Comparison of Smooth-Gel Hyaluronic Acid Dermal Fillers with Cross-linked Bovine Collagen: A Multicenter, Double-Masked, Randomized, Within-Subject Study

LESLIE S. BAUMANN, MD,* AVA T. SHAMBAN, MD,† MARY P. LUPO, MD,‡ GARY D. MONHEIT, MD,§ JANE A. THOMAS, AAS, CCRA,‖ DIANE K. MURPHY, MBA,‖ AND PATRICIA S. WALKER, MD, PhD,¶ FOR THE JUVÉDERM VS. ZYPLAST NASOLABIAL FOLD STUDY GROUP

BACKGROUND A new family of next-generation non-animal hyaluronic acid (HA) dermal fillers was approved by the FDA in June 2006. Compared with other HA fillers available in the United States at the time of writing, these new fillers have a higher concentration of HA, higher concentration of cross-linked HA, and a smooth consistency—which should promote long-lasting corrections and a smooth, natural look and feel postinjection.

OBJECTIVE The objective was to compare the effectiveness and safety of these smooth-gel HA dermal fillers with bovine collagen for nasolabial fold (NLF) correction.

METHODS AND MATERIALS A total of 439 subjects with moderate or severe NLFs received one of three types of smooth-gel HA dermal filler (in one NLF) and cross-linked bovine collagen (in the other NLF) and were evaluated for ≤24 weeks.

RESULTS All three HA dermal fillers achieved considerably longer-lasting clinical correction than bovine collagen; 81% to 90% of HA dermal filler–treated NLFs maintained a clinically significant improvement from baseline for ≥6 months. Up to 88% of subjects preferred the HA dermal fillers over bovine collagen. All fillers were similarly well tolerated.

CONCLUSION The smooth-gel HA dermal fillers offer longer-lasting correction than bovine collagen—which may lessen the frequency that repeat treatments are needed. Also, they were preferred by the vast majority of subjects—which should promote patient satisfaction.

Dr Baumann is a paid investigator and advisory board member for Inamed and Allergan. Drs Shamban, Lupo, and Monheit were paid investigators and were provided the equipment and product used in the study. Jane Thomas, Diane Murphy, and Patricia Walker are employees, and stock holders with stock options, of Allergan.

Hyaluronic acid (HA)-based gels are now the gold standard in dermal fillers, with more cosmetic procedures in the United States using these fillers than all other fillers combined.1 The widespread acceptance of HA fillers is testament to their biocompatibility (unlike protein-based fillers, they are composed of polysaccharides that exhibit no species specificity), the stability of their cross-linked HA in vivo (which promotes longevity of clinical improvement2), and their good record of safety and effectiveness in other countries where they have been in use for many years.

A new family of dermal fillers (the Juvéderm dermal fillers, Allergan, Santa Barbara, CA) was approved by the U.S. Food and Drug Administration (FDA) in June 2006. They are manufactured differently from other HA fillers previously approved by the FDA and, as a result, have a different consistency. A proprietary manufacturing process (known as Hylacross technology) avoids the need to press the filler through sieves to “size” the gel and produces a gel with a smooth consistency. The difference between this and the granular and uneven consistency of earlier HA fillers can be seen visually under a microscope.3

*University of Miami Cosmetic Center, Miami, Florida; †Laser Institute for Derm and European Skin Care, Santa Monica, California; ‡Tulane University, New Orleans, Louisiana; §Total Skin and Beauty Dermatology Center, Birmingham, Alabama; ¶Allergan, Santa Barbara, California

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Compared with other HA fillers available in the United States at the time of writing, the new smooth-gel HA dermal fillers also contain a higher total concentration of HA—24 mg/mL compared with 20 mg/mL with Restylane (Medicis, Scottsdale, AZ) and 5.5 mg/mL with Captique and Hylaform (Allergan, formerly Inamed, Santa Barbara, CA). In addition, they contain a higher concentration of cross-linked HA. As cross-linking the HA helps protect it from degradation in the body, a higher concentration of cross-linked HA allows for a greater portion of the product to contribute to the clinical improvement.

The smooth gel HA dermal fillers are derived from *Streptococci equi* and have been used successfully in Europe and Canada (marketed as Juvederm by the Corneal Group and by Allergan, formerly Inamed, and in some countries as Hydrafill by Allergan, formerly Inamed). Within this family of dermal fillers are three products—J30 (Juvederm 30), 24HV (Juvederm Ultra), and 30HV (Juvederm Ultra Plus)—which differ from each other in the proportion of un-cross-linked HA (“un-cross-linked HA” includes lightly cross-linked chains and fragments in addition to un-cross-linked HA) and the degree of cross-linking of HA (data on file, Allergan, 2006). The 24HV dermal filler is for contouring and adding volume to facial wrinkles and folds using a 30-gauge needle. The 30HV dermal filler is for adding volume to, and correcting, deeper folds and wrinkles using a 27-gauge needle. The J30 dermal filler is for the correction of fine facial wrinkles (although it is not currently marketed in the United States). The 24HV and 30HV dermal fillers contain a higher proportion of un-cross-linked HA than the J30 dermal filler, and the 30HV dermal filler is more highly cross-linked than the J30 and 24HV dermal fillers.

A multicenter, double-masked, randomized, within-subject study has been performed to compare the effectiveness and safety of these three HA dermal fillers with those of a cross-linked bovine collagen filler for nasolabial fold (NLF) correction.

Methods

Subjects

Subjects were eligible for enrollment into the study if they were at least 30 years of age and had fully visible bilateral NLFs that were approximately symmetrical. The NLFs were required to be both moderate or both severe (on a scale of none, mild, moderate, severe, and extreme) as judged by two investigators. The deepest part of the fold was used for the assessment of severity.

Subjects were required to have had no hypersensitivity responses after two injections of bovine collagen within 12 months of study entry and to refrain from undergoing other antiwrinkle treatment in the nasolabial and perioral areas before and during the study period. (Sunscreen was allowed, however.) Females of childbearing potential were required to have a negative urine pregnancy test and to use reliable contraception while participating in the study.

Exclusion criteria included a history of anaphylaxis, atopy, allergy to meat or lidocaine, or multiple severe allergies; hypersensitivity to bovine collagen or HA; receipt of immune therapy or a history of autoimmune disease; a tendency to develop hypertrophic scarring; pregnancy or breastfeeding; use in the 4 weeks before study randomization (or intent to use during the study) of oral retinoids, over-the-counter or prescription antiwrinkle treatments, microdermabrasion, or chemical peels in the NLF area; and any prior cosmetic procedure or tissue augmentation at the NLF injection site in the 6 months before study entry (or intent to undergo such a procedure during the study).

The study was approved by the relevant institutional review boards, all subjects signed informed consent, and the study protocol conformed to the guidelines of the 1975 Declaration of Helsinki.

Treatment

Each study site had a single treating investigator and a single evaluating investigator, both of whom were...
physician specialists in cosmetic dermatology or plastic surgery and had extensive experience in the use of dermal fillers. The evaluating investigator and the subjects were masked to treatment groups but, because of visual differences in the fillers, the treating investigator could not be masked.

Subjects were randomly assigned to receive one of three smooth-gel HA dermal fillers—J30 (Juvéderm 30), 24HV (Juvéderm Ultra), or 30HV (Juvéderm Ultra Plus)—intradermally to the NLF on one side of the face. In all subjects, the NLF on the other side of the face was treated with a cross-linked bovine collagen filler (Zyplast, Allergan, formerly Inamed).

Before treatment, the area to be treated was disinfected thoroughly, and equal amounts of 5% lidocaine were applied topically to the right and left NLFs for anesthesia. The treating investigators were instructed to fill each NLF to full correction (100% of the defect) but not to overcorrect and then to massage the treated area to ensure that the filler was uniformly distributed. The amount injected was determined by the length and depth of the NLF. Injections were performed using 30-gauge × 0.4-in. intradermal injection needles (RJ MAXflo, RJ Development Corp., Peabody, MA) for the HA fillers and the 30-gauge × 0.5-in. needles included in the U.S. commercial packaging for the bovine collagen filler. The investigators were instructed to introduce the needle at a 45° angle to the skin and to then inject slowly into the middermis at multiple injection points in the NLF area.

Up to three treatments were allowed over a 4-week period (initial treatment plus up to two touch-ups approximately 2 weeks apart) to achieve optimal correction of the NLFs. The level of correction was assessed by the evaluating investigator at Weeks 2 and 4 after the initial treatment and, if less than optimal, the treating investigator was directed to retreat the undercorrected NLF(s) with the same filler(s) assigned previously.

### Outcome Measures

The severity of each NLF was determined by the evaluating investigator via a live assessment using the 5-point Wrinkle Assessment Scale (WAS) together with a validated photographic guide. The WAS scale is defined as 0 = none (no wrinkle), 1 = mild (shallow, just perceptible wrinkle), 2 = moderate (moderately deep wrinkle), 3 = severe (deep wrinkle, well-defined edges but not overlapping), and 4 = extreme (very deep wrinkle, redundant fold, overlapping skin). The subjects made live self-assessments of NLF severity using the same WAS scale but without photographs. At the study exit, the subjects were asked to guess which filler had been injected in which NLF and to report which filler (if any) they preferred in terms of overall effects of treatment.

Subjects were provided with a diary in which they were asked to report their observations of common treatment site reactions on a daily basis from 30 minutes after the first treatment (Day 0) through Day 13 after each treatment (including touch-ups, if any). Any additional adverse events reported by the subject or observed by the investigators were also recorded. Subjects were followed up at office visits at least every 4 weeks for up to 24 weeks after their last treatment. Some subjects had additional follow-up if they returned after the end of the study—e.g., for the complimentary repeat treatment that had been offered to them on entering the study.

### Statistical Analyses

Statistical analyses were performed on the intent-to-treat population for effectiveness data and on the “as-treated” population for safety data. An α level of .05 was used to determine statistical significance. The improvements in NLF severity score were compared to baseline using a signed rank test. The proportion of NLFs with a clinically significant improvement (≥ 1-point reduction in NLF severity score relative to baseline) was compared to baseline using a one sample binomial test (using the exact method).
Results

Subjects

A total of 439 subjects were randomized and treated (the intent-to-treat population), of whom 423 (96%) completed the 24-week follow-up period. No subjects discontinued due to lack of effectiveness or adverse events.

The mean age of the subjects was 49 years (range, 26–75 years) and the majority were female (92%). Overall, 74% were Caucasian and 26% were non-Caucasian (12% Hispanic, 11% African American, 2% Asian, and 1% other). The full range of Fitzpatrick skin types was represented (4% I, 24% II, 35% III, 20% IV, 13% V, 3% VI). Demographic details were comparable in all treatment groups, and 34% to 39% of subjects were known to have previously received treatment with botulinum toxin type A in the upper face.

Effectiveness

All the HA dermal fillers resulted in a mean improvement (i.e., a reduction) from baseline in NLF severity score that was clinically significant at every time point (Figures 1 and 2). Furthermore, the HA dermal fillers provided longer-lasting clinical correction than bovine collagen—the mean level of improvement in NLF severity score at 24 weeks after last treatment was ≥ 1 point with the HA dermal fillers (i.e., still a clinically significant improvement from baseline) and no more than 0.5 point with bovine collagen (Figures 1 and 2, Table 1). The proportion of NLFs retaining this clinically significant level of improvement at 24 weeks after last treatment was 81% with J30 dermal filler, 88% with 24HV dermal filler, and 90% with 30HV dermal filler compared with 45%, 36%, and 40% in the corresponding bovine collagen–treated NLFs (Figure 3, Table 1). Photographic documentation shows that clinically significant improvement was maintained not only up to 24 weeks after last treatment but, in subjects who returned after the end of the study, for longer periods also (Figure 4). Sustained clinical improvement for 11 and 17 months after last treatment is shown in two subjects (Figure 4).

For all of the fillers, the majority of subjects had only one treatment visit (i.e., no touch-ups) and the total injection volume was lower with the HA dermal fillers (median, 1.6 mL; range, 0.8–5.6 mL) than with bovine collagen (median, 2.0 mL; range, 0.8–7.7 mL).

Safety

The frequency and severity of treatment site reactions were similar for all the fillers (Table 2), and there were no treatment-related adverse events other than those localized to the area of injection. For all treatment groups, the majority of treatment site reactions were mild to moderate in severity, did not
require intervention, and lasted no more than 7 days. The only significant treatment-related adverse event reported was a sterile abscess at the injection site 4 months after treatment with bovine collagen. The pattern and incidence of treatment site reactions were generally similar between Caucasian and non-Caucasian subjects.9

Subject Preferences

At study end, while still masked to treatment assignment, the vast majority of subjects preferred their HA filler over bovine collagen—78% with J30, 88% with 24HV, and 84% with 30HV dermal filler (Figure 5). Subjects’ guesses of which filler had been used on which side of their face were incorrect more frequently than they were correct.

Discussion

The results of this multicenter, double-masked, randomized, within-subject study demonstrate two clinically important findings—that the smooth-gel HA dermal fillers offer longer-lasting correction of NLFs than bovine collagen and that the vast majority of subjects prefer these smooth-gel fillers to bovine collagen.
The longer-lasting correction is demonstrated by the considerably greater proportion of HA dermal filler–treated NLFs maintaining a clinically significant improvement from baseline compared with bovine collagen–treated NLFs—81% to 90% versus 36% to 45% at 24 weeks after the last treatment. It appears that clinical correction is maintained in many subjects beyond 24 weeks, and extended follow-up will help evaluate the true longevity of the clinical improvements. Photographic documentation published here and elsewhere\textsuperscript{8–10} demonstrates excellent clinical correction and a smooth natural look that is maintained up to and well beyond 24 weeks in some subjects—including through 17 months in one subject (who returned approximately 11 months after exiting the study). This is consistent with the

![Figure 4. Photographic documentation of the longer-lasting clinical improvement with the smooth-gel HA dermal fillers relative to bovine collagen, the good local tolerability of these HA dermal fillers, and the smooth natural look attainable.](image)

**TABLE 2.** Treatment Site Reactions Occurring with an Incidence of at Least 10%

<table>
<thead>
<tr>
<th>Treatment site reaction</th>
<th>Subjects (%)</th>
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<tbody>
<tr>
<td></td>
<td>J30</td>
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<tr>
<td>Injection site induration</td>
<td>91</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>90</td>
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<tr>
<td>Injection site edema</td>
<td>89</td>
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<tr>
<td>Injection site pain</td>
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<td>Injection site nodule</td>
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</tr>
<tr>
<td>Injection site discoloration</td>
<td>31</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>28</td>
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longevity of 12 to 15 months that has previously been reported with one of these fillers (Juvéderm 30 dermal filler) in Europe. The overwhelming preference of the subjects for the smooth-gel HA dermal fillers is presumably at least partly attributable to the long-lasting effects of the fillers as well as their natural look and feel posttreatment.

The longer-lasting corrections attained with the new fillers are likely attributable to the high concentration of HA and high concentration of cross-linked HA in the gels. The proprietary manufacturing process ensures that the gels are both smooth and malleable—which helps to achieve a smooth and natural look and feel postinjection. As new HA fillers have become available in recent years, many clinicians have come to consider that key criteria for an “ideal filler” should include easy injectability, the ability to achieve persistent clinical corrections, and the avoidance of animal-derived ingredients (to promote biocompatibility). All three of the smooth-gel HA dermal fillers studied in this trial meet these criteria.

The subjects’ inability to correctly guess which filler had been used on which side of their face confirmed the successful masking of the formulations. (This is in contrast to the FDA Advisory Panel’s conclusion of incomplete masking reported for a similar trial comparing an HA filler of granular consistency with bovine collagen.) The effectiveness results from this trial are consistent with those from other trials that show that, compared with cross-linked bovine collagen, HA fillers can result in longer-lasting clinical improvement and require a lower injection volume for optimal correction. In the study presented here, the median injection volumes were 1.6 mL for each of the J30, 24HV, and 30HV dermal fillers and 2.0 mL for bovine collagen. The previously mentioned study had a considerably smaller proportion of subjects with severe NLFs at baseline (34% had severe NLFs compared with >57% in our trial) which, as would be anticipated, resulted in lower mean injection volumes (1.0 mL for the HA filler of granular consistency and 1.6 mL for the bovine collagen filler). Additionally, this earlier study limited the injection volume to no more than 1.5 mL per treatment session, whereas our study had no predetermined maximum treatment volume and investigators were instructed to inject as much filler as needed to obtain optimal correction of each NLF. A report in the literature suggests that, in clinical practice, the typical injection volume of the HA filler with granular consistency used in the previous study is actually 1.5 mL for NLF correction (i.e., considerably higher than reported in the study by Narins and coworkers).

Conclusions

The new smooth-gel HA dermal fillers (Juvéderm 30, Juvéderm Ultra, and Juvéderm Ultra Plus) were highly effective in correcting NLFs for 6 months or longer posttreatment and achieved considerably longer-lasting improvements than bovine collagen. As a result, it is expected that repeat treatments will be required less frequently than with bovine collagen. The persistent corrections attained with the smooth-gel HA dermal fillers are likely at least partly attributable to the high concentration of HA and high concentration of cross-linked HA in these next generation formulations.

The majority of subjects achieved optimal correction with only a single injection of the HA dermal filler (i.e., without any need for touch-ups) and all of the fillers were similarly well tolerated. The overwhelming majority of subjects expressed a preference for the smooth-gel HA dermal fillers over bovine collagen—suggesting that patient satisfaction is likely to be greater with these fillers.
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References


Address correspondence and reprint requests to: Leslie Baumann, MD, University of Miami Cosmetic Center, Nichols Building, 4701 N. Meridian Avenue, Suite 7450, Miami Beach, FL 33140, or e-mail: lsb@derm.net