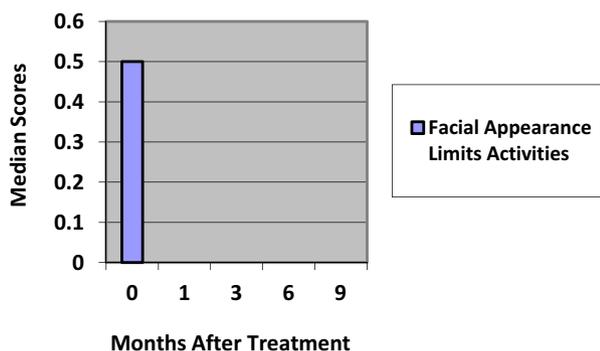


Figure 7 The median scores for how subjects' facial appearance limits social and professional activities at baseline (0 months) and follow-up visits.

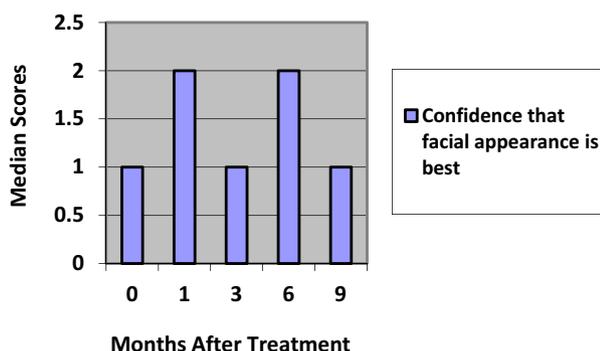


Figure 8 The median scores for subjects' confidence that their facial appearance is the best it can be at baseline (0 months) and follow-up visits.

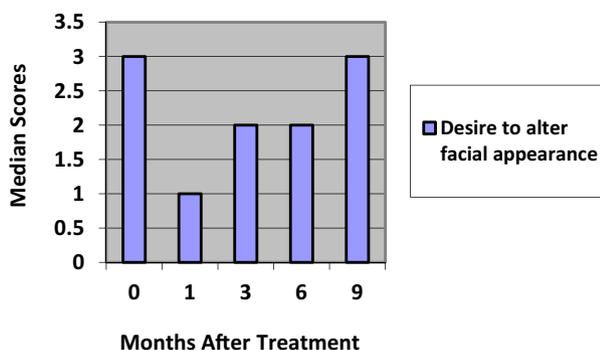


Figure 9 The median scores for whether or not subjects would like to alter their facial appearance at baseline (0 months) and follow-up visits.

some subjects slightly less at 1 month, but the effect did not increase or persist.

When subjects were asked whether their facial appearance made them look older to others, the med-

ian grade (Fig. 6) decreased from 2.0 to 1.0 at 1 month. The median value remained at 1.0 at 3, 6, and 9 months. When proportions among grades for each time point were compared to baseline, the decrease was significant at 1 month ($P = 0.0063$), but not at 3 months ($P = 0.0321$), 6 months ($P = 0.0517$), or 9 months ($P = 0.1687$). This apparent paradox may be due to the different distributions at later time points. These data suggest that improvement occurs at approximately 1 month and may continue to a small but variable degree for several additional months.

When subjects were asked whether their facial appearance limited their social and professional activities, the median scores (Fig. 7) were low (0.0–0.5) throughout the study and differences in proportions were not significant. This suggests that subjects did not believe their facial appearance would limit their activities at any time during the study period.

When subjects rated their confidence that their facial appearance was the best it could be, median scores (Fig. 8) increased and decreased during the study, suggesting that the changes were probably random. Differences in proportions from baseline were not significant at any time point, suggesting that subject confidence in facial appearance during the study did not change in a predictable manner.

When subjects were asked whether they would like to alter the appearance of their upper face, median scores (Fig. 9) decreased from baseline at 1, 3, and 6 months and returned to the baseline value at 9 months. When proportions among grades for each time point were compared to baseline, the decrease was significant at 1 month ($P = 0.0017$), 3 months ($P = 0.0011$), and 6 months ($P = 0.0030$). These data suggest that subject desire to alter the appearance of the upper face decreased to a minimum at approximately 1 month after treatment and the effect persisted up to 6 months and possibly an additional 2 months.

The number of subjects who stated they looked younger after treatment reached a maximum (14/20, 70%) 1 month after treatment, decreased at 3 months (8/18, 44%), and decreased further at 6 months (3/18, 17%) and 9 months (4/18, 22%). This suggests that the treatment effect for age appearance is strongest and approximately 1 month and begins to decrease at 2–3 months. At the end of the study, most subjects (14/18, 78%) stated that they would recommend the treatment to a friend. Most subjects (15/18, 83%) stated they would undergo the treatment again. Most subjects (11/18, 61%) had received a botulinum toxin treatment at an earlier time.

Among the 11 subjects who had received an earlier treatment of botulinum toxin alone, seven rated the combination treatment superior to botulinum toxin alone, three said equal, and 1 said inferior. Subjects had previously been treated on the forehead ($n = 3$), crow's feet ($n = 2$), glabella ($n = 2$), face ($n = 1$), eyebrow ($n = 1$), around eyes ($n = 2$), and the lip ($n = 1$). All three subjects who had not received an earlier treatment of botulinum toxin alone speculated that the combination results would have been superior to those of botulinum toxin alone.

Clinical photographs at baseline and at the 1-month follow-up visit are presented in Figs 10–12.

Adverse events

Adverse events are shown in Table 2. All were mild.

Discussion

To the author's knowledge, this is the first study of the use of ABO and HA in combination for rejuvenating the temporal and glabella areas. Prior work by Carruthers and Carruthers has demonstrated that combina-

tions of HA and botulinum toxins work synergistically for the treatment of glabellar rhytids⁸ but to our knowledge, this approach has not been applied to include the temporal face. This combination approach follows the consensus recommendations of Carruthers and colleagues² which state, "Current concepts of facial aging embrace the importance of changes resulting from volume loss as well as repetitive muscle activity over time."

Although the traditional goals of cosmetic procedures have been to optimize appearance and minimize adverse effects,⁹ treatment success also depends on patient satisfaction, which is the most important indicator of success in cosmetic surgery.^{10–12} This assertion is supported by Carruthers and colleagues¹³ who noted that because esthetic treatments are often initiated by patients (rather than physicians), the value of patient perspective is particularly important. Carruthers and colleagues used several questionnaires to evaluate various aspects of patient satisfaction after facial rejuvenation with either onabotulinumtoxinA, hyaluronic acid, or both. For example, female subjects in this study completed a Look and Feel of the Lips and Mouth Questionnaire designed to measure how the



Figure 10 A 62-year-old woman (a) before treatment and (b) 1 month after treatment with the combination of abobotulinumtoxinA and hyaluronic acid.

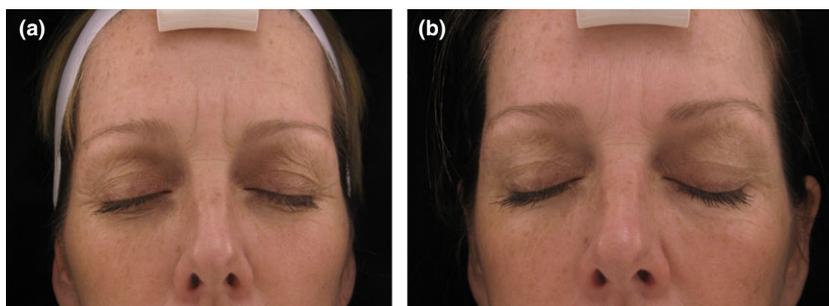


Figure 11 A 42-year-old woman (a) before treatment and (b) 1 month after treatment with the combination of abobotulinumtoxinA and hyaluronic acid.



Figure 12 A 53-year-old woman (a) before treatment and (b) 1 month after treatment with the combination of abobotulinumtoxinA and hyaluronic acid.

Table 2 Adverse events during study period

Adverse event (no. subjects)	Caused by treatment?
Muscle pain, temporal area ($n = 1$)	Perhaps
Hypertension ($n = 1$)	No
Muscle spasm ($n = 2$)	No
Anemia ($n = 1$)	No
Upper respiratory infection ($n = 1$)	No
Herniated disk ($n = 1$)	No
Inflammation ($n = 1$)	No
Blepharochalasis ($n = 1$)	Perhaps

patient's lip and mouth affected her facial appearance and made her look older, angry, sad, or unattractive.

Quality of life (QOL) has also been explored in this context. Numerous studies have shown that both surgical and nonsurgical cosmetic procedures can help to improve the QOL and psychological health in patients. They felt healthier, more satisfied with their appearance, and more confident after treatment.¹⁴ Data are limited, however, on the effects of nonsurgical cosmetic procedures on QOL; most studies have focused on patients with facial lipoatrophy associated with human immunodeficiency virus infection.⁹

The present study used a questionnaire developed by the authors to assess patient concerns about facial appearance throughout the study period.

Investigator assessments indicate that improvement in glabellar lines, crow's feet, and temporal assessment scores were greatest 1 month after a single treatment (with or without a touch-up) and the levels of improvement persisted for approximately two additional months. For glabellar lines, the improvement pattern is roughly comparable to that of an earlier study⁸ in which a combination of botulinum toxin A and HA provided "100% esthetic improvement" in the resting appearance of glabellar lines 1 week after the

addition of HA. In this study, however, improvement was evaluated using a Facial Wrinkle Scale and botulinum toxin was injected 1 week before HA rather than during the same treatment session as in the present study.

As for crow's feet, the improvement pattern was similar to that of glabellar lines, with maximum improvement at 1 month, persistence for several additional months, and return to baseline at 6 months. Results were similar to those of a previous study¹⁵ in which crow's feet were treated with botulinum toxin type A alone. In that study, change from baseline was greatest at 30 days (1 month) and assessment scores returned to baseline at approximately 120 days (4 months). Differences in duration of improvement may be due to the absence of HA in the latter treatment protocol.

Similar trends were observed in subject concerns about various aspects of their facial appearance such as perceived (upper face) age, perceived social and professional limitations, and desire to alter their facial appearance.

Regarding combination treatments, Fagien and colleagues¹⁶ suggested that patient satisfaction may improve when botulinum toxin type A is combined with other types of treatment and when more than one area of the face is treated. Brandt and colleagues³ reported that HA fillers alone or in combination with botulinum toxin can be used to smooth out fine wrinkles around the eyes and that this same combination produces optimal correction for deep glabellar furrows. Although the present study did not include a treatment arm of either ABO or HA alone for comparison, 64% of subjects previously treated with botulinum toxin rated our combination treatment as superior to botulinum toxin alone. Although our subject groups are small, our results are consistent with those of a recent study¹³ in which patient-reported outcomes showed that onabotulinumtoxinA in combination with HA

cohesive gel filler resulted in greater improvement in lower face rejuvenation than either treatment alone at most time points over 24 weeks.

Adverse events were mild and transient and limited to muscle pain in the temporal area and blepharochalasis. Limitations of the study include the small number of subjects, the absence of a control (e.g., either botulinum toxin or HA alone), and the uncertain recall of subjects treated previously with botulinum toxin alone.

The validity of a patient satisfaction questionnaire is also limited by patients' expectations and perceptions of treatment success and the absence of formal validation of the questionnaire. Some may want to appear younger, while others may wish to feel more attractive, rested, or less stressed.¹² Survey timing may also cause patient satisfaction ratings to fluctuate.¹⁶

The authors of the present study did not intend to address all the psychological aspects of cosmetic procedures. Our results, however, provide clues to the expectations and perceptions of patients desiring treatment of their upper face, thus providing a basis for further research and more effective communication between dermatologists and their cosmetic patients.

Conclusion

The combination of abobotulinumtoxinA and hyaluronic acid appears to rejuvenate the periorbital, temporal, glabellar, and crow's feet areas with minimal adverse effects. Future studies may help to evaluate optimal amounts of botulinum toxins and fillers for optimal outcomes. Patient satisfaction with this combination procedure is high and it is likely that use of this combination for an upper face lift will increase as physicians become more versed in combination treatments of the upper face.

Disclosures

This study was funded by a research grant by Medicis Pharmaceutical Corp. Dr. Beer is a consultant and shareholder for Allergan, Inc.

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