The Long-Term Efficacy and Safety of a Subcutaneously Injected Large-Particle Stabilized Hyaluronic Acid–Based Gel of NonAnimal Origin in Esthetic Facial Contouring

Claudio DeLorenzi, MD,* Michael Weinberg, MD,† Nowell Solish, MD,‡ and Arthur Swift, MD§

BACKGROUND Nonanimal stabilized hyaluronic acid (NASHA) offers longer-lasting correction than many other injectable products and is associated with low risk of immunogenic and hypersensitivity reactions. A new large-particle stabilized hyaluronic acid–based gel has been developed to restore facial volume and define facial contours.

OBJECTIVE This study was conducted to assess the long-term efficacy and safety of a large-particle stabilized hyaluronic acid–based gel in patients seeking facial contouring.

METHODS Fifty-seven adult patients seeking esthetic cheek or chin augmentation or both received subcutaneous or supraperiosteal injections or both of large-particle stabilized hyaluronic acid–based gel (20 mg/mL). Efficacy was assessed subjectively using the Global Aesthetic Improvement Scale at intervals up to 12 months after treatment.

RESULTS After treatment, patients and investigators independently considered treatment sites to be at least somewhat improved in 91% and 96% (6 months), 68% and 77% (9 months), and 58% and 52% (12 months) of cases, respectively. Patient- and investigator-assessed treatment response rates (the proportion of patients showing at least moderate improvement) were 72% and 81% (6 months), 42% and 40% (9 months), and 21% and 15% (12 months), respectively. Most commonly reported adverse events were local injection-site reactions, skin induration, and implant mobility.

CONCLUSION This large-particle stabilized hyaluronic acid–based gel is well tolerated and provides relatively long-lasting esthetic correction of the cheeks and chin after subcutaneous or supraperiosteal injection.

Claudio DeLorenzi, MD, Michael Weinberg, MD, Nowell Solish, MD and Arthur Swift, MD, have been consultants to both Medicis Inc. and Q-Med AB, and have received payment for clinical research and training preceptorships. Q-Med AB provided the material used, and the authors (investigators) were paid for their parcticipation in the study.

The youthful face is not defined solely by the absence of lines and wrinkles but by the distinctive volumetric distribution of soft tissues.[1] Facial rejuvenation procedures have traditionally relied upon excision and suspension techniques to counteract the effects of gravity, but surgical face-lifts are of limited effectiveness in reversing the contour changes and volume loss resulting from soft-tissue redistribution and depletion.[2–4] Therefore, structural volume enhancement of the chin, lips, and cheeks, through autologous fat grafting or the use of subcutaneous fillers, is increasingly being used to supplement surgical and nonsurgical facial rejuvenation procedures.[5]

Hyaluronic acid is a viscoelastic, nonstructural component of the dermis that is chemically homogenous across all animal species and tissues.[6] Because natural hyaluronic acid is highly susceptible to enzymatic degradation and is rapidly resorbed in

*The DeLorenzi Clinic, Kitchener, Ontario, Canada; †Mississauga Cosmetic Surgery Centre, Mississauga, Ontario, Canada; ‡Cosmetic Care and Laser Surgery Centre, Toronto, Ontario, Canada; §Aesthetilase, The Centre for Cosmetic and Laser Surgery, Westmount, Quebec, Canada

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situ, it must be stabilized to form an insoluble hydrogel matrix to support its cosmetic application.[7] Nonanimal stabilized hyaluronic acid (NASHA, Q-Med AB, Uppsala, Sweden) is produced from a highly purified hyaluronic acid preparation of bacterial (streptococcal) origin. The use of a nonanimal source reduces the likelihood of antigenic contamination and subsequent hypersensitivity reactions.[8,9] Stabilization of hyaluronic acid, achieved by cross-linking individual polymer chains, does not compromise its biocompatibility.

Various injectable NASHA preparations of different gel particle sizes, including Restylane, Restylane Perlane, and Restylane Fine Lines, have been developed as instant esthetic treatments for facial soft-tissue augmentation. Clinical studies indicate that these NASHA gels are effective in augmenting the lips[10,11] and in correcting marionette lines, facial wrinkles, and nasolabial folds;[10,12–15] there are also indications that they offer more durable esthetic improvement than bovine collagen[14,16] or avian hyaluronic acid.[17] Other hyaluronic acid–based dermal fillers currently available for the correction of wrinkles and folds include Hylaform and Juvederm. Despite the presence of various dermal fillers available for these indications, there is a current lack of hyaluronic acid–based products available that have been specifically designed to provide deep-volume enhancement of facial tissue.

Restylane SubQ is a new large-particle stabilized hyaluronic acid gel preparation consisting of larger gel particles than other products in the Restylane range (1 mL of product contains 1,000 gel particles, compared with 100,000 particles/mL in Restylane). It is intended for injection in the subcutaneous and supraperiosteal facial planes to replace lost volume and to create more-defined facial contours. Restylane SubQ is currently approved in the European Union, Australia, Brazil, Canada, Colombia, Iran, Israel, Korea, Phillipines, and Russia and is available only to physicians trained by the manufacturer (Q-Med AB) in its clinical use.

The purpose of this open-label study was to assess the long-term (12-month) efficacy and safety of this large-particle stabilized hyaluronic acid in esthetic facial contouring. The interim (3-month) results of this study have previously been published.[18]

Materials and Methods

Materials

Restylane SubQ is a clear, colorless, viscoelastic gel consisting of NASHA (20 mg/mL) dispersed in physiological saline solution. The study material (2 mL) was supplied in a 3-mL glass syringe and injected using a sterilized 16-gauge Coleman infiltration cannula (7 or 9 cm in length) with a blunt tip (Byron Medical Inc., Tucson, AZ). Each study center was supplied with five types of cannula; for most administrations, a Coleman COL-I7 infiltration cannula (7 cm, with a blunt, distally closed tip and a single opening) was used.

Patient Selection and Study Design

This prospective, open-label study, performed at four centers in Canada, recruited adult outpatients (aged ≥ 18) of either sex seeking cheek or chin augmentation therapy or both for esthetic purposes. For study inclusion, patients were required to agree to abstain from other cosmetic procedures (e.g., further augmentation therapy, botulinum toxin injections below the eyebrow, laser or chemical skin resurfacing, or face-lift procedures) for the duration of the study. Patients who had undergone facial tissue augmentation therapy or laser or chemical peeling procedures within the previous 6 months or esthetic facial surgery within the previous 12 months were excluded from the study. In addition, patients presenting with active skin disease or inflammation affecting the intended treatment area, those with known allergy or hypersensitivity to local anesthetics or previous adverse reactions to NASHA, and those currently taking anticoagulant or antiplatelet drugs were excluded from participation. The use of anticoagulants, aspirin, and nonsteroidal anti-inflam-

matory drugs was prohibited until the injection site had completely healed.

The Western Institutional Review Board (Olympia, WA) and the Canadian regulatory authorities (Therapeutic Program Directorate, Ottawa) approved the study protocol, and the study was performed in accordance with the principles of the Declaration of Helsinki, the International Conference of Harmonization guidelines for Good Clinical Practice, and local regulatory requirements. All patients provided written informed consent before entry to the study.

Injection Technique

The treatment area was cleaned with an antiseptic solution, and if local anesthesia was required, a lidocaine (0.5 or 1.0%)–adrenaline solution was injected at the planned incision site. Additional anesthesia was provided, if required, using a regional nerve block or subcutaneous injection of lidocaine and adrenaline at the proposed implantation site. A dermal incision 1 to 2 mm in length was made with a scalpel (11 blade) or sharp-tipped injection needle to allow transdermal insertion of a blunt-tipped 16-gauge cannula for administration of study product into the subcutaneous adipose tissue or supraperiosteal level, as appropriate. The NASHA gel was injected in small aliquots throughout the area requiring augmentation by manipulating the cannula into a different tract after each injection, using a tunnelling technique. A maximum of 10 mL (five syringes) of NASHA could be administered to up to three separate anatomical sites (chin and both cheeks) during each treatment session. After implantation, the treatment area was massaged to conform to the contour of the surrounding tissue, and if necessary, ice was applied briefly to reduce any swelling. The principal goal of cheek augmentation was to enhance the appearance of the area immediately anterior to the zygomatic bone, although in practice, the entire region below the inferior orbital margin, lateral to the melolabial fold, was treated. The lowermost extent of the treatment zone was left to the discretion of the practitioner, but for most, a line drawn transversely through the oral commisures delineated the inferiormost limit of the treatment zone; the posterior border corresponded to a vertical line through the mid-temple region.

Evaluation

After initial treatment with NASHA (at baseline), patients returned to the clinic 4 weeks later to determine whether a repeat treatment (touch-up) was necessary to correct for any asymmetry or unevenness. This visit served as a follow-up visit to assess safety and efficacy if no touch-up was required; if touch-up was required, a follow-up visit was arranged 4 weeks later. Subsequent follow-up visits were arranged at 3, 6, 9, and 12 months after baseline.

The investigator (one investigator was designated for each study center) and the patient conducted clinical efficacy assessments independently. Clinical efficacy was assessed subjectively using the five-grade Global Aesthetic Improvement Scale (GAIS; worse, no change, somewhat improved, moderately improved, very much improved). The patient's visual appearance at each follow-up visit was compared with an archival photograph taken before treatment. Patients and physicians were then asked, "How would you describe the degree of improvement?" Possible responses were very much improved, moderately improved, somewhat improved, no change, and worse. In those cases in which treatment was applied to more than one site, efficacy assessments were based on the overall esthetic impression (i.e., treatment sites were considered collectively for each patient). Patients considered to be moderately or very much improved based on the investigators' and patients' GAIS assessments were classified as treatment responders.

Safety assessments, based on directly observed and spontaneously reported adverse events, were performed at each treatment session and at each follow-up visit. Adverse events were assessed for seriousness (serious or nonserious), intensity (mild, moderate, or

severe), and relationship to the study treatment (possibly or probably related, unrelated). Any treatment-related adverse event that was present at the last clinic visit was followed up until it resolved or was classified as chronic or stable.

Statistics

Sample size calculations were based on the two-sided 95% confidence interval (CI) for the proportion of patient-assessed GAIS treatment responders at 3 months (previously reported as 84%),[17] allowing a CI width of 30% or less. Assuming a 20% combined dropout and protocol violation rate, the required sample size was deemed to be 55 patients.

Data were summarized descriptively. All efficacy and safety analyses were based on patients who received at least one NASHA treatment. Data were presented in an observed-case manner, with no imputations for missing values.

Results

Patient Disposition and Demographic Characteristics

Of 59 patients screened, 57 satisfied the study entry criteria and were treated with NASHA, thus comprising both the safety and efficacy populations. This group comprised 55 women and two men, ranging in age from 23 to 76 (mean 52.7), and was predominantly Caucasian (96.5%). Thirty-nine patients (68.4%) had previously undergone one or more facial dermatologic procedures, most commonly plastic surgery (rhinoplasty, blepharoplasty, and face-lifts), soft-tissue augmentation therapy, and botulinum toxin injection. Of the 57 patients treated at baseline, 44 completed 12 months' follow-up with no major protocol violations. Eight patients were classified as major protocol violators because of failure to attend the 3-month follow-up visit within the stipulated time frame ($n = 6$), recent lip augmentation therapy ($n = 1$), or recent chemical peeling ($n = 1$), and a further five patients discontinued the study prematurely (4 were lost to follow-up, and 1 withdrew consent to participate). Patients were evaluated at 3 months ($n = 55$), 6 months ($n = 54$), 9 months ($n = 53$), and 12 months ($n = 52$) post-treatment.

Extent of Exposure to Treatment

All 57 patients underwent initial treatment with NASHA. Ninety-eight cheeks and 16 chins were treated. On initial treatment, the mean volumes of gel injected into each cheek and chin were 2.2 mL (range 0.7–5.0 mL) and 2.1 mL (range 0.6–5.5 mL), respectively, whereas the mean total volume administered to each patient was 4.3 mL (range 1.3–9.0 mL). Thirteen patients (23%) subsequently received touch-up injections of NASHA at a total of 20 treatment sites (chin: 7 sites; cheeks: 13 sites). During touch-up, the mean volumes of gel injected into each cheek and chin were 1.0 mL (range 0.3–2.6 mL) and 1.0 mL (range 0.5–1.8 mL), respectively, whereas the mean total volume administered to each patient was 1.5 mL (range 0.5–5.3 mL). NASHA was generally injected into the subcutaneous adipose tissue but was typically performed at deeper (submuscular or supraperiosteal) levels at anatomical sites (chin and upper cheeks) overlying bone. In all cases, local anesthetic was used at the initial treatment and at the touch-up treatment sessions.

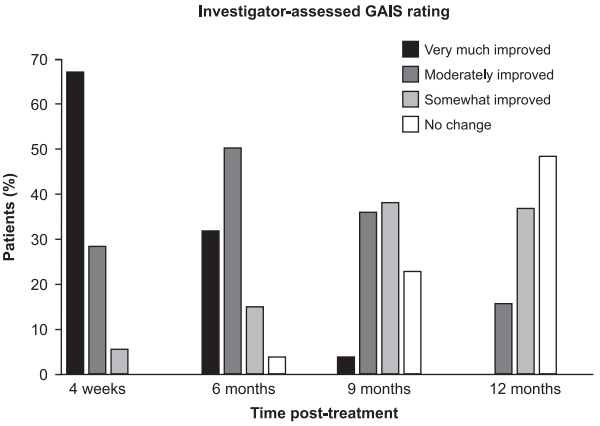

Figure 1. Categorical outcomes based on percentage of patients ascribed each score by investigators using the Global Aesthetic Improvement Scale (GAIS) score at 4 weeks and 6, 9, and 12 months post-treatment.

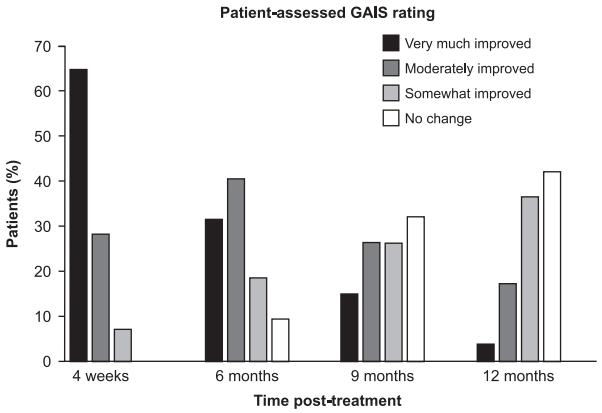

Figure 2. Categorical outcomes based on percentage of patients attaining each score using the patient-assessed Global Aesthetic Improvement Scale (GAIS) score at 4 weeks and 6, 9, and 12 months post-treatment.

Efficacy

Independent GAIS assessments performed by investigators (Figure 1) and patients (Figure 2) indicated a high level of satisfaction with treatment, particularly during the first 6 months. Thus, at 1, 3, and 6 months post-treatment, 100%, 96%, and 91% of patients, respectively, and 100%, 100%, and 96% of investigators, respectively, reported an esthetic improvement (somewhat, moderately, or very much improved) at the treatment site(s). Moreover, the esthetic effect was well maintained at 9 months post-treatment, with 68% of patients and 77% of investigators considering the esthetic result to be an improvement over the pretreatment appearance. Twelve months after treatment, the majority of patients (58%) and investigators (52%) felt that some degree of improvement had been achieved.

Patient- and investigator-assessed treatment response rates (the proportion of patients indicating that the treatment site was moderately or very much improved) were 93% and 95%, respectively, at 4 weeks post-treatment, declining to 72% and 81%, respectively, at 6 months, to 42% and 40%, respectively, at 9 months, and to 21% and 15%, respectively, at 12 months post-treatment.

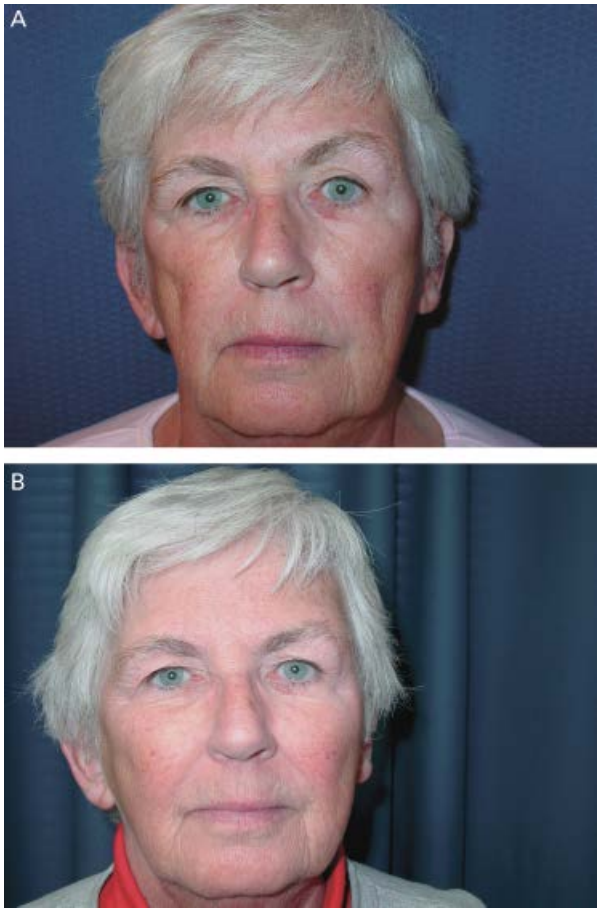

Figure 3. Photographic images depicting the facial area of a representative patient (A) before treatment and (B) at 6 months after treatment. Both cheeks (areas of approximately 30 × 60 mm) were treated. The right cheek was injected with 5 mL of large-particle stabilized hyaluronic acid (5 mL 0.5% lidocaine); the left cheek was injected with 3 mL (5 mL 0.5% lidocaine). The patient and investigator rated treatment at 6 months to have moderately improved the patient's appearance.

Representative photographic images of the face taken before and after treatment with NASHA are presented in Figures 3 and 4.

Safety

During the 12-month follow-up period, treatment-related adverse events (local injection-site reactions, implantation complications, skin tightness, and induration) of predominantly mild intensity were reported in 58% of patients. The most commonly reported events were local injection-site reactions such as swelling, tenderness or redness, bruising,

Figure 4. Photographic images depicting the facial area of a representative patient (A) before treatment and (B) at 6 months after treatment. Both cheeks (areas of approximately 35 × 60 mm) were treated. The right cheek was injected with 5 mL of large-particle stabilized hyaluronic acid (5 mL 0.5% lidocaine); the left cheek was injected with 4 mL of large-particle stabilized hyaluronic acid (5 mL 0.5% lidocaine). The patient rated her appearance as having moderately improved at 6 months; the investigator rated her appearance to be very much improved at 6 months.

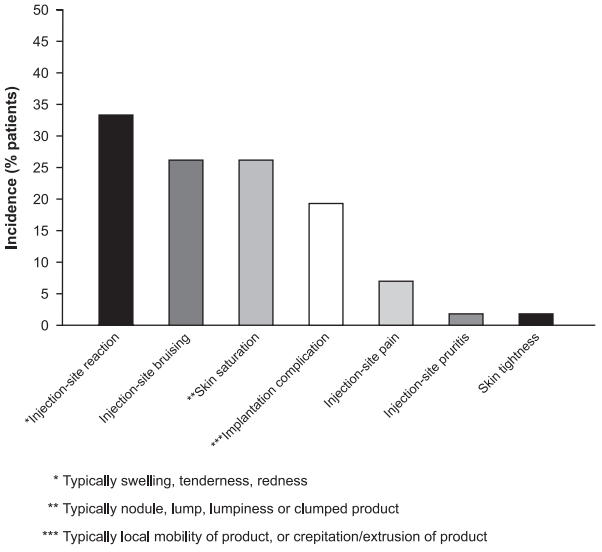

Figure 5. Incidence (%) of treatment-related adverse events during the 12-month follow-up phase ($n = 75$).

pain, and pruritus (37% of patients). Twenty-six percent of patients reported skin indurations (defined as nodules, lumpiness, clumping, or hard mass), and 19% reported implantation complications (local mobility or extrusion of the implant) (Figure 5).

The majority (70%) of treatment-related events appeared on the day of treatment or the following day. Injection-site reactions typically lasted for 1 to 2 weeks. Injection-site pain was generally short lasting (2–8 days' duration) and mild, although one patient experienced severe facial pain, possibly attributable to intramuscular injection of the gel. Skin induration was frequently delayed in onset and of mild intensity but long lasting, persisting for approximately 4 months on average.

Product mobility (i.e., product movement within the zone of injection) of mild or moderate intensity was reported in 10 patients (18%); in nine of these the affected site was the cheek. This complication, which typically arose within the first 2 weeks, tended to be persistent (mean duration 3 months) and in three cases remained ongoing at 12 months. There were no signs of any patients experiencing inflammation. Product mobility resolved spontaneously in four patients, but the implant was aspirated using a moderate-gauge (18 G) needle in two patients. The injection volume per cheek in patients reporting product mobility tended to be higher than in unaffected patients (mean 2.8 mL (range 1.2–5.0 mL) vs 2.0 mL (range 0.7–5.0 mL)), whereas of the 10 patients reporting product mobility, six had previously undergone midfacial plastic surgery.

No patients withdrew from the study because of adverse events, although eight patients (8.7%) had

their implants removed because of skin induration ($n = 5$), skin induration associated with product mobility ($n = 2$), or a delayed-onset injection-site reaction ($n = 1$). In these patients, partial or complete aspiration of the implant (performed as late as 12 months after initial treatment) led to resolution.

Discussion

For the patient requiring large-volume facial soft-tissue augmentation, treatment options are limited. Autologous fat transfer has long been the treatment of choice for adding volume to the mid-face and rejuvenating facial contours. Nevertheless, although liposculpting with autologous fat grafts can offer long-lasting cosmetic correction of deep contour defects,[19] results are highly variable and strongly dependent on technique. Lipotransfer involves harvesting and processing fat, which is time consuming and can result in trauma and potential concave deformities at the harvesting site. Furthermore, initial overcorrection at the treatment site is required because the degree of fat resorption is frequently unpredictable,[20] so repeat grafting over several treatment sessions, each accompanied by extensive postoperative swelling, may be required. Moreover, to ensure graft survival, the fat has to be dispensed in small deposits over a large tissue area using a multichannel technique.[21]

Because experience with the use of this large-particle stabilized hyaluronic acid–based gel for facial contouring is limited, one of the aims of this study was to gather information regarding the preferred technique for administering the material at different anatomical locations. The unblinded nature of the efficacy assessments and the subjectivity of the efficacy evaluation limited this study. However, although the GAIS has yet to be formally validated, it has been used in a number of clinical studies of cosmetic treatments.[14,16,18,22–24] Despite these limitations, the results of this clinical study suggest that the material offers an attractive alternative to autologous fat transplants. The large-particle stabilized hyaluronic acid–based gel is easy to administer and is provided ready to use in prefilled syringes, and it offers an instant and predictable degree of soft-tissue augmentation through a nonsurgical procedure and is generally well tolerated; moreover, it provides clinically relevant esthetic correction that is maintained for at least 9 months post-treatment in the majority of patients. Even 12 months after the initial treatment, more than half of patients report some degree of cosmetic improvement over their pretreatment appearance. Persistent improvements have been reported up to 12 months post-treatment with Restylane SubQ for augmentation of the cheeks and chin.[24,25]

The study was not designed to assess how bothersome adverse events were to patients, so no information is available regarding the extent to which adverse events such as induration and product mobility affected patient satisfaction with treatment. However, because clinical experience in the use of this large-particle stabilized hyaluronic acid–based gel for facial contouring is limited, this study presented a valuable opportunity to assess how best to administer the product at different anatomical sites. Because investigators were permitted some degree of flexibility in injection technique, a number of recommendations can be proposed to reduce the risk of complications. The authors have further lessons from their continued use of the product, subsequent to this reported study.

This large-particle stabilized hyaluronic acid–based gel must be injected below the dermis into the subcutaneous tissue. Although the original intention was to use blunt cannulas of internal diameters of 19 gauge to inject the product, this large-particle stabilized hyaluronic acid–based gel is malleable enough to pass through narrower needles, albeit at higher pressures.

There is also a possibility that the product may be injected with a sharp needle rather than a blunt cannula, as performed in this study. Use of a sharp needle may offer greater possibilities for injecting small volumes at distinct locations without any

significant tissue distortion, which in turn may contribute to a lower risk of product displacement. For example, large-particle stabilized hyaluronic acid–based gel can be administered easily through 18- and 20-gauge needles, although sharp-needle injection of filler material significantly increases the risk of vascular embolization, which has been reported to cause necrosis, blindness, and stroke.[26–28] Embolic events, including potentially severe and fatal cases, may occur because of high pressure injection of material directly into a blood vessel using a sharp needle to inject filler material. Precautions must therefore be taken to avoid intravascular injection. It is essential that techniques such as aspiration before injection are used to avoid this complication. Other methods that will minimize the risk of intravascular injection are the use of local anesthetic containing adrenaline to induce local vasoconstriction, the application of ice packs to the skin before injection, and use of a microbolus injection technique. Using these precautions, one of the authors has subsequently treated several individuals for chin and cheek augmentation.

Small areas of irregularity, or small nodules, should respond to massage to even out the fill effect in the immediate post-treatment period. If induration persists, the use of nonsteroidal anti-inflammatory drugs and topical corticosteroid creams is advised; antibiotics can be prescribed if infection is suspected. If the patient remains troubled by induration, the product is readily amenable to aspiration with a moderate-gauge needle, or if complete removal of the product is desired, injection with hyaluronidase may be used.

The requirement that the product does not adhere in any way to the surrounding tissues limits the quantity of NASHA that can be injected in any one area. Use of a microdroplet technique to disperse the gel throughout the tissues results in greater stability. In addition, large volumes placed in a single pocket may become mobile. Furthermore, they may behave like an implant; a capsule may form that may later contract in a manner analogous to the well-described complication of breast capsular contraction.[29] Excessive boluses of implanted gel may have accounted for the high incidence (18%) of product mobility seen in this study. This complication was considerably more frequent in patients receiving 5 mL or more than in those receiving a total of less than 5 mL of NASHA in the cheeks (47% vs 9%). It may be advisable to limit the volume injected at the initial treatment session to 2 mL per cheek or chin and to administer small aliquots within the tissues. If the esthetic correction proves suboptimal, treatment can be repeated in the form of a touch-up injection (up to 2 mL per treatment site) administered 4 to 6 weeks later. Injection above the inferior orbital rim should be avoided because this will mimic enlarged lower eyelid fat pockets and create an unesthetic result. In addition, subcutaneous tissue changes occurring postsurgery may be additional risk factors for product mobility, because the majority of patients reporting product mobility had previously undergone midfacial surgical procedures. As with persistent induration, the product can be aspirated using a medium-gauge needle if mobility is excessively bothersome to the patient.

In conclusion, the findings of this study indicate that large-particle stabilized hyaluronic acid–based gel provides relatively long-lasting esthetic correction of the cheeks and chin after subcutaneous or supraperiosteal injection. Overall, this product appears to be well tolerated, and this study raised no major safety concerns. With growing clinical experience, it is likely that further refinement of injection technique will result in additional improvements in efficacy and safety.

References

1. Little JW. Volumetric perceptions in midfacial aging with altered priorities for rejuvenation. Plast Reconstruct Surg 2000;105: 252–66.

2. Shuster S, Black MM, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. Br J Dermatol 1975;93:639–43.

3. Kohn RR, Schnider SL. Collagen changes in aging skin. In: Balin AL, Kligman AM, editors. Aging and the Skin. New York: Raven Press; 1989. p. 121–39.

4. Raine-Fenning NJ, Brincat MP, Muscat-Baron Y. Skin aging and menopause. Implications for treatment. Am J Clin Dermatol 2003;4:371–8.

5. Rohrich RJ, Rios JL, Fagien S. Role of new fillers in facial rejuvenation: a cautious outlook. Plast Reconstruct Surg 2003;112:1899–902.

6. Larsen NE, Pollack CT, Reiner K, et al. Hylan gel biomaterial: dermal and immunologic compatibility. J Biomed Mater Res 1993;27:1129–34.

7. Band PA. Hyaluronan derivatives: chemistry and clinical applications. In: Laurent TC, editor. The Chemistry, Biology and Medical Applications of Hyaluronan and its Derivatives. London: Portland Press; 1998. p. 33–42.

8. Friedman PM, Mafong EA, Kauvar ANB, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. Dermatol Surg 2002;28:491–4.

9. Hamilton RG, Abmli D, Strobos J, Adkinson F. Immunogenicity Studies of Cosmetically Administered Nonanimal-Stabilized Hyaluronic Acid Particles. Dermatol Surg 2007;33:S176–85.

10. Bosniak S, Cantisano-Zilkha M. Restylane and Perlane: a six-year clinical experience. Oper Tech Oculoplast Orb Reconstruct Surg 2001;4:89–93.

11. Carruthers J, Klein AW, Carruthers A, et al. Safety and efficacy of nonanimal stabilized hyaluronic acid for improvement of mouth corners. Dermatol Surg 2005;31:276–80.

12. Olenius M. The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles, and folds. Aesth Plast Surg 1998;22:97–101.

13. Duranti F, Salti G, Bovani B, et al. Injectable hyaluronic acid gel for soft tissue augmentation: a clinical and histologic study. Dermatol Surg 1998;24:1317–25.

14. Narins RS, Brandt F, Leyden J, et al. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 2003;29:588–95.

15. Carruthers J, Carruthers A. A prospective, randomized, parallel-group study analyzing the effect of BTX-A (Botox) and nonanimal-sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects. Dermatol Surg 2003;29:802–9.

16. Lindqvist C, Tveten S, Bondevik BE, Fagrell D. A randomized, evaluator-blind, multicenter comparison of the efficacy and tolerability of Perlane versus Zyplast in the correction of nasolabial folds. Plast Reconstruct Surg 2005;115:282–9.

17. Carruthers A, Carey W, De Lorenzi C, et al. A randomized, double-blind comparison of the efficacy of two hyaluronic acid derivatives, Restylane Perlane and Hylaform®, in the treatment of nasolabial folds. Dermatol Surg 2005;31:1591–8.

18. DeLorenzi C, Weinberg M, Solish N, Swift A. A multicenter study of the efficacy and safety of subcutaneous Restylane in aesthetic facial contouring: an interim report. Dermatol Surg 2006;32:208–15.

19. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. Aesthet Plastic Surg 1995;19:421–5.

20. Coleman SR. Structural fat grafts. Clin Plastic Surg 2001;28:111–9.

21. Sommer B, Sattler G. Current concepts of fat graft survival: histology of aspirated adipose tissue and review of the literature. Dermatol Surg 2000;26:1159–66.

22. Beer K. A randomized, evaluator-blinded comparison of efficacy of hyaluronic acid gel and avian-sourced hylan B plus gel for correction of nasolabial folds. Dermatol Surg 2007;33:928–36.

23. Lindqvist C, Tveten S, Bondevik BE, Fagrell D. A randomized, evaluator-blind, multicenter comparison of the efficacy and tolerability of Perlane versus Zyplast in the correction of nasolabial folds. Plast Reconstr Surg 2005;115:282–9.

24. Bugge H, Negaard A, Skeie L, Bergersen B. Hyaluronic acid treatment of facial fat atrophy in HIV-positive patients. HIV Med 2007;8:475–82.

25. Lowe N, Grover R. Injectable hyaluronic acid for malar and mental enhancement. Dermatol Surg 2006;32:881–5.

26. Castillo GD. Management of blindness in the practice of cosmetic surgery. Otolaryngol Head Neck Surg 1989;100:559–62.

27. Feinendegen DL. Autologous fat injection for soft tissue augmentation in the face: a safe procedure? Aesth Plast Surg 1998;22:163–7.

28. Silva MT, Curi AL. Blindness and total ophthalmoplegia after aesthetic polymethylmethacrylate injection: case report. Arq Neuropsiquiatr 2004;62:873–4.

29. Zahavi A, Sklair ML, Ad-El DD. Capsular contracture of the breast: working towards a better classification using clinical and radiologic assessment. Ann Plast Surg 2006;57:248–51.

Address correspondence and reprint requests to: Claudio DeLorenzi, MD, FRCS, 11 Agnes Street, Kitchener, Ontario, Canada N2G 2E7, or e-mail: cdelorenzi@gmail.com