Injectable synthetic hyaluronic acid is biodegradable and biocompatible with human hyaluronic acid. Soft tissue augmentation with this product does not require prior skin testing and provides robust augmentation. Its ability to attract and maintain significant amounts of water accounts for the volume and duration of correction that persists until the stabilized gel is completely metabolized. (Aesthetic Surg J 2004;24: 361-364)

On November 21, 2003, the U.S. Food and Drug Administration (FDA) advisory panel on general and plastic surgery devices recommended the approval of 2 hyaluronic acid (HA)–based dermal filler products for the “correction of soft tissue contour deficiencies.” On December 12, 2003, the FDA approved the use of injectable Restylane gel (Q-Med, Uppsala, Sweden) for the treatment of facial wrinkles. Later, on April 23, 2004, the FDA approved Hylaform (Inamed, Santa Barbara, CA). The approval of these HA products is a significant development in facial aesthetics tantamount to the introduction and approval of bovine collagen in 1981.

Biology

HA, also known as hyaluronan, is named for its glassy appearance (the Greek word for glass is hyalos). The presence of a sugar is denoted by “uronic acid.” HA belongs to, and is the most abundant member of, a group of compounds called glycosaminoglycans or acid mucopolysaccharides that make up the cutaneous dermal ground substance. This amorphous substance fills the extracellular spaces between collagen fibers and bundles. It is identical in chemical and molecular form in all tissues and mammals and is therefore species-nonspecific. HA has a simple chemical structure: a linear polysaccharide of repeating disaccharide units of N-acetylglucosamine and D-glucuronic acid.

The HA molecule is a long chain with intertwining coils having a polar nature that attracts water (hydrophilic). In connective tissue, HA’s main biologic function is to create volume and lubricate the intracellular structures by forming a gelatinous matrix in which collagen and elastin fibers are embedded and held together in proper alignment.

A direct correlation exists between the amount of HA in dermal tissue and the content of water in the dermis, and, therefore, the elastoviscous properties of the extracellular matrix. The concentration of naturally occurring HA in the skin decreases with age, resulting in decreased elasticity and ability to hold water (hydration), which renders the dermis less voluminous and increases the tendency of the skin to form wrinkles.

Although first isolated in 1934, HA was not developed as a dermal filler until 1989, when Endre Balazs appreciated its biocompatibility and lack of immunogenicity. A dual mechanism of action accounts for the improvement of facial wrinkles: HA integrates into dermal tissue, then attracts and binds to water molecules, which sustains the augmentation. In its natural unmodified state, implanted exogenous HA is rapidly degraded by hyaluronidase and has a half-life of 12 to 24 hours. To improve its resistance to enzymatic breakdown and increase tissue viability and in situ residency, the HA molecule must be stabilized through a chemical process of cross-linking.

There are 2 broad types of cross-linked HA: (1) animal-derived and (2) non–animal-derived synthetic HA (NASHA). Each type has 3 distinct formulations.

Animal-Derived HA

The animal-derived form of HA, avian (extracted from rooster combs), is manufactured by Genzyme Corp. (Boston, MA) and marketed by Inamed Corp. (Santa Barbara, CA). It is distributed as Hylaform (Hylan B) in 3 concentrations: Hylaform Fine Line, for superficial lines and wrinkles; Hylaform, for deeper lines, wrinkles, and folds; and Hylaform Plus for deep folds.
Non–Animal-Derived Synthetic HA

To date, 2 separate forms of NASHA have been generated from *Streptococcus* bacterial fermentation: Juvederm and Restylane (Medicis Aesthetic, Scottsdale, AZ). Inamed Corp. recently acquired the rights to market the Juvederm class, which, when approved, will also be distributed in 3 concentrations, designated 18, 24, and 30 to correspond with the depth of depression requiring correction. These products are approved and available for use outside the United States. The Restylane family of products—its members designated Restylane Fine Lines, Restylane, and Perlane—is similarly targeted to different depths of rhytids (Table).

Outside of the United States the HAs are the most popular filling agents. The 2 recently approved products, Restylane and Hylaform, have already made significant inroads into the dermal filler market as physicians in the United States are fast becoming acquainted with the benefits and techniques of HA injection.

Restylane

In 1996, the Swedish company Q-Med launched the first bacteria-derived HA (NASHA) for cosmetic use under the trade name Restylane. Since then, about 1 million patients have been successfully treated in more than 60 countries. Restylane is a clear, colorless, non-particle gel that consists of non-animal-derived, stabilized HA (20 mg/mL), suspended in physiologic saline solution (pH 7.0). It is available in individually packed syringes marked to indicate that they contain 0.7 mL of gel; however, the syringes are overfilled, and contain about 0.8 mL of material. In Europe and Canada, Restylane is also available in 0.4-mL syringes. The disposable single-use syringes are accompanied by separate 30-gauge 0.5-inch needles and have labels that can be removed and affixed to patient records. The product can be stored at room temperature. Skin testing to rule out hypersensitivity is not needed, which is advantageous because patients can be evaluated and treated during the initial consultation.

Approved for “correction of moderate to severe facial wrinkles and folds, such as the nasolabial folds,” Restylane is used primarily in the lower third of the face and the perioral area, including the vermilion border and oral commissures and, adjunctively, for static rhytids that persist after chemodenervation with botulinum toxin (Figure).

As opposed to other fillers, Restylane does not contain lidocaine to minimize injection pain. As a means of ensuring patient comfort, some type of anesthesia—a topical preparation such as Ela-Max (Ferndale Labs, Ferndale, MI) or Betacaine (Canderm Pharma, Inc., St. Laurent, Quebec, Canada), a nerve block (infraorbital, mental, or both) may be administered prior to injection. The injection technique is operator-dependent, but most physicians administer the product in a fashion similar to that used to administer other dermal filling agents — with the bevel of the 30-gauge needle positioned up and using serial puncture, linear threading, or a combination of the two methods.

The material is placed in the middle to deep dermis, only to the point of correction, without overcorrecting the cutaneous defect. Restylane is more viscous than many other injectables, especially collagen products, and has different flow characteristics. Therefore greater pressure must be applied to the plunger of the syringe. Following injection, manual massage of the treated area aids uniform distribution of the material and reduces the risk of contour irregularities.

Treatment with Restylane is often associated with temporary postinjection tenderness and edema. The application of ice immediately after treatment reduces these normal sequelae, as well as any erythema that might occur. It is not necessary for patients to restrict their activities after treatment, and the use of facial preparations and makeup may be resumed. As with most dermal fillers, Restylane’s results are immediate; however,

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Treatment with Restylane is often associated with temporary postinjection tenderness and edema. The application of ice immediately after treatment reduces these normal sequelae, as well as any erythema that might occur. It is not necessary for patients to restrict their activities after treatment, and the use of facial preparations and makeup may be resumed. As with most dermal fillers, Restylane’s results are immediate; however,
they are longer-lasting. The durability of correction seems to vary, but in the only published study comparing Restylane with bovine collagen (Zyplast), not only was less Restylane required for optimal cosmetic result, but Restylane also proved more durable. The ability of Restylane to attract and maintain significant amounts of water accounts for the volume and duration of correction that persists until the stabilized gel is completely metabolized, a process called isovolemic degradation. Reports suggest that the implanted material (and the correction) can persist for 6 to 9 months, depending on skin type, area of treatment, and amount of filler injected. Anecdotal reports indicate that with each subsequent treatment, some reservoir of product may persist; a smaller volume is needed each time to achieve a similar cosmetic result.

Complications

Adverse sequelae such as discomfort, burning, erythema, edema, and ecchymosis are the same as those seen with any other percutaneous injection. Technique-related complications range from contour irregularities and persistent beading due to superficial placement to necrosis resulting from vascular occlusion. Immunogenicity and the incidence of allergic reactions are the subjects of much discussion. Hypersensitivity responses were reported to be 0.15% in 1999, but after a new batch of HA was introduced in 2000 with the amount of protein reduced to 6 times less than that previously used, the incidence of hypersensitivity was reduced to 0.06%. It seems that a direct correlation exists between allergy and the reduction in protein load, but a response to HA itself cannot be entirely excluded.

Hylaform

Hylaform, also known as Hylan B gel, is the avian-based, FDA-approved Restylane counterpart in the HA family and has a very similar profile to Restylane. It too is available as a clear gel in overfilled, disposable 1 mL plastic syringes with adhesive labels and 30 gauge 0.5 inch needles and can be stored at room temperature. It has an HA concentration of 5.5 mg/mL with a particulate size of 500 microns. Although animal-derived, it does not require initial skin testing to exclude allergic reactions. (This information was based on the use of Synvisc [Wyeth, Philadelphia, PA], a very similar product that has been injected by orthopedic surgeons into joints for many years without any reported problems relating to avian proteins.) The injection technique, FDA approved indications, and complications seem to parallel Restylane.

At present, in the wake of the seeming avalanche of new options for filler materials and FDA approval of 2
new HA products, Restylane and Hylaform may establish themselves as the new gold standard for soft tissue augmentation. Whether in the final analysis they prove to be the ideal fillers, they nevertheless fulfill many requirements: they are extremely biocompatible with human HA, do not mandate initial screening tests, are biodegradable, and provide more robust and longer augmentation. Ultimately these alternatives are an advantage for both physicians and patients alike as they provide yet another safe and effective means to temporarily improve and reduce facial rhytids. Certainly it will be very exciting for physicians to be able to offer patients newer HA products as they evolve and become available.

Bibliography


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