Persistence and Improvement of Nasolabial Fold Correction with Nonanimal-Stabilized Hyaluronic Acid 100,000 Gel Particles/mL Filler on Two Retreatment Schedules: Results up to 18 Months on Two Retreatment Schedules

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BACKGROUND Nonanimal-stabilized hyaluronic acid (NASHA) fillers are frequently used for facial soft tissue augmentation. Their long-term efficacy and the effects of different retreatment schedules are not well established.

OBJECTIVE This is an 18-month interim analysis of a 30-month study to evaluate the efficacy and persistence of NASHA 100,000 gel particles/mL filler with two different retreatment schedules.

METHODS This multicenter, randomized, evaluator blinded study enrolled 75 patients with moderate to severe nasolabial folds. Patients were randomized to retreatment of one nasolabial fold at 4.5 months and the contralateral fold at 9 months after correction of both folds at the initial visit.

RESULTS Wrinkle Severity Rating Scale scores improved significantly (p<.001) from baseline, with mean improvements ranging from 1.1 to 1.7 grades. Almost all patients (97%) responded satisfactorily, and the efficacy of the retreatment schedules did not differ significantly. Adverse events, primarily swelling and bruising, occurred in 33% of patients; none were serious.

CONCLUSION The improvements seen after initial treatment with NASHA 100,000 gel particles/mL filler persisted for up to 18 months with one retreatment. The response was equivalent for retreatment at 4.5 and 9 months.

Medicis funded the trial. The camera was on loan from Canfield.

Over the past two decades, soft tissue augmentation using injectable fillers has become a standard clinical approach for correcting age-related facial defects. The first commonly used injectable filler material was bovine collagen, which effectively corrects facial defects. However, the collagen is resorbed by the body within a few months. This limits its duration of action, with approximately 75% of the correction lost by 6 months after treatment.1 Stabilized hyaluronic acid gel fillers, first evaluated in 1998, provide good efficacy with a considerably longer duration of action.2,3 The first injectable stabilized hyaluronic acid filler approved by the US Food and Drug Administration, a nonanimal-stabilized hyaluronic acid (NASHA) 100,000 gel particles/mL filler, was introduced in the United States in 2003 and has been shown to be safe and effective while providing a much longer duration of action than that of collagen fillers.4 The use of hyaluronic acid gel fillers has increased considerably since that time, with several other stabilized hyaluronic acid gel fillers introduced to the US market. They are currently the most commonly used injectable fillers by a wide margin. According to the American Society for Aesthetic Plastic Surgery, hyaluronic acid gels account for approximately 80% of the nearly 2 million soft tissue filler injections performed in 2006.5

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The prolonged efficacy of stabilized hyaluronic acid gel fillers is attributed to cross-linking between hyaluronic acid polymers and to gradual absorption of water as the filler degrades. Some data suggest that stabilized hyaluronic gels stimulate collagen synthesis and inhibit collagen breakdown, which may contribute to their effectiveness and long duration of action. Despite the long duration of action, retreatment is typical because the efficacy of the filler gradually declines as it is resorbed by the body.

Several studies have demonstrated that NASHA and other stabilized hyaluronic acid gels are safe, effective, and well tolerated for correcting defects in various facial sites, particularly in the lower face. These studies had durations of 1 year or less and therefore did not investigate retreatment schedules or the longer-term effects of stabilized hyaluronic acid gel fillers. The authors are not aware of any published trials that evaluated different retreatment schedules or presented data on the efficacy and safety of stabilized hyaluronic gel fillers over periods longer than 6 months. This interim analysis evaluates the efficacy and persistence of NASHA 100,000 gel particles/mL filler for the correction of nasolabial folds at up to 18 months after the initial treatment and compared the effects of 4.5- and 9-month retreatment schedules.

Methods

Study Design

This is a multicenter, randomized, evaluator-blinded study with a planned enrollment of 75 patients at three centers. The study used a bilateral comparison design. The planned study duration is 30 months; this is an 18-month report. All patients received an injection of NASHA 100,000 gel particles/mL filler in both nasolabial folds at the first visit, with touch-up injections as needed at the 2-week follow-up visit. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review board. Patients were then randomized to retreatment of one nasolabial fold at 4.5 months and retreatment of the other nasolabial fold at 9 months. The goal of each treatment was to achieve an optimal cosmetic result, defined as the best result possible for the individual patient as determined by the investigator providing the treatment.

The randomization determined which nasolabial fold was retreated at 4.5 months. Patients randomized to schedule A had their right nasolabial fold treated at 4.5 months and their left fold treated at 9 months; patients randomized to schedule B were treated in the reverse order. Thus, each patient served as his or her own control, with outcomes compared between the contralateral sides. Randomization was balanced within each study site. To ensure evaluator blinding, one investigator administered the treatments and a second investigator conducted the evaluations. The trial patients were not blinded to their treatment.

Patients were required to be adult, to be not pregnant or breastfeeding, and to have nasolabial folds with a severity of 3 or 4 on the Wrinkle Severity Rating Scale. Exclusion criteria included skin disease, laser, or chemical peel procedures within 6 months and facial tissue augmentation or other aesthetic facial surgery within 9 months. Patients were required to abstain from exclusionary procedures for the duration of the trial.

Injection Materials

The NASHA 100,000 gel particles/mL filler used was Restylane (Medicis Aesthetics, Scottsdale, AZ [Restylane is a trademark of HA North American Sales AB]). The gel is supplied as a 20 mg/mL suspension in 1.0 mL of a physiologic saline solution (pH 7.0), which is packaged in a disposable 1.0-mL syringe with a sterilized 30-gauge 0.5-inch needle.

Injection Technique

The injection site was cleaned with an appropriate antiseptic solution, and the filler was injected into the mid to deep dermis. The injection technique, depth of injection, and volume of administered
material were at the discretion of the investigator performing the injection. Injection techniques used included linear threading, a series of punctal injections, or a combination of the two. Regardless of the technique, the goal of treatment was a 100% correction of the nasolabial fold with no overcorrection.

**Follow-Up Visits**

Each study participant made at least seven visits. During Visit 1, patients who gave informed consent underwent a screening evaluation, baseline assessment, randomization, and initial treatment. This interim study includes follow-up visits at Week 2 (Visit 2), at 4.5 months (Visit 3), Month 9 (Visit 4), Month 12 (Visit 5), Month 15 (Visit 6), and Month 18 (Visit 7). Touch-up treatments could be given at the treating investigator’s discretion at the 2-week follow-up visit (Visit 2). If this occurred, the visit was redesignated as Visit T, a new Visit 2 was scheduled 2 weeks later, and Visit 3 was scheduled for 4.5 months after the touch-up treatment. At Visit 3 (Month 4.5), one side of the nasolabial fold was retreated to optimal cosmetic correction. At Visit 4 (Month 9), the contralateral side was retreated. No touch-up treatments were performed after either retreatment. At each follow-up visit, patients were photographed with a standard camera (Canfield, Fairfield, NJ) and assessed for efficacy and adverse events. For the efficacy assessment, both the evaluating investigator and the patient evaluated the nasolabial folds using the Wrinkle Severity Rating Scale and the Global Aesthetic Improvement Scale. Assessments were done before any treatment was provided.

**Study Measures**

The primary efficacy measure for this interim report was the evaluator’s rating on the Wrinkle Severity Rating Scale in the intent-to-treat population. Secondary efficacy measures included the patient’s self-rating on this scale and the evaluator and patient ratings on the Global Aesthetic Improvement Scale.

**Wrinkle Severity Rating Scale**

The Wrinkle Severity Rating Scale is a validated 5-point scale based on the current appearance rather than a comparison to the pretreatment appearance. The ratings are 1 = absent (no visible fold), 2 = mild (shallow fold), 3 = moderate (moderate fold, not visible when stretched), 4 = severe (prominent, long, deep folds), and 5 = extreme (extremely deep and long folds; detrimental to facial appearance).

**Global Aesthetic Improvement Scale**

The Global Aesthetic Improvement Scale is a 5-point scale that rates global aesthetic improvement from the pretreatment appearance. The ratings are worse, no change, improved, much improved, and very much improved.

Assessments using both the Wrinkle Severity Rating Scale and the Global Aesthetic Improvement Scale were made by the treating investigator at baseline to determine whether the patient met the study inclusion and exclusion criteria and by both the patient and the blinded, independent evaluating investigator at baseline and at each follow-up visit. Each nasolabial fold was rated separately (right and left). Satisfactory response was defined as an improvement of at least one grade on the evaluator’s Wrinkle Severity Rating Scale.

**Results**

**Patient Characteristics and Demographics**

A total of 75 participants enrolled in the study. The participants’ mean age (± SD) was 53.8 (± 8.41) years. The majority were female (93%) and white (67%). Eight percent of the participants had a history of prior augmentation. There were no statistically significant demographic differences between the two treatment groups (Table 1). Of the 75 participants, 39 were randomized to schedule A (right fold at 4.5 months, left at 9 months) and 36 were randomized to schedule B (left fold at 4.5 months, right at 9 months). A total of 44 patients received a touch-up treatment, 67 received the 4.5-month retreatment, and 63 received the 9-month...
TABLE 1. Demographic and Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Schedule A (right side first)</th>
<th>Schedule B (left side first)</th>
<th>All Patients</th>
<th>p Value*</th>
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<tr>
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<td>38</td>
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<td>Median (range)</td>
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<td>52.5 (38–73)</td>
<td>54 (26–73)</td>
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<td><strong>Age distribution, n (%)</strong></td>
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<td>&lt;50 years</td>
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<td>4 (11)</td>
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<td><strong>Female gender, n (%)</strong></td>
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<td>38 (97)</td>
<td>32 (89)</td>
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<td>10 (28)</td>
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<td>Prior augmentation, n (%)</td>
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<td>1 (3)</td>
<td>5 (14)</td>
<td>6 (8)</td>
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</table>

*p value from exact χ² test for the categorical variables and from an analysis of variance with term for treatment for the continuous variables.

retraining and completed their 18-month follow-up visit. The volume of NASHA 100,000 gel particles/mL filler injected was not significantly different between the two retraining schedules (p = .206).

**Efficacy**

The satisfactory response rate at 18 months was 97%, with an improvement of at least one grade in the evaluator’s Wrinkle Severity Rating Scale score occurring in 61 patients of the 63 who completed the study. A majority of patients, up to 57%, improved by at least two grades at up to 18 months post-retraining. Of these, 36 improved at least two grades on the side treated at 4.5 months, and 34 improved at least two grades on the side treated at 9 months. The median Wrinkle Severity Rating Scale score improved from 3 (moderate) at baseline to 2 (mild) at 18 months, with approximately 33% of folds improving to Grade 1 (no visible fold; Figure 1). Response was stable and persisted over time, with little or no significant difference between 4.5- and 9-month retraining schedules.

Evaluator mean Wrinkle Severity Rating Scale score for patients in both treatment arms significantly improved at each time point compared to baseline (p < .001; Figure 2). From a mean (+ SD) baseline score of 3.4 (± 0.62), mean Wrinkle Severity Rating Scale scores improved by 1.7 grades at 2 weeks after the initial therapy. A mean improvement ranging from 1.1 to 1.8 grades was maintained throughout the trial. There were no significant differences between the two treatment arms at any time point (p values ranged from .08 to .66), although there was a nonsignificant trend (p = .102) toward a better score at 9 months for folds that were retreated at 4.5 months. Patient Wrinkle Severity Rating Scale scores were somewhat lower than those of the investigators but showed similar sustained improvement.

Investigator ratings on the Global Aesthetic Improvement Scale were 3.6 points (much improved) at 2 weeks, 3.4 points before the 4.5-month retraining, at least 3.4 points before the 9-month retraining, 3.5 points at 12 months, at least 3.6 points at 15 months, and 3.7 points at 18 months. Average patient Global Aesthetic Improvement Scale ratings improved from 2.4 points at the touch-up visit to 3.8 points at the 18-month visit. At no time did the improvements differ according to whether the retraining was performed at 4.5 or 9 months.
Safety Analysis

No allergic reactions were reported by patients in either treatment group. Adverse events were reported by 33% of the participants. The most common adverse events were swelling (23%) and/or bruising (20%) at the injection site. These adverse events resolved over time. Other adverse events occurred in less than 5% of the participants. No treatment-related adverse event was rated as serious.

Discussion

These results demonstrate that NASHA 100,000 gel particles/mL filler is efficacious and safe for correcting nasolabial folds according to both evaluator and patient Wrinkle Severity Rating Scale and Global Aesthetic Improvement Scale measurements. With retreatment at 4.5 or 9 months, the efficacy persists for up to 18 months after the initial treatment. Almost all patients (97%) had at least one grade improvement at 18 months (13.5 or 9 months posttreatment) and a majority, up to 57%, had an improvement of at least two grades. The short-term results of this study are consistent with earlier studies of NASHA 100,000 gel particles/mL filler, which showed significant improvement at periods up to 6 months posttreatment.4,7-9

Efficacy and persistence to 18 months were comparable whether retreatment occurred at 4.5 or 9 months after the initial treatment. Although less convenient for the patient, the trend toward improved correction at 9 months for the 4.5-month retreatment schedule suggests that early retreatment may halt or slow deterioration of the initial treatment as well as result in a continued response for at least 1 year without additional treatment. Given the
absence of data for follow-up periods longer than 18 months, the possibility remains that the early retreatment correction will deteriorate sooner than the late retreatment correction. Thus, the available data do not clearly favor either retreatment schedule over the other. Until long-term data are available, decisions on retreatment schedules should be based on discussions between the patient and the physician and should consider both the patient’s convenience and the available data on the duration of effect.

The mean Wrinkle Severity Rating Scale scores improved steadily after retreatment, with the degree of correction at 18 months almost as high as the correction at 2 weeks. This result is the opposite of what would be expected if degradation of the NASHA gel was the primary determinant of the duration of effect.

It is not clear why early retreatment at 4.5 months provides long-term results equivalent to those of late retreatment at 9 months or why the level of correction improved after retreatment. The earlier retreatment schedule may slow the rate of resorption of the gel after retreatment, perhaps by maintaining tissue expansile tension. This effect may be amplified by biologic activity: fibroblasts that are stretched by mechanical tension may stimulate new collagen production and inhibit collagen breakdown. These effects could persist longer than the space-filling effects of the injected gel. The combination of slow resorption and biologic activity stimulated by gel injection that compensates for resorption may account for the prolonged efficacy of the NASHA gel and the equivalence of long-term results from early and late retreatment.

In conclusion, soft tissue augmentation with injectable NASHA 100,000 gel particles/mL filler is safe and effective for correcting nasolabial fold defects. With retreatment at 4.5 or 9 months, the efficacy of the NASHA 100,000 gel particles/mL filler persists for up to 18 months from the initial treatment.

Figure 2. Mean investigator Wrinkle Severity Rating Scale (WSRS) scores (intent-to-treat population). Error bars represent the standard deviation.
REFERENCES


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COMMENTARY

Physicians and patients have casually noted for years that volume requirements are less and that treatment intervals grow longer with repeat injections of hyaluronic acid undertaken to maintain optimal correction of nasolabial folds. This elegant study proves an 18-month persistence of optimal correction achieved after one repeat treatment with 20 mg/cm³ cross-linked hyaluronic acid (Restylane). Recent studies analyzing repeat treatment with a 24 mg/cm³ cross-linked hyaluronic acid (Juvederm) have produced similar results. 1,2 Explanations may be attributed to stimulation of de novo collagen synthesis 3 or perhaps by accumulation of product.

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References

