Not All Hyaluronic Acid Dermal Fillers Are Equal

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Hyaluronic acid (HA) dermal fillers are a valuable tool in cosmetic dermatology. A number of HA products are currently available and differ in characteristics that can affect their longevity and special uses. Among the various HA products I have used, I have found that Juvéderm™, which has the highest concentration of HA and a smooth, homogeneous composition, provides excellent results and a high degree of patient satisfaction.

The use of hyaluronic acid (HA) dermal fillers comprises a large and important part of many cosmetic dermatology practices. According to the American Society for Aesthetic Plastic Surgery, of the more than 9 million nonsurgical cosmetic procedures performed in the United States in 2006, almost 2 million (20.7%) used soft tissue fillers.[1] A number of dermal fillers are approved by the US Food and Drug Administration (FDA) (Table 1),[2] with HA gels accounting for the vast majority (81%) of those used regularly in daily practice. In fact, their use has grown approximately 34% each year since 2004, and in 2006, injection of HA fillers was second only to injection of botulinum toxin type A as the most frequently performed nonsurgical cosmetic procedure—coming in at 13.9% and 27.8%, respectively.[1,3]

Over the years, I have used many HA products and have found them to be a wonderful tool in my practice and an ideal complement to other nonsurgical treatments, including botulinum toxin type A injections and antiaging skin care regimens.

HA gels are "natural" fillers in that HA itself is a major component of the connective tissue matrix in the dermis. The HA content of the dermis decreases with age, which is thought to contribute to the development of wrinkles and folds.[4] Because HA is highly hydrophilic, it attracts and retains water within the extracellular space, increasing dermal volume. Additionally, because the chemical structure of HA is uniform across different species (unlike collagen), it has low immunogenic potential and requires no skin testing before treatment.

Many manufacturers have overcome the relatively short half-life of HA (in vivo, ≈20 hours) by developing cross-linking technologies that allow them to create HA gels (also known as hylans), which contain high amounts of water (95% of weight). HA gels' greater longevity is also due to their unique property of isovolemic degradation: as individual HA molecules in the gel matrix degrade, the remaining molecules bind more water, maintaining the same overall volume, until the last of the HA molecules are broken down. Thus, depending on their specific characteristics (eg, concentration of HA, degree of cross-linking), HA gel fillers last from 3 to 9 months or longer. Additionally, because the viscosity of HA gels decreases with increasing shear force, they can easily pass through a small-gauge needle in a low-viscous state, then regain their viscosity upon implantation, making migration unlikely.[5]

Currently, there are 7 FDA-approved HA gel products available in the United States (Table 2).[6-9] Each is approved for mid- to deep-dermal implantation for the correction of moderate to severe facial wrinkles and folds (eg, nasolabial folds, oral commissures, and periocular rhytides). In my experience, HA gels are also very effective for shaping and augmenting lips, elevating brows, and treating tear-trough deformities and deep scars. As shown in Table 2, HA products differ in terms of cross-linking, HA concentration, and gel particle size, which can affect their longevity and special uses. For example, Restylane®, which has a small particle size of approximately 260 µm, is appropriate for moderate

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Table 2
Profile of Hyaluronic Acid Fillers[6-9]

Product	Specialized Use*	Duration	Source	% Hyaluronic Acid Polymers and Monomers Cross-linked†; Cross-linking Agent	Hyaluronic Acid Concentration	Gel Particle Diameter‡
Juvéderm™ Ultra	Moderate wrinkles and folds, lip enhancement, mid-depth implantation	1 y	Bacterial fermentation	≈90%, 6%; 1,4-butanediol diglycidyl ether	24 mg/mL	No particles; homogeneous gel
Juvéderm Ultra Plus	Deep folds, facial contours, lip enhancement, deep implantation	1 y	Bacterial fermentation	≈90%, 8%; 1,4-butanediol diglycidyl ether	24 mg/mL	No particles; homogeneous gel
Restylane®	Moderate wrinkles and folds, lip enhancement, mid-depth implantation	4–6 mo	Bacterial fermentation	≈80%, 1%; 1,4-butanediol diglycidyl ether	20 mg/mL	≈260 µm
Perlane®	Deep folds, facial contours, lip enhancement, deep implantation	4–6 mo	Bacterial fermentation	≈80%, 1%; 1,4-butanediol diglycidyl ether	20 mg/mL	≈1000 µm
Hylaform®	Moderate wrinkles and folds, lip enhancement, mid-depth implantation	3–6 mo	Chicken combs	≥95%, 20%; divinyl sulfone	4.5–6.0 mg/mL	≈500 µm
Hylaform Plus	Deep folds, facial contours, lip enhancement, deep implantation	3–6 mo	Chicken combs	≥95%, 20%; divinyl sulfone	4.5–6.0 mg/mL	≈700 µm
Captique™	Moderate wrinkles and folds, lip enhancement, mid-depth implantation	3–6 mo	Bacterial fermentation	≥95%, 20%; divinyl sulfone	4.5–6.0 mg/mL	≈500 µm

*All hyaluronic acid fillers shown are approved for mid- to deep-dermal implantation for the correction of moderate to severe facial wrinkles and folds.

†One or both of 2 ways are usually used to characterize the degree of cross-linking: polymer and monomer. Values for both are presented here. Polymer cross-linking is an estimate of the number of hyaluronic acid polymers that have any cross-linking to other hyaluronic acid polymers, whereas monomer cross-linking, which is more often reported, refers to the approximate proportion of monomer units (within the polymers) that are cross-linked. One cautionary note: although greater cross-linking is associated with greater longevity of the injected hyaluronic acid gel, different manufacturers arrive at values using different methods (eg, % by weight vs % by moles), making comparisons difficult.

‡Diameters were calculated based on the reported values from the manufacturer (for Perlane, Hylaform, and Captique) or based on particle volume and the formula for sphere volume [volume = $(4/3) \times \pi \times \text{radius}^3$], solving for radius and multiplying by 2 for the diameter (eg, Restylane size is 100,000 particles per mL, or 10^{-5} mL per sphere, so diameter is ≈260 µm).

wrinkles and folds and mid-depth implantation. Perlane®, on the other hand, with large particles of approximately 1000 µm, is better suited for deeper wrinkles and folds and deep implantation.

Unlike collagen fillers, HA fillers do not contain a local anesthetic. This, along with their greater viscosity, can produce discomfort during injection, and I have found that using a local anesthetic or dental block can improve patient comfort. According to their indication, HA fillers should be injected intradermally. If injected too deeply or intramuscularly, the duration of effect may be reduced because of absorption of the product, and if

injected too superficially, visible areas of excess fullness, skin discoloration, or both may result.[10] As generally recommended,[2] I inject to 100% of the volume needed for correction, without overcorrecting. Following treatment, bruising may occur around the injection site because of the structural similarities of HA to those of heparin, which may attract inflammatory mediators to the injection site and accelerate HA degradation, shortening the duration of correction.[4]

THE ROAD TO FDA APPROVAL

The FDA's approval of Juvéderm™, a next-generation HA dermal filler, was based largely on data from a double-blind, randomized, within-subject, controlled, multicenter study.[11] A total of 439 subjects were followed for 24 weeks after injection with one of 3 Juvéderm formulations (Juvéderm Ultra, Juvéderm Ultra Plus, or Juvéderm 30) in one nasolabial fold (NLF) and bovine-based collagen (considered the standard filler at the time) in the other. The investigator and an independent expert reviewer evaluated the severity of participants' NLFs using a photographic NLF severity scale of 0 to 4 (where 0=no wrinkle and 4=very deep wrinkle with redundant fold and overlapping skin), and each study participant made independent self-assessments of NLF severity using a nonphotographic 5-point grading scale (where 0=no wrinkle and 4=very deep wrinkle with redundant fold and overlapping skin).

The findings showed that Juvéderm provided a more persistent wrinkle correction than did bovine-based collagen over the 6-month course of the study, with up to 90% of subjects maintaining at least a 1-grade improvement in NLF correction with Juvéderm compared with 36% to 45% with bovine collagen. At the conclusion of the study, up to 88% of subjects expressed a preference for Juvéderm, whereas only 5% to 12% preferred the bovine-based collagen product. There were no clinically meaningful differences in the 2 products in terms of injection-site reactions. In addition, among nonwhite patients (all Fitzpatrick skin types), Juvéderm was found to be safe and effective and demonstrated no increased risk of hyperpigmentation or hypertrophic scarring.[7]

A subanalysis of 87 participants in this study who had severe NLFs (rated as 3 on the scale of 0–4) showed that Juvéderm Ultra Plus resulted in better improvement from week 4 through the end of the study at week 24.[12] By the end of the study, 85% of subjects expressed a preference for Juvéderm compared with only 10% for bovine-based collagen.

In general, adverse events with Juvéderm reported in clinical studies were usually mild to moderate, did not require intervention, and lasted 7 days or less.[11] The most common side effects included temporary injection-site reactions, such as redness, pain and tenderness, firmness, swelling, lumps and bumps, and bruising.

A NEXT-GENERATION DERMAL FILLER ENTERS THE MARKET

I was introduced to Juvéderm shortly after its approval in June 2006 and immediately began evaluating it in my practice. Compared with other HA products, Juvéderm is unique in that it has the highest concentration of HA (24 mg/mL). Additionally, all other HA products have a granular consistency (the granules can actually be visualized under 2.4× magnification), which can result in patient discomfort during injection and a lumpy feeling underneath the skin's surface following treatment. In contrast, Juvéderm is developed using a proprietary Hylacross™ technology, which results in a smooth, homogeneous, and malleable gel that flows easily into the skin, creating a smooth, natural look and feel. I believe these unique attributes of Juvéderm compared with those of other HA fillers have resulted in the improved clinical outcomes and greater overall patient satisfaction I have seen in my practice.

The Figure shows typical results with Juvéderm in treating NLFs. Following are summaries of 2 patient cases treated with Juvéderm in my practice.

CASE REPORTS

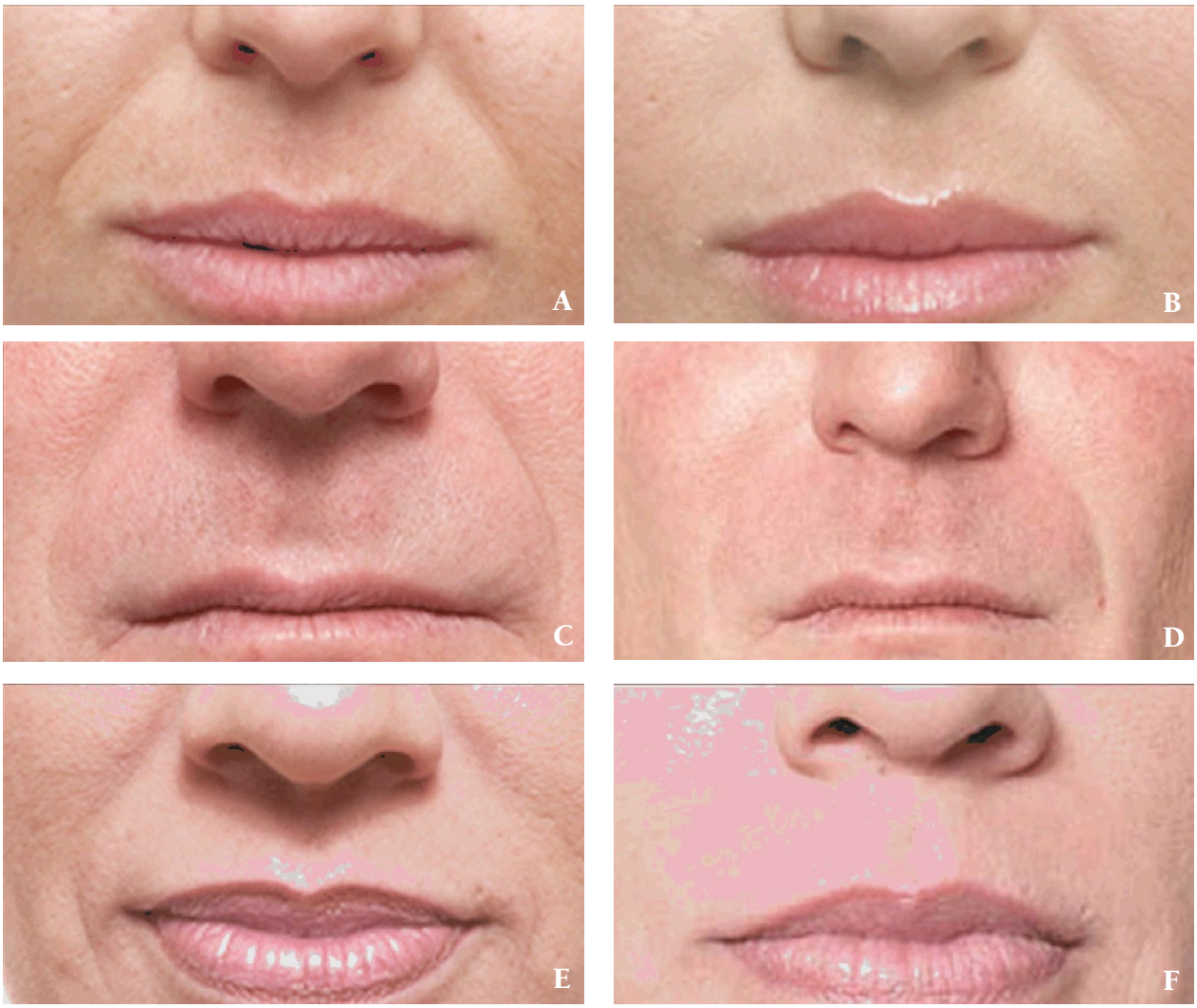
Patient 1

This patient was a 57-year-old white woman with a history of a face-lift, corrugator muscle excision, and blepharoplasty performed 5 years earlier. She was happy overall with her face-lift but was unhappy with the deep NLFs that remained.

The patient wanted her deep NLFs corrected, and her expectations were very realistic. On a scale of 1 to 5 (where 1=no wrinkle and 5=very deep wrinkle with redundant fold and overlapping skin), wrinkling of her NLFs was rated a 4. The treatment plan was to use 4 syringes of Juvéderm Ultra Plus to achieve full correction. Topical lidocaine 2.5% and prilocaine 2.5% was applied with occlusion more than 1 hour before injection.

I applied a serial puncture injection technique to the mid dermis using a 30-gauge needle. Four syringes of Juvéderm Ultra Plus (1.6 mL per treatment site) were injected into each side of the nasolabial area. No tissue blanching during the injections was observed. The patient had some postoperative swelling of the treatment areas, which subsided over the next 2 days. Juvéderm provided nearly complete correction of the NLFs.

In addition, the patient was unhappy that her glabellar area still made her appear as if she were frowning despite her previous corrugator muscle excision. Botulinum toxin



Nasolabial folds before (A, C, E) and after (B, D, F) treatment with Juvéderm™ Ultra.

type A was injected into the glabellar area to completely correct this problem.

The patient was evaluated 6 months later. Only the uppermost corners of her nasolabial areas needed correction. I used one syringe of Juvéderm Ultra (0.8 mL), since only a small touch-up was needed to achieve full correction of this small area. The patient achieved nearly complete correction of the treated area; based on the 5-point scale, the remaining nasolabial wrinkle was barely rated a 1. The patient was extremely satisfied with both her original treatment and the small touch-up that was needed.

Patient 2

This patient was a 42-year-old white woman with a history of severe facial acne in her late 30s. She had completed a course of isotretinoin 7 years previously, which cured her cystic acne, but she was left with multiple areas of dermal scarring. Several chemical peels and application of a topical retinoid cream gave her some mild improvement, but the deeper scars on her cheeks and chin area were still prominent.

The patient expressed a desire for the acne scars to be corrected. I counseled her that although the scars would be improved, 100% correction was not realistic. I decided to employ 2 syringes of Juvéderm Ultra to fill in and correct the dermal scarring.

Topical lidocaine 2.5% and prilocaine 2.5% was applied with occlusion 1 hour before injection. I applied a serial puncture injection technique using a 30-gauge needle to fill each individual scar to the deep dermis. The patient had some postoperative swelling and bruising that lasted several days.

The patient was evaluated 3 months later, and she was quite happy with the improvement. I decided to touch up some of the deeper acne scars; this was done using one syringe (0.8 mL) of Juvéderm Ultra. The patient was extremely satisfied with her treatment and said she would gladly repeat it in the future.

SUMMARY

HA dermal fillers are very useful in correcting facial wrinkles and folds and, in my experience, shaping and augmenting lips, elevating brows, and treating tear-trough deformities and deep scars. HA fillers have a number of advantages over other dermal fillers, including a smoother, more natural-looking result. Currently available HA fillers differ in terms of their degrees of cross-linking, HA concentration, and gel particle size, all of which can affect how long they last and the applications for which they are best suited. In my experience, Juvéderm, which has the highest concentration of HA and is a gel rather than particulate, has produced very good, natural-looking results and a high degree of patient satisfaction.

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