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SUPPLEMENT

## Restylane SubQ, a Non-Animal Stabilized Hyaluronic Acid Gel for Soft Tissue Augmentation of the Mid- and Lower Face

**Alexis Verpaele, MD; and Anders Strand, MD**

Dr. Verpaele is Assistant Clinical Professor, Department of Plastic Surgery, Ghent University Hospital and Director, Coupure Center for Plastic Surgery, Ghent, Belgium. Dr Strand is from Q-Med AB, Uppsala, Sweden.

*For people requiring large volumes to shape facial contours, add volume to a sunken midface, or correct asymmetry, the options today are limited. Fat injections for adding volume, solid implants for cheeks and chin enhancement, face lift and injectable permanent or semi-permanent products are some of the alternatives used. With the trend towards less invasive and nonpermanent alternatives to plastic surgery, the use of injectable filler materials for facial rejuvenation and correction of soft-tissue defects is becoming increasingly popular. These materials provide volume expansion within the dermis, thereby smoothing out overlying facial wrinkles and enhancing facial contours. Ease of application, minimal procedural discomfort, and rapid patient recovery make injectable fillers well suited for outpatient use. Ideally, a filler material should be biocompatible, nontoxic, nonimmunogenic, and nonmigratory. Several biomaterials have been developed, such as bovine collagen, autologous and allogeneic human collagen, autologous fat, fibroblasts, and hyaluronic acid. However, although they are largely biocompatible, reabsorption and lack of sustained cosmetic effect are major drawbacks. Non-animal stabilized hyaluronic acid (NASHA) offers a longer-lasting aesthetic effect than bovine collagen or avian hyaluronic acid in facial soft-tissue augmentation, and a potentially lower risk of inflammatory reactions. Restylane SubQ is a new NASHA product indicated for deep subcutaneous or supraperiosteal injection to replace volume loss in facial adipose tissues and create more defined facial contours. (Aesthetic Surg J 2006;26(suppl):S10-S17.)*

Statistics from the American Society for Aesthetic Plastic Surgery show that use of nonsurgical cosmetic procedures in the United States increased by 51% between 2003 and 2004.<sup>1</sup> As patients look toward less invasive and nonpermanent alternatives to plastic surgery, augmentation of facial features using injectable filler materials is fast becoming one of the most frequently performed aesthetic procedures. These viscoelastic materials provide volume expansion within the dermis and subcutaneous tissues, smoothing out facial wrinkles and folds and enhancing facial contours.

In addition to providing naturalistic volume expansion, the ideal filler material for soft tissue augmentation should be (1) nonimmunogenic and free of infectious agents; (2) easy to inject and allow rapid patient recovery; (3) natural looking and nonpalpable in situ; (4) nonmigratory; and (5) provide a long-lasting (but not permanent) and satisfying esthetic effect.

In recent years various new injectable fillers have become available, including synthetic products and autologous and heterologous natural materials.<sup>2</sup> These filler materials have their own specific merits and drawbacks.

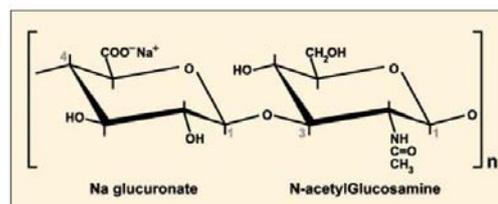
### Materials for Soft Tissue Volume Augmentation

Lipofilling, the technique of harvesting autologous fat at one site and injecting it at another site, is a well-established, safe, and natural way of altering face and body contours. Under optimal conditions, the procedure achieves good tissue augmentation and a durable cosmetic effect, with approximately 50% of the injected material persisting for at least 2 years.<sup>3,4</sup> However, there are limitations to this technique: the procedure is consuming of time and personnel, and moderate overcorrection is required at the initial treatment session, as subsequent fat resorption is unpredictable. Implantation of excessive amounts of fat can result in considerable edema and inflammation and also tends to promote local devascularization, which may cause cystic steatonecrosis. Moreover, fat must be injected in small deposits over large areas to ensure survival of the implanted fat. This results in a long recovery period for patients because of extensive swelling and bruising after treatment. Another disadvantage of lipofilling is that it requires a sterile setting and may involve pain at both the donor and injection sites, thus requiring use of locoregional anesthesia. Moreover, in some cases (most

notably, the patient with human immunodeficiency virus [HIV]-associated facial lipoatrophy), identification of an appropriate donor site may be complicated by a shortage of subcutaneous tissue.

For volume augmentation, permanent fillers such as polyacrylamide gels are also used. One such gel is Aquamid (Contura International A/S, Copenhagen, Denmark), in which the majority of the implant volume (97.5%) is composed of water (the remaining 2.5% is made of polyacrylamide). The cross-linked polyacrylamide forms a gel that does not contain any solid microparticles. Once injected, the gel becomes a stable part of the connective tissue. As with all permanent products, there is a risk of fibrosis and encapsulation of the implant. Complications can also manifest years after treatment, as changes in facial structure in the vicinity of the implant lead to loss of implant stability. Permanent injectables offer obvious benefits to patients and physicians in terms of convenience and cost. However, a prudent approach to their use is called for; reports in the literature indicate the possibility of long-term complications after injection of these materials.<sup>5,6</sup> It is important to realize that facial contours change over time—and permanent fillers may create an unnatural appearance as aging progresses. Any untoward consequence would be difficult or maybe even impossible to correct without surgical intervention. At least one European prospective multicenter study has been conducted that included 15 centers in 6 countries involving 247 patients. The study evaluated the safety and long-term cosmetic results of facial corrective plastic surgery.<sup>7</sup> In addition, an ongoing, retrospective, single-center European study is investigating the safety and long-term cosmetic results of Aquamid.

The semi-permanent filler Sculptra (Dermik Laboratories, Berwyn, PA) (also known as New Fill) is a pulverized crystalline form of poly-L-lactic acid (PLLA), a material known for its use in resorbable suture material, as well as for temporarily creating tissue barriers to separate different tissues in posttrauma and postsurgical healing situations. PLA acts as a volume expander for facial restructuring, and treatment involves several injections administered at monthly intervals. The effect of PLA is to create an increased skin thickness through fibroblast stimulation. Specifically, the PLA stimulates thickening of the collagen layer under the skin as the small PLA particles are encapsulated by fibrous tissue due to a foreign-body reaction. Thereafter, PLA particles are slowly resorbed and the remnants are removed by macrophages. The



**Figure 1.** Hyaluronic acid consists of repeating disaccharide units of sodium glucuronate and N-acetylglucosamine arranged in a linear chain.

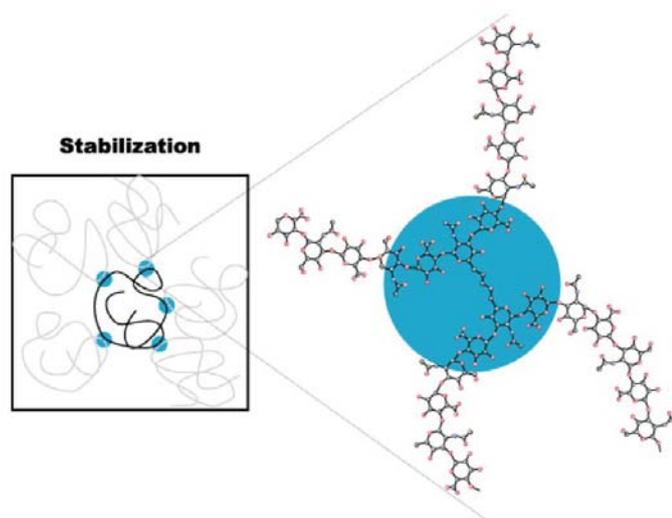
duration of the cosmetic effect is reported to vary from months to years. Sculptra is FDA-approved for patients with HIV-associated facial lipoatrophy. In the VEGA trial,<sup>8</sup> an open, noncomparative pilot study involving 50 patients, Sculptra significantly improved the restoration of facial thickness in HIV patients with facial loss of subcutaneous fat. Complications were mild, but palpable subcutaneous micronodules were observed in 22 (44%) patients, suggesting that this product is less suitable for superficial injection or for lip augmentation. In 6 of the 22 patients, these nodules resolved spontaneously after 2 years.

### Hyaluronic Acid

In light of the limitations and disadvantages of these soft-tissue augmentation materials, another approach using a hyaluronic acid-based preparation has been explored.

Hyaluronic acid is a uniform, unbranched polysaccharide chain consisting of repeating disaccharide units of sodium glucuronate and N-acetylglucosamine (Figure 1). In solution, the polysaccharide chain bends and adopts an expanded coil-like structure. Crucially, hyaluronic acid has identical chemical composition in all species and tissues, making it nonimmunogenic and an ideal candidate for use as a filler material. Hyaluronic acid is found in all vertebrates, forming an essential component of the connective tissues, dermis, joints, interstitial membranes, and the vitreous body of the eye. The main function of hyaluronic acid in the extracellular matrix is stabilization of extracellular structures and formation of the matrix fluid in which elastic fibers and collagen are intermixed. Hyaluronic acid is strongly hydrophilic, conferring a natural hydrating function in the skin that contributes to its suppleness and turgor. While hyaluronic acid is abundant in neonates, production declines with age, causing dermal dehydration and signs of aging.

In view of its structural role in the tissues, protective effects on the cell membrane, and viscoelastic properties,



**Figure 2.** Stabilization of hyaluronic acid in non-animal stabilized hyaluronic acid is achieved by cross-linking adjacent molecules, resulting in formation of a stable 3-dimensional hydrophilic matrix (gel).

hyaluronic acid is an ideal substance to fill skin depressions and provides a natural look and structural stability.<sup>4</sup> Nearly 900,000 hyaluronic acid injections were performed in the United States in 2004, making it the most commonly used soft-tissue filler.<sup>1</sup> Corresponding statistics for the rest of the world are not available; however, because hyaluronic acid products have been available outside the United States for many years, it is likely that the total number of treatments performed worldwide would be appreciably higher.

#### Non-Animal Stabilized Hyaluronic Acid

In non-animal stabilized hyaluronic acid (NASHA), a biosynthetic hyaluronic acid product produced by the fermentation of streptococcal bacteria is used. These bacteria synthesize hyaluronic acid within the cell membrane, from which it is extruded into the extracellular medium. Harvesting is achieved by means of extraction and purification by alcohol precipitation. The use of NASHA reduces impurities and ensures the absence of immunologically active proteins and biologically active animal components, including viruses. No skin test is required prior to treatment with NASHA-based products.

The hyaluronic acid molecule must be modified to prolong its half-life in vivo.<sup>9</sup> Endogenous hyaluronic acid undergoes extremely rapid metabolic turnover,

and has a tissue half-life ranging from 0.5 to a few days.<sup>10,11</sup> Hyaluronic acid can be modified through cross-linking of adjacent polymer chains to form a high-molecular-weight (~10 million Daltons) compound. In NASHA, the hyaluronic acid molecule has been stabilized through the introduction of minute amounts of cross-links between its constituent polysaccharide chains, resulting in the formation of an entangled matrix (gel) that is able to hold large volumes of water (Figure 2). The hyaluronic acid molecules in NASHA are loosely interlinked in a 3-dimensional gel structure that allows unhindered passage of nutrients, oxygen, and hormones, thereby enabling normal tissue function. The stabilization of the hyaluronic acid in NASHA results in prolongation of the tissue residence time to almost 12 months but does not reduce its biocompatibility. The compound remains resorbable, although it is degraded much more slowly than other hyaluronic acid preparations.

Metabolism of NASHA requires the degradation of the 3-dimensional hyaluronic acid gel matrix. The most probable means of degradation is by free radicals, which are present in very low concentrations in normal tissue. The NASHA gel is subject to isovolemic degradation, which enables the initial volume to be maintained throughout the degradation phase. When a stabilizing bridge disappears, water takes its place. The less concen-



**Figure 3.** The various non-animal stabilized hyaluronic acid preparations are designed to match the dermal structure at a specific level of injection.

trated the NASHA gel becomes, the more water each molecule is able to bind. The result is that the same volume can be maintained with less implant material. Finally, the implant is fully degraded.

#### Currently Available NASHA-Based Products

NASHA has been used in a number of products for various clinical purposes, including urological (vesicoureteral reflux and stress urinary incontinence), orthopedic (knee and hip osteoarthritis), and facial aesthetic indications. All NASHA-based products are based on the same gel with the same high concentration of stabilized hyaluronic acid (20 mg/mL), and differ only in terms of the gel particle size. Five NASHA-based products are currently available, although in the United States only one of these products (Restylane) is approved by the FDA for instant aesthetic treatments:

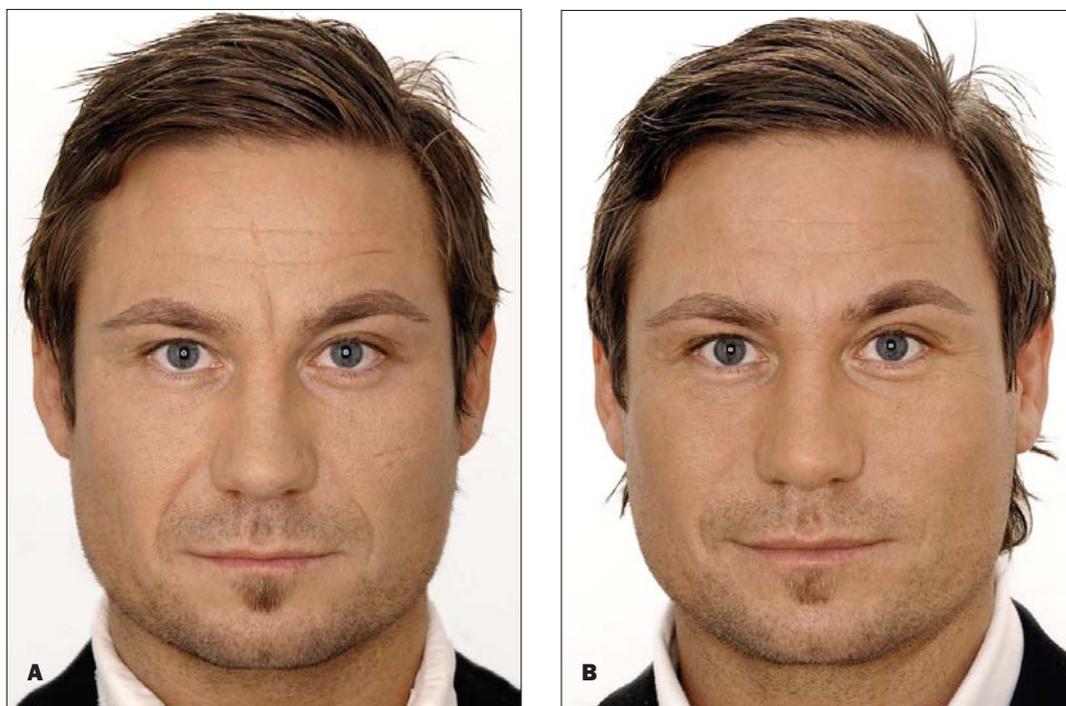
- Restylane Touch: intended to fill out very thin and delicate wrinkle areas, primarily around the eyes and mouth (available in most countries outside the United States).
- Restylane: intended to fill out moderate wrinkles, smooth out scars and folds, and add volume to the lips (available worldwide).
- Restylane Perlane: intended to fill out deeper wrinkles and give volume to lips and skin indentations (available in most countries outside the United States).

- Restylane SubQ: intended for deep subcutaneous and/or supraperiosteal injection to allow more extensive facial volume augmentation and structural support (available within Europe).
- Restylane Vital: for skin rejuvenation (available within Europe).

The various dermal layers of the skin are characterized by different tissue structures. If small implant particles are injected into deep tissue they could be lost; conversely, if larger particles are injected into the superficial dermis they may stretch or tear the much smaller matrix, producing uneven treatment results and possible trauma. For optimal lift and augmentation, the different NASHA products are designed to match the density of the tissues into which they are injected. Restylane Perlane (with its large gel particles) is intended for injection into the deep dermis, Restylane for injection into the middle dermis, and Restylane Touch (with the smallest gel particles) for injection into the superficial dermis<sup>4</sup> (Figure 3).

The duration of the cosmetic effects varies between individual patients, but is generally of the order of 6 to 12 months.

Some common injection-related reactions may occur after injection of the Restylane products. These reactions include erythema, swelling, pain, itching, and discoloration or tenderness at the implant site. Typically, resolution is spontaneous within a few days



**Figure 4. A,** Pretreatment view of a 35-year-old man who requested treatment of a forehead scar, nasolabial folds, and glabella fold. **B,** Posttreatment view 2 weeks after injection of Restylane for the forehead (3 mL) and Restylane Perlane for the nasolabial and glabellar folds (1 mL).

after injection into the skin. Delayed, localized inflammatory reactions (1 in every 10,000 treatments) have been reported to occur with the Restylane products. These have consisted of swelling and induration at the implant site, sometimes accompanied by edema in the surrounding tissue. Erythema, tenderness and, in rare cases, acne form papules may occur. In pronounced cases, a short course of oral corticosteroids may prove effective.

#### Evidence From Clinical Trials

Extensive clinical experience gained from intradermal application of NASHA in over 3 million instant aesthetic treatments since its initial launch in 1996 confirms its effectiveness, safety, and extremely low risk of inflammatory reactions. Clinical studies indicate that NASHA gels are effective in augmenting the lips<sup>12</sup> and correcting marionette lines, facial wrinkles, and nasolabial folds.<sup>12–17</sup> Moreover, they offer a more durable aesthetic result than either bovine collagen<sup>15,18</sup> or avian hyaluronic acid.<sup>19</sup>

Representative photographs of the aesthetic results obtained following treatment with intradermal NASHA preparations are shown in Figures 4 to 6.

A retrospective worldwide review of the tolerability of NASHA in facial soft-tissue augmentation showed that an adverse event was reported in 1 of every 650 patients (0.15%) treated with the product in 1999.<sup>20</sup> Treatment-related adverse events were transient and included redness, swelling, localized granulomatous reactions, and bacterial infection. Adverse event rates decreased to 1 in every 1800 patients (0.06%) in 2000 with the introduction of a more purified hyaluronic acid raw material. Inflammatory reaction was the most common adverse event, affecting 1 in every 5,000 patients.<sup>20</sup>

#### Restylane SubQ—a New NASHA Preparation Product

Restylane SubQ consists of the same NASHA gel used in other Restylane products, but it has a larger



**Figure 5. A,** Pretreatment view of a 67-year-old woman before correction of nasolabial folds, the glabella area, jawline, lipline, and corners of the mouth. **B,** Posttreatment view 2 weeks after injection of Restylane Perlane (1 mL) and Restylane (4 mL). Restylane was used for the nasolabial and glabellar folds and the lipline. Both Restylane and Restylane Perlane were used for the mouth corners.

gel-particle size (approximately 1,000 particles/mL). It is intended for deep subcutaneous and/or supraperiosteal injection to allow more extensive facial volume augmentation or sculpturing. The subcutis consists mainly of adipose tissue and is looser and less vascularized than the dermis, making it a more suitable matrix for implantation of Restylane SubQ. Possible indications for Restylane SubQ include augmentation of normal facial features (eg, malar and chin enhancement), facial reconstruction (eg, treatment of posttraumatic facial asymmetry), and correction of facial concave deformities. Another promising potential indication for Restylane SubQ is the treatment of HIV-associated facial lipoatrophy.

Treatment results are immediate and are estimated to last for at least 9 to 12 months after the initial treatment. Restylane SubQ is currently approved in Europe and can be used as an alternative or a complement to traditional face lifts. Preliminary (3-month) findings of a 12-month Canadian study of Restylane SubQ in cheek and chin augmentation indicated good efficacy,

with the vast majority of patients (84%) and investigators (95%) reporting moderate or good cosmetic improvement at 3 months after the initial treatment.<sup>21</sup> The longest follow-up in the senior author's (A.V.) experience is 12 months, with full correction being retained at this time.

### Conclusion

The use of injectable materials for soft tissue augmentation is becoming increasingly popular. Restylane is a NASHA gel that produces predictable and long-lasting instant aesthetic results. The newest product in the Restylane range, Restylane SubQ, is a large-volume, soft tissue filler suitable for facial augmentation and reconstruction. Ideal candidates for Restylane SubQ treatment include those requiring augmentation of normal cheeks and chin, reconstructive treatment, and correction of concave deformities. With the limited number of products currently available for this indication, Restylane SubQ offers a new treatment approach that is both safe and effective. ■



**Figure 6. A,** Pretreatment view of a 39-year-old woman with deep tear troughs. **B,** Posttreatment view 2 months after administration of Restylane Perlane (0.3 mL on each side) deep on the orbital rim through 2 or 3 injection sites.

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Reprint requests: Anders Strand, MD, Q-Med AB, Seminariegatan 21, Uppsala SE-752 28, Sweden.