Although the product is not currently marketed for breast enhancement, it is estimated that tens of thousands of women have undergone breast treatments with stabilized hyaluronic acid (HA) gel, and therefore, long-term follow-up data are of great relevance.

This prospective study assessed gel degradation rates using magnetic resonance imaging and long-term safety and efficacy outcomes, 24 months after breast enhancement with HA gel injections.

**MATERIALS AND METHODS**

An open, multicenter study was conducted across 6 centers (France and Sweden) in eligible women (brassiere cup size, A/B) aged 25–60 years. Subjects received an injection of up to 100 mL of HA gel (Macrolane VRF30, Q-Med AB, Uppsala, Sweden) into each breast (between the glandular tissue and fibroareolar tissue). Subjects received 1 treatment of HA gel (maximum, 100 mL/breast); a subgroup underwent retreatment 9 months later. Follow-up was conducted for 24 months after last treatment; endpoints included magnetic resonance imaging for estimation of gel degradation, adverse events, breast examinations, Global Esthetic Improvement Scale, and satisfaction ratings. Seventy-one subjects received 1 treatment, with 22 (31%) receiving retreatment after 9 months. Twenty-four months after last treatment, the mean percentage of remaining gel was 17% in the single-treatment group and 21% in the retreatment group; complete degradation had not occurred in any subject. The most commonly reported treatment-related adverse events were implant-site nodules, medical device implantation events, capsular contracture associated with breast implant, and injection-site nodules; most were mild to moderate and required no intervention. Based on subject Global Esthetic Improvement Scale ratings, 36% of breasts in the single-treatment group and 50% of breasts in the retreatment group were improved 24 months after last treatment, but subject satisfaction had returned to baseline levels. Some gel remained in all subjects 24 months after last treatment. Although single treatment and retreatment were generally well tolerated, physicians need to be aware of common treatment-related complications to manage them adequately.

**Summary:** Long-term follow-up data following 2 breast enhancement treatments with stabilized hyaluronic acid (HA) gel are limited. Although HA gel is no longer marketed for breast enhancement, there is a clinical need for information about follow-up of previously treated women. A multicenter, noncomparative study was conducted in women seeking breast enhancement. Subjects received 1 treatment of HA gel (maximum, 100 mL/breast); a subgroup underwent retreatment 9 months later. Follow-up was conducted for 24 months after last treatment; endpoints included magnetic resonance imaging for estimation of gel degradation, adverse events, breast examinations, Global Esthetic Improvement Scale, and satisfaction ratings. Seventy-one subjects received 1 treatment, with 22 (31%) receiving retreatment after 9 months. Twenty-four months after last treatment, the mean percentage of remaining gel was 17% in the single-treatment group and 21% in the retreatment group; complete degradation had not occurred in any subject. The most commonly reported treatment-related adverse events were implant-site nodules, medical device implantation events, capsular contracture associated with breast implant, and injection-site nodules; most were mild to moderate and required no intervention. Based on subject Global Esthetic Improvement Scale ratings, 36% of breasts in the single-treatment group and 50% of breasts in the retreatment group were improved 24 months after last treatment, but subject satisfaction had returned to baseline levels. Some gel remained in all subjects 24 months after last treatment. Although single treatment and retreatment were generally well tolerated, physicians need to be aware of common treatment-related complications to manage them adequately. (Plast Reconstr Surg Glob Open 2015;3:e575; doi: 10.1097/GOX.0000000000000554; Published online 8 December 2015.)
and the pectoralis major muscle fascia), according to the instructions for use, after local anesthetic. A subgroup was offered retreatment 9 months later. Touch-up treatments of up to 20 mL per breast were permitted after initial treatment and retreatment in cases of unevenness and/or asymmetry. The study was performed in accordance with the Declaration of Helsinki and approved by local ethical committees. Subjects provided written informed consent.

Degradation and localization of HA gel was assessed by magnetic resonance imaging at baseline and 12 and 24 months after a single injection or at baseline; 6 months after initial injection; 0–2 weeks before retreatment; and 6, 9, and 15 months after retreatment. The study was performed in accordance with the Declaration of Helsinki and approved by local ethical committees. Subjects provided written informed consent.

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RESULTS

Seventy-one subjects received an initial injection of HA gel, and 22 subjects underwent retreatment (Table 1).

Degradation and Localization of HA Gel

The percentage of remaining gel at 24 months after initial injection was variable among individuals but was higher in the retreatment group [mean: 28% (range: 4–72%)] compared with the single-treatment group [mean: 17% (range: 4–30%)]. However, 24 months after the last treatment, there was no difference in remaining gel between the 2 treatment groups.

Adverse Events

In the single-treatment group, 127 AEs in 33 subjects were considered related to HA gel or injection procedure; 96% were of mild-to-moderate intensity, and most (87%) did not require intervention (Table 2). One subject had a serious AE (implant-site bacterial infection caused by *Peptostreptococcus* species), judged to be related to the injection procedure but not to the study product. The breast was drained, and the infection was treated with antibiotics. There was some residual scarring at the incision site. Common AEs included implant-site nodules (n = 15), medical device implantation events (ie, perception or unevenness of the study product; n = 13), and capsular contracture (n = 11). These AEs were judged to be of mild-to-moderate intensity, had a mean time to onset of 2–5.5 months, and resolved within 3–10 months.

In the retreatment group, 70 AEs in 20 subjects were considered related to the study product or injection procedure; 46 occurred in the 24 months after retreatment. Over the 24-month follow-up for the retreatment group, 92% of treatment-related AEs were mild to moderate, and 70% did not require intervention (Table 2). Two subjects had serious postoperative implant-site infections after retreatment. One case (caused by *Staphylococcus aureus*) was severe and judged to be related to the injection procedure but not to the study product; the other case of infection could not be determined, was of moderate severity, and was judged to be related to the study product and injection procedure. Both subjects were treated with antibiotics. Common AEs included implant-site nodules (n = 14) and injection-site nodules (n = 9). These AEs were judged to be of mild-to-moderate intensity and had a mean time to onset of 2–3 months after initial treatment, 3–9 months after retreatment, and with the exception of 1 subject (mild injection-site nodules), and all AEs had resolved by 24 months.

Subject Diaries

All subjects who completed diaries recorded at least 1 expected adverse reaction during the 14 days after treatment/retreatment with the majority assessed as mild to moderate.

Breast Examinations and Radiology

The majority of subjects had normal findings throughout the assessment period. There were no
new (compared with screening) abnormal mammography findings 24 months after the initial treatment. For most subjects, radiologists generally considered digital mammography alone unacceptable for diagnostic screening purposes, 24 months after initial treatment. High-resolution ultrasonography alone was considered acceptable for diagnostic purposes in the majority of subjects but could not replace mammography. A combination of digital mammography and ultrasonography was considered to provide sufficient diagnostic information.

GEIS Assessments

Overall (both groups combined), 85.5% of breasts (95% confidence interval: 78.0—91.2) were improved according to the subject GEIS 6 months after initial treatment (primary endpoint; Fig. 1). Corresponding percentages for investigator and independent evaluator assessments were generally higher compared with subject assessments (data not shown).

The percentage of breasts rated as improved by subjects, 24 months after last treatment, was comparable between treatment groups ($P = 0.473$).

Subject Satisfaction

In total, 98% of single-treated subjects reported satisfaction with their breasts in general, 6 weeks after treatment, compared with 32% of subjects before treatment (Fig. 2). All retreated subjects

Table 1. Demographic and Injection Data, ITT Population

| Demographic Characteristics | Single (N = 49) | Retreatment (N = 22) | Total (N = 71) |
|----------------------------|---------------|---------------------|---------------|
| Mean (range) age, yr       | 37.6 (22.3–59.5) | 41.9 (25.8–59.3) | 38.9 (22.3–59.5) |
| Mean (range) BMI, kg/m²    | 20.5 (14.9–26.2) | 21.7 (16.2–29.0) | 20.9 (14.9–29.0) |
| Mean (range) skin-fold thickness on pinch test, cm | 3.2 (2.0–5.0) | 3.0 (2.0–6.0) | 3.2 (2.0–6.0) |
| Previous esthetic procedures, n (% subjects) | 9 (18.4) | 3 (13.6) | 12 (16.9) |
| History of breastfeeding,* n (% subjects) | 22/27 (81.5) | 20/20 (100.0) | 42/47 (89.4) |
| Brasiliere cup size,† n (% subjects) | A65–A85
  15 (30.6) | 9 (40.9) | 24 (33.8) |
  B65–B85
  33 (67.3) | 13 (59.1) | 46 (64.8) |
  C75 | 1 (2.0) | 0 | 1 (1.4) |

| Injection data | Single (N = 49) | Retreatment (N = 22) |
|----------------|---------------|---------------------|
| Mean (SD) volume of HA gel injected at initial treatment, both breasts (including touch-up), mL | 200.8 (8.6) | 200.0 (10.7) |
| Mean (SD) volume of HA gel injected at retreatment, both breasts (including touch-up), mL | NA | 161.4 (30.7) |
| Mean (SD) volume of HA gel injected for all treatments and touch-ups, mL | NA | 361.4 (35.6) |

*Denominator is the number of subjects in the ITT population who have been pregnant and delivered.
†French brassiliere sizes were converted to European standard sizes.
BMI, body mass index; ITT, intention-to-treat; NA, not applicable.

Table 2. Summary of Reported AEs

| AE, n (% Subjects) | Single Treatment (N = 49) | Retreatment (N = 22) |
|-------------------|--------------------------|---------------------|
|                   | Initial Treatment | Second Treatment |
| AEs related to study product and/or injection procedure | | |
| Total | 33 (67.3) | 12 (54.5) |
| Serious | 1 (2.0) | 0 |
| No AEs | 10 (20.4) | 3 (13.6) |
| Treatment-related AEs by MedDRA (15.0) preferred term* | | |
| Axillary pain | 2 (4.1) | — |
| Breast tenderness | 2 (4.1) | 1 (4.5) |
| Capsular contracture associated with breast implant | 11 (22.4) | 3 (13.6) |
| Device deployment issue | 2 (4.1) | 1 (4.5) |
| Hypoesthesia | 4 (8.2) | 2 (9.1) |
| Implant-site induration | 2 (4.1) | — |
| Implant-site infection | 1 (2.0) | — |
| Implant-site nodule | 15 (30.6) | 3 (13.6) |
| Implant-site pain | 3 (6.1) | — |
| Injection-site nodule | 4 (8.2) | 2 (9.1) |
| Lymphadenopathy | 9 (18.4) | 8 (36.4) |
| Medical device implantation | 13 (26.5) | 1 (4.5) |

*That occurred in ≥2 subjects in at least one treatment group (single-treatment group or retreatment group).
MedDRA, Medical Dictionary for Regulatory Activities.
were satisfied with their breasts in general up to 3 months after initial treatment, compared with 36% of subjects before initial treatment (Fig. 2). There was no significant difference in subject satisfaction between treatment groups, 24 months after last treatment.

**DISCUSSION**

This is the first long-term evaluation of gel degradation, safety, and aesthetic outcomes after 2 injections of HA gel for breast enhancement. These findings indicate that gel degradation was not complete in any subjects, 24 months after last treatment. Additionally, HA gel can obscure breast tissue on screening mammography, which can be overcome through a combination of digital mammography and ultrasonography.

Treatment with HA gel was associated with subject-assessed improvements in breasts at 6, 12, and 24 months. Retreatment significantly improved subject GEIS assessments and satisfaction, 12 and 24 months after initial treatment. There was no difference between treatment groups 24 months after the last treatment, reflecting the product’s biodegradable nature. Treatments were received at the study start; a weak incentive to return may account for the subjects lost to follow-up. Nevertheless, these follow-up data should guide physicians on the appropriate care after breast enhancement with HA, with information from longer-term follow-ups recommended.

The time of onset for most AEs was less than 6 months, with severity mild to moderate, and the majority had resolved at 24 months, even though HA gel was still present. Three subjects developed...
infections, despite antiseptic wash before treatment. Therefore, additional preventive measures to reduce the risk of infection should be considered.

In conclusion, although single treatment and re-treatment of HA gel were generally well tolerated, physicians should be aware of common and more serious treatment-related complications (eg, infection) and the need for adjunctive ultrasonography when doing mammography screening.

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