Persistence of Nonanimal Stabilized Hyaluronic Acid Filler in Nasolabial Fold Correction: An Investigator and Participant Evaluation

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Building on the benchmarks set by bovine collagen, nonanimal stabilized hyaluronic acid fillers have been increasingly used in the United States for nasolabial fold (NLF) correction since initial approval from the US Food and Drug Administration in late 2003. More durable and less immunogenic than collagen, nonanimal stabilized hyaluronic acid fillers have been shown to be safe and effective in the treatment of moderate to severe NLFs.

A recent study evaluating NLF correction with 2 retreatment schedules demonstrated a duration of effect of up to 18 months as assessed by blinded evaluators. The authors reviewed the results of this study and included their perspective on improvement as assessed by participants and the treating investigator.

This randomized study included 75 participants at 3 centers whose NLFs were rated as 3 or 4 on the Wrinkle Severity Rating Scale (WSRS). During the initial visit, each participant's NLFs were treated, with touch-up injections at 2 weeks as needed. For each participant, 1 NLF was re-treated at 4.5 months and the other was re-treated at 9 months. During an 18-month period, each participant had at least 7 follow-up visits. At baseline, the treating investigator, blinded evaluator, and participant assessed the NLFs using the WSRS scores and the Global Aesthetic Improvement Scale.

For both retreatment schedules, the majority of participants demonstrated significant improvement in both WSRS and Global Aesthetic Improvement Scale scores for up to 18 months by both investigator and participant assessments.

This prolonged duration of persistence is likely to increase patient satisfaction and improve patient retention.

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In recent years, the number of cosmetic procedures performed in the United States has increased. Statistics from the American Society of Aesthetic Plastic Surgery show that more than 10 million of these procedures were performed in 2008, of which 83% were nonsurgical.[1] Nearly 1.3 million procedures involved injection of hyaluronic acid (HA)–based dermal fillers, demonstrating their standing as the most popular, nonpermanent injectable materials currently available for soft tissue facial correction.[1]

Before the development of HA-based dermal filler agents, collagen was widely used but provided only temporary improvement (about 2–3 months).[2] Nonanimal stabilized HA (NASHA) dermal fillers have been shown to be safe and effective and to have a longer duration of action than collagen while avoiding the risks for immunogenicity and hypersensitivity.[2,3] In a study comparing Restylane, a small gel particle (SGP) NASHA filler, with Zyplast, a collagen filler for the treatment of nasolabial folds (NLFs), investigators and patients judged SGP-HA to have a significantly more durable effect than collagen at 6 months posttreatment.[4]

A recent study investigated the persistence of the same SGP-HA filler with 100,000 gel particles/mL up to 18 months following treatment in participants with moderate to severe NLFs.[5] This was a multicenter, randomized, evaluator-blinded study in which 75 participants were enrolled. In this study, both NLFs were injected with SGP-HA at baseline (including an optional touch-up as needed at the 2-week follow-up visit). One NLF was then re-treated at 4.5 months, and the contralateral NLF was re-treated at 9 months after initial treatment. Correction in both NLFs was assessed at 18 months. In this within-patient comparison, each participant served as his or her own control, allowing researchers to compare baseline wrinkle severity against the results of subsequent evaluations.

STUDY OBJECTIVES

The primary objective was to evaluate the duration of NLF correction for the 2 retreatment schedules based on the proportion of participants with improvement of at least 1 grade from baseline in the Wrinkle Severity Rating Scale (WSRS) as assessed by the blinded evaluator at 18 months (Table 1). Secondary objectives included blinded evaluator WSRS assessments at all follow-up visits (ie, at week 2 and at 4.5, 9, 12, and 15 months after initial treatment); participant WSRS ratings at all follow-up visits; and investigator and participant ratings of improvement from baseline using the Global Aesthetic Improvement Scale (GAIS) at all follow-up visits up to 18 months (Table 2). Participant assessment of improvement is important because of the role it potentially plays in determining patient satisfaction, which may influence patient retention.

Table Not Available Online

TABLE 2

Breakdown of the 5-Point GAIS

0	Worse than the original condition
1	No change from baseline
2	Improved from baseline
3	Much improved from baseline but not optimal for this participant
4	Very much improved; the optimal cosmetic result in this participant

Abbreviation: GAIS, Global Aesthetic Improvement Scale.

STUDY PARTICIPANTS

Adult male participants and nonpregnant and nonbreast-feeding female participants with NLFs with a WSRS score of 3 (moderate) or 4 (severe) were included in the study. Participants were excluded from the study if they had active or chronic skin disease, had undergone laser or chemical peel procedures within 6 months, or had facial tissue augmentation or aesthetic facial surgery within 9 months. No investigational drugs or devices could be used within 30 days of study treatment. Of the 75 participants enrolled in the study, 69 (92%) were naïve to treatment, with no history of prior augmentation.

INJECTION TECHNIQUE

The treatment site was cleaned with antiseptic solution and, using a thin gauge needle, SGP-HA filler was administered into the deep dermis, the surface layer of the subcutis, or both. Although the depth of injection and

the quantity of SGP-HA varied according to the treating investigator's evaluation, a maximum dose of 1.5 mL per treatment session was recommended to achieve 100% correction of each NLF. Investigators used either the linear threading or serial puncture injection technique, or a combination of the two. Forty-four participants (59%) received a touch-up treatment 2 weeks after initial treatment. No touch-up visits were provided after the 4.5- and 9-month follow-up.

RESULTS

Assessment by the blinded evaluators at 18 months demonstrated that nearly all participants had at least 1 grade improvement in WSRS score, whether they were re-treated at 4.5 or 9 months (97% and 95%, respectively), with a majority of participants (57%) demonstrating improvement of at least 2 grades (Table 3 and Table 4). At the same visit, the majority of study participants assessed their improvement in WSRS scores as being at least 1 grade on

TABLE 3

Blinded Evaluator's Assessment: Proportion of Participants With at Least 1 Grade Improvement in WSRS from Baseline

	Side Assigned to Retreatment at 4.5 mo[a]			Side Assigned to Retreatment at 9 mo[a]		
Visit	n/N	*P*(SD%)	95% CI	n/N	*P*(SD%)	95% CI
2 wk	66/71	93.0 (3.0)	84.3%–97.7%	69/71	97.2 (2.0)	90.2%–99.7%
4.5 mo	56/66	84.9 (4.4)	73.9%–92.5%	54/67	80.6 (4.8)	69.1%–89.2%
9 mo	56/64	87.5 (4.1)	76.9%–94.5%	53/65	81.5 (4.8)	70.0%–90.1%
12 mo	60/62	96.8 (2.2)	88.8%–99.6%	57/63	90.5 (3.7)	80.4%–96.4%
15 mo	58/63	92.1 (3.4)	82.4%–97.4%	58/64	90.6 (3.6)	80.7%–96.5%
18 mo	61/63	96.8 (2.2)	89.0%–99.6%	61/64	95.3 (2.6)	86.9%–99.0%

Abbreviations: CI, confidence interval; SD, standard deviation; WSRS, Wrinkle Severity Rating Scale.
[a] Visits where participants were re-treated, in which grading was performed before retreatment.

TABLE 4

Blinded Evaluator's Assessment: Mean WSRS and Mean Improvement in WSRS from Baseline

	Side Assigned to Retreatment at 4.5 mo[a]			Side Assigned to Retreatment at 9 mo[a]		
Visit	No.	WSRS Mean (SD)	Change From Baseline, Mean (SD)	No.	WSRS, Mean (SD)	Change From Baseline Mean (SD)[b]
Screening	74	3.4 (0.60)	N/A	75	3.4 (0.60)	N/A
2 wk	71	1.7 (0.81)	1.7 (0.81)	71	1.7 (0.72)	1.7 (0.71)
4.5 mo	66	2.3 (0.78)	1.1 (0.72)	67	2.3 (0.89)	1.1 (0.83)
9 mo	64	2.2 (0.82)	1.3 (0.73)	65	2.3 (0.85)	1.1 (0.84)
12 mo	62	2.1 (0.65)	1.3 (0.65)	63	2.1 (0.78)	1.3 (0.80)
15 mo	63	2.0 (0.72)	1.5 (0.74)	64	2.0 (0.73)	1.4 (0.75)
18 mo	63	1.8 (0.65)	1.7 (0.74)	64	1.8 (0.70)	1.6 (0.77)

Abbreviations: SD, standard deviation; WSRS, Wrinkle Severity Rating Scale.
[a] Visits where participants were re-treated, in which grading was performed before retreatment.
[b] Mean changes from baseline are significantly different from 0 at all follow-up visits (paired *t*-test $P<.001$).

TABLE 5

Participants With at Least 1 Grade Improvement in GAIS From Baseline: Assessment by Treating Investigator and Participants

Visit	Side Re-treated at 4.5 mo[a]		Side Re-treated at 9 mo[a]	
	Treating Investigator, n (%)	Participant, n (%)	Treating Investigator, n (%)[b]	Participant, n (%)[c]
2 wk	72 (100)	71 (100)	71 (100)	70 (100)
4.5 mo	67 (100)	67 (100)	66 (98.5)	66 (98.5)
9 mo	64 (98.5)	64 (98.5)	64 (98.5)	61 (93.9)
12 mo	64 (100)	63 (98.4)	64 (100)	63 (98.4)
15 mo	64 (100)	62 (96.9)	64 (100)	63 (98.4)
18 mo	63 (100)	62 (96.9)	62 (98.4)	61 (95.3)

Abbbreviation: GAIS, Global Aesthetic Improvement Scale.
[a] Visits where participants were re-treated, in which grading was performed before retreatment.
[b] Based on data from 71 participants.
[c] Based on data from 70 participants.

TABLE 6

Mean GAIS Score: Assessment by Treating Investigator and Participants

Visit	Side Re-treated at 4.5 mo, Mean (SD)[a]		Side Re-treated at 9 mo, Mean (SD)[a]	
	Treating Investigator	Participants	Treating Investigator[b]	Participant[c]
2 wk	3.6 (0.55)	3.2 (0.79)	3.6 (0.55)	3.2 (0.78)
4.5 mo	3.4 (0.65)	2.9 (0.77)	3.4 (0.71)	2.9 (0.79)
9 mo	3.5 (0.69)	3.0 (0.83)	3.4 (0.71)	2.8 (0.89)
12 mo	3.5 (0.62)	3.1 (0.75)	3.5 (0.62)	3.2 (0.77)
15 mo	3.7 (0.49)	3.1 (0.81)	3.6 (0.52)	3.1 (0.80)
18 mo	3.7 (0.54)	3.2 (0.88)	3.7 (0.57)	3.2 (0.92)

Abbbreviation: GAIS, Global Aesthetic Improvement Scale.
[a] Mean improvements are significantly different from 1 (no change) at all follow-up visits (1-sample *t*-test $P<.001$).
[b] Based on data from 71 participants.
[c] Based on data from 70 participants.

the side re-treated at 4.5 months (85%) and the side re-treated at 9 months (78%). In addition, most participants assessed by the treating investigator (98% to 100%) and self-assessed participants (95% to 97%) had an improvement in GAIS score of at least 1 grade at all follow-up visits up to 18 months compared with baseline appearance (Table 5). According to the treating investigator's assessment at 18 months, the mean GAIS score was the same (3.7) for both sides, with no difference by retreatment schedule. Similarly, the participant mean GAIS assessment at 18 months was the same (3.2) for both re-treated sides (Table 6). The mean improvement in GAIS score from baseline at all visits was statistically significant ($P<.001$) for follow-up assessments by the treating investigator and the participant. There were no differences in improvement between the 2 retreatment schedules.

DISCUSSION

In this study, the WSRS scores continued to show statistical significance after initial treatment through 18 months

for both retreatment schedules. Based on the anticipated gradual degradation of SGP-HA material, it has been surmised that this effect may be due to the mechanical stretching of the dermis that occurs in SGP-HA–injected areas, leading to the activation of dermal fibroblasts that result in the stimulation and production of new collagen fibers.[5,6] In addition, throughout the process of degradation, water is attracted to the site of implantation and continues to bind to HA molecules and maintains space as the filler material is physiologically reabsorbed.[7]

The results of this study confirm what the authors observe in patients who present in their practices when they follow a similar routine retreatment schedule of every 4 to 6 months. Because early retreatment seems to halt or slow deterioration of the initial treatment, patients do not have to wait until they experience an increase in wrinkle severity to receive a planned retreatment. Because patients receive consistent results and maintain good correction for extended periods, patient satisfaction is increased, which leads to improved patient retention. The duration of correction is sufficient to warrant treatments with this injectable material at the identified intervals.

CONCLUSION

In the 2008 study by Narins and colleagues,[5] treatment of NLFs with the SGP-HA 100,000 gel particles/mL filler was shown to be safe and effective, with an 18-month correction duration when initial treatment was followed by retreatment at either 4.5 or 9 months. The improvement in NLF severity from baseline, as assessed by the blinded evaluator, treating investigator, and participants, was statistically significant. Although the investigator's assessment of efficacy is a valued outcome measure, participants' self-assessment plays an essential role by reflecting long-term patient satisfaction and patient retention, and as such should be seriously considered.

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