Safety Data of Injectable Nonanimal Stabilized Hyaluronic Acid Gel for Soft Tissue Augmentation

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BACKGROUND. **Nonanimal hyaluronic acid gel was recently developed for soft tissue augmentation and volume expansion and has been shown to offer several advantages in comparison to other augmentation materials. There are rare reports of adverse events believed to be secondary to trace amounts of proteins in the hyaluronic acid raw material.**

OBJECTIVE. **To determine the safety profile of nonanimal stabilized hyaluronic acid gel (Restylane, Perlane, Restylane Fine Lines, Q-Med AB, Uppsala, Sweden) for soft tissue augmentation using a retrospective review of all adverse events data from Europe, Canada, Australia, South American, and Asia from 1999 and 2000.**

RESULTS. **Data from an estimated 144,000 patients treated in 1999 indicated the major reaction to injectable hyaluronic acid was localized hypersensitivity reactions, occurring in approximately 1 of every 1400 patients treated. In 1999 there was an adverse event reported for 1 of every 650 patients (0.15%) treated. These were temporary events that included redness, swelling, localized granulomatous reactions, bacterial infection, as well as acneiform and cystic lesions. For 2000 there was an estimated 262,000 patients treated with hyaluronic acid gel. The total number of adverse events was 144, corresponding to one adverse event for every 1800 patients (0.06%) treated. The major adverse event was again hypersensitivity, occurring in 1 of every 5000 patients treated.**

CONCLUSION. **According to the reported worldwide adverse events data, hypersensitivity to nonanimal hyaluronic acid gel is the major adverse event and is most likely secondary to impurities of bacterial fermentation. According to data from 2000, the incidence of hypersensitivity appears to be declining after the introduction of a more purified hyaluronic acid raw material.**

R. G. GERONEMUS, MD IS A MEMBER OF THE ADVISORY BOARD OF Q-MED. P. M. FRIEDMAN, MD, E. A. MAFONG, MD, A. N. B. KAUVAR, MD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

AS THE demand for soft tissue augmentation grows, the search for the ideal augmentation material continues. Hyaluronic acid gel was recently developed for soft tissue augmentation and has been shown to offer several advantages in comparison to other augmentation materials.[1] Although not currently approved by the U.S. Food and Drug Administration (FDA), it is widely used in Europe and Canada for improved facial contouring and correction of soft tissue defects.[2] Hyaluronic acid is a glycosaminoglycan polysaccharide composed of alternating residues of the monosaccharides d-glucuronic acid and N-acetyl-d-glucosamine forming a linear polysaccharide chain.[1] Glycosaminoglycans, which are abundant in fetal skin, decrease rapidly and are low by adulthood.[3] This compound provides the elastoviscous matrix within which other structures of connective tissue are located.

Restylane, Perlane, and Restylane Fine Lines (Q-Med AB, Uppsala, Sweden) are nonanimal stabilized hyaluronic acid (NASHA) gels biotechnologically manufactured by bacterial fermentation, and reportedly have less hypersensitivity than bovine collagen. They are derived from fermentation of specific strains of streptococci and are then alcohol precipitated, filtered, and dried. The nonanimal origin of hyaluronic acid gel should eliminate the potential for antigenic stimulation. Safety trials in several animal species found that a stabilized form of hyaluronic acid does not elicit humoral or cell-mediated immune reactions.[4]

Lupton and Alster[2] recently reported the first case of cutaneous hypersensitivity to hyaluronic acid gel that occurred after the patients' third treatment session. A potential allergy to an impurity of the bacterial fermentation of the modified hyaluronic acid gel was felt to be the etiology. Shafir et al.[5] reported a sterile abscess that developed in a patient 2 months after several injections of Restylane into her lips and nasolabial folds. In a series of 158 patients treated with hyaluronic acid gel, transient adverse events were seen in 12–13%, which included bruising, erythema, edema,

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Table 1. Reported Adverse Events in 1999 and 2000

	1999		2000	
Adverse effect type	*Number of adverse events*	*Incidence[a] of adverse events (per 100 treated)*	*Number of adverse events*	*Indicidence[a] of adverse events (per 100 treated)*
Hypersensitivity	104	0.07	52	0.02
Injection site inflammation	68	0.05	49	0.02
Other	50	0.04	43	0.02
Total	222	0.15	144	0.06

[a]Assuming 144,000 patients treated in 1999 and 262,000 in 2000 (based on the number of syringes sold).

and slight discomfort at the treatment sites. These reactions were self-limited, resolving in 1–3 days.[1] In a series of 100 patients treated by Olenius,[6] there were no adverse events noted at the 6- and 12-month follow-up.

In order to determine the safety profile of hyaluronic acid gel, we reviewed the reported worldwide adverse events database of Q-Med Esthetics to better determine the safety profile of hyaluronic acid gel for soft tissue augmentation.

Materials and Methods

We performed a retrospective review of the worldwide data gathered by the manufacturer on reported adverse events data from physicians using nonanimal stabilized hyaluronic acid gel. Adverse reactions were defined as all reported signs and symptoms that were felt to be related to the injection of stabilized hyaluronic acid gel. The database included data gathered from physicians in Europe, Canada, Australia, South America, and Asia from 1999 and 2000. Practitioners are actively encouraged to report any adverse reactions to nonanimal hyaluronic acid gel to the Medical Affairs and Safety Department of Q-Med AB. During this time period approximately 406,000 patients were treated with nonanimal hyaluronic acid gel, as determined by the volume of syringes sold. The rate of adverse events was calculated by dividing the number of adverse events reported to the manufacturer by the estimated number of patients treated in the same year.

Results

Table 1 presents the rates of adverse events in 1999 and 2000. There were 222 adverse events reported from an estimated 144,000 patients treated in 1999, corresponding to one adverse event reported for every 650 patients treated. The major reaction to injectable hyaluronic acid was localized hypersensitivity reactions, occurring in approximately 1 of every 1400 patients treated. These consisted of swelling, erythema, and induration at the implant site (Figure 1), sometimes with edema in the surrounding tissues with a median duration of 15 days. There were no reports of systemic symptoms or anaphylaxes.

There were 68 cases of injection site inflammation, corresponding to 1 of every 2100 patients treated. These included redness, edema, and tenderness (Figure 2) shortly after injection, and were described as mild to moderate and self-limiting, with an average duration of 4 days. This reaction started either shortly af-

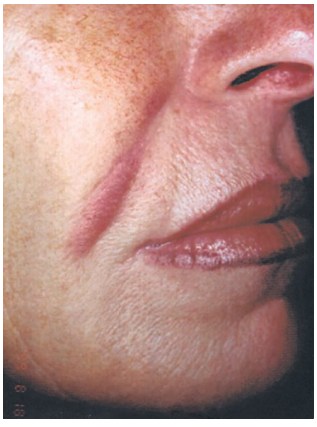

Figure 1. Hypersensitivity reaction to hyaluronic acid gel with erythema and induration at the implant site.

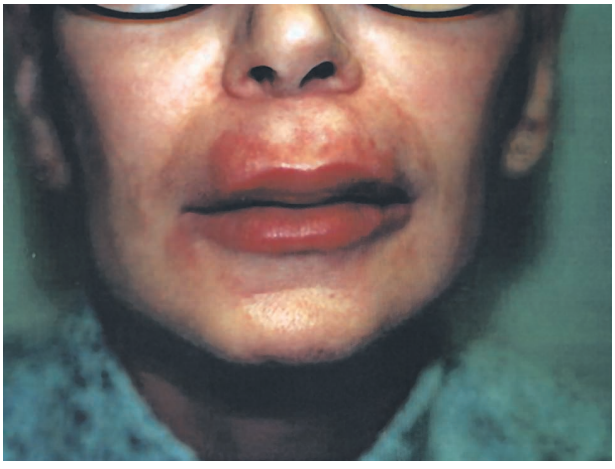

Figure 2. Transient redness and edema of the lips noted shortly after injection.

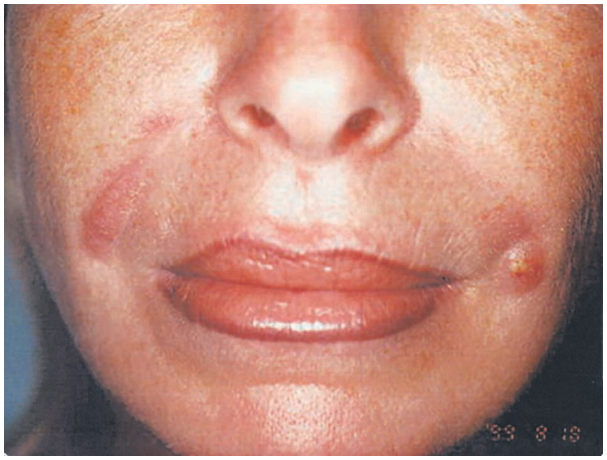

Figure 3. Cystic nodule of the left melolabial fold noted 2 weeks after injection.

ter injection or after a delay of 2 days. There were also rare reports of localized granulomatous reactions, bacterial infection, as well as acneiform and cystic lesions (Figure 3).

In 2000 there were an estimated 262,000 patients treated with Restylane. The total number of adverse events was 144, corresponding to one adverse event for every 1800 patients treated. The most significant adverse event was again localized cutaneous hypersensitivity, occurring in 1 of every 5000 patients treated. The average time to onset was 22 days, with a duration of approximately 15 days. Injection site inflammation was seen in 49 patients, consisting of erythema, swelling, pain, itching, discoloration, tenderness, or temporary palpable lumpiness at the implant site. Typical resolution was spontaneously occurring within 1–2 days after injection in the skin or 1 week after injection into the lips. Two cases of injection site necrosis were reported in the glabelar area a few days after injection, likely secondary to compression of vascular supply from excessive use of product. There were again rare reports of localized granulomatous reactions, bacterial infection, as well as acneiform and cystic lesions.

Discussion

Nonanimal hyaluronic acid gel has the same soft tissue augmentation indications as bovine collagen. The largest drawback to the use of bovine collagen is the risk of hypersensitivity. Data from clinical experience in more than 300,000 treated patients has indicated that the major reaction to injectable collagen has been a localized hypersensitivity reaction to bovine collagen in 3–5% of tested or treated subjects,[7] as well as reports of systemic symptoms.[8,9] One to 3% of patients with one negative skin test will subsequently develop a reaction at the treatment site, and therefore double skin testing is advocated.[10,11]

The use of nonanimal hyaluronic acid gel for soft tissue augmentation represents an exciting new alternative to bovine collagen. Hyaluronic acid is a natural polysaccharide that occurs as an important structural element in the skin, subcutaneous, and connective tissue. Hyaluronic acid in its pure form is a highly biocompatible substance that has an identical form in all living organisms, eliminating the necessity of preliminary skin testing.

Based on the data presented here, the overall proportion of patients experiencing an adverse event was 0.15% in 1999 and 0.06% in 2000. These numbers compare favorably with the incidence of adverse events observed with collagen. It is possible that the number of patients treated was overestimated, since it was based on the number of syringes sold. In addition, adverse events may have been underreported. Both case scenarios would result in underestimation of the incidence of adverse events. However, allowing for even fairly large amounts of error would result in a still rather low incidence of adverse events. For instance, using the higher 1999 incidence rates, if the number of patients treated was only half our estimate, the overall incidence of adverse effects would be 0.3% and if only one in five adverse events were reported, the overall incidence would be 0.8%. Assuming simultaneous overestimation by half of the number of patients treated and reporting of only one in five adverse events would result in an overall incidence of adverse events of 1.4% and an incidence of hypersensitivity of 0.7%. Using similar assumptions with the 2000 data results in an overall incidence of 0.6% and an incidence of hypersensitivity of 0.2%.

Hypersensitivity to hyaluronic acid, which is most likely secondary to impurities of bacterial fermentation, was the major adverse event reported. In several cases following typical hypersensitivity reactions, IgE and IgG antibodies were measured and were normal. Micheels[12] reported on possible allergic reactions in eight patients treated with hyaluronic acid gel (Restylane and Hylaform) between 1995 and 1998, and encouraged skin testing prior to treatment. Lowe et al.[13] reported delayed inflammatory skin reactions to hyaluronic acid fillers (Hylaform and Restylane) in 3 of 709 patients (0.42%) treated between September 1996 and September 2000, and encouraged further exploration of the need for skin testing. Manna et al.[14] compared certain lots of Hylaform to certain lots of Restylane manufactured in 1997 and found a higher protein load present per milliliter of gel in Restylane.

In order to reduce the frequency of hypersensitivity reactions, a hyaluronic acid raw material was introduced in mid-1999 with trace amount of proteins six times lower than the raw material previously used. The

current level of protein was recently analyzed by two independent laboratories in Italy and Sweden and found to be in the range of 13–17 μg/ml of product, which is approximately the same as that found in Hyalaform.[15] To assess the impact of this change in composition, we examined the data on the type of batch ("old" or high protein content, versus "new" or low protein content) used in patients who experienced adverse events in 1999. These data were available for 157 patients: 118 patients received the old batch, whereas 39 received the new batch. In 1999 we estimated that 49,000 patients were treated with the old batch, whereas 95,000 were treated with the purified batch. Therefore adverse events occurred 5.9 times more frequently with the old batch than with the new batch.

In addition, in 2000, a decrease in the incidence of all adverse effects in general, and of hypersensitivity events in particular, was observed. Whereas the estimated number of patients treated almost doubled in 2000 as compared to 1999, the total number of adverse events reported in 2000 was 35% smaller, and the number of hypersensitivity reactions 50% smaller in 2000 than in 1999. The decrease in incidence could also result from a change in patterns of reporting of adverse events, with doctors not reporting adverse events in 2000 that they would have reported in 1999. Such a change in reporting patterns is more likely to happen for mild and transient reactions than serious ones. Finally, a delay in reporting adverse events should be considered. It is possible that some adverse events occurring in 2000 have not yet been reported, so the decrease in incidence may not be as large as the current value. However, the lag time in reporting rarely exceeds 6 months, therefore many additional adverse events for 2000 are unlikely. Ongoing FDA studies of NASHA for facial wrinkles and folds will provide additional data regarding their safety profiles.

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References

1. Duranti F, Salti G, Bovani B, Calandra M, Rosati ML. Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histologic study. Dermatol Surg 1998;24:1317–25.
2. Lupton JR, Alster TS. Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. Dermatol Surg 2000;26:135–7.
3. Meyer LJ, Ster R. Age-dependent changes of hyaluronan in human skin. J Invest Dermatol 1994;102:385.
4. Company Reports Q-Med Sweden. Seminariegatan 21, 752 28 Uppsala, Sweden.
5. Shafir R, Amir A, Gur E. Long-term complications of facial injection with Restylane. Plast Reconstr Surg 2000;106:1215–6.
6. Olenius M. The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles, and folds. Anesth Plast Surg 1998;22:97–101.
7. DeLustro F, Mackinno V, Swanson NA. Immunology of injectable collagen in human subjects. J Dermatol Surg Oncol 1988;14(suppl 1):49–55.
8. Cooperman LS, Mackinnon V, Bechler G, Pharriss BB. Injectable collagen: a six-year clinical investigation. Aesthetic Plast Surg 1985;9:145.
9. Castrow FF, Krull EA. Injectable collagen implant—update. J Am Acad Dermatol 1983;9:889.
10. Stegman SJ, Chu S, Armstrong R. Adverse reactions to bovine collagen implants: clinical and histologic features. J Dermatol Surg Oncol 1998;14(suppl):39–48.
11. Elson ML. The role of skin testing in the use of collagen injectable materials. J Dermatol Surg Oncol 1989;15:301–3.
12. Micheels P. Human anti-hyaluronic acid antibodies: is it possible? Dermatol Surg 2001;27:185–91.
13. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shaw K. Hyaluronic acid skin fillers: adverse reactions and skin testing. J Am Acad Dermatol 2001;45:930–33.
14. Manna F, Dentini M, Desideri P, De Pita O, Mortilla E, Maras B. Comparative chemical evaluation of two commercially available derivatives of hyaluronic acid (hylaform from rooster combs and restylane from streptococcus) used for soft tissue augmentation. J Eur Acad Dermatol Venereol 1999;13:183–92.
15. Company Report Q-Med Sweden. Protein content in Q-Med esthetic products (restylane, restylane fine lines, perlane). Uppsala, Sweden: 2001.