Immediate and Delayed Hypersensitivity Reactions to Restylane

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We report two cases of hypersensitivity reactions to Restylane. In the first case, edema developed in a 57-year-old Hispanic woman 10 minutes after injection of 0.7 mL of Perlane around her upper commissures and Botox in her upper face. The patient had been skin tested for Restylane several months earlier and showed no positive reaction. In the second case, intermittent swelling and induration developed in a 77-year-old Caucasian woman 3 weeks after she received Restylane injections limited to the nasolabial folds. Currently, skin testing prior to hyaluronic acid treatment is not required. Our experience and reports in the literature suggest that while skin testing is unlikely to predict acute reactions to HA, it would be helpful in identifying patients at risk for delayed, long-term reactions. (Aesthetic Surg J 2005;25:489-491.)

Restylane (Q-Med AB, Uppsala, Sweden) is a sterile gel consisting of non-animal stabilized hyaluronic acid (HA) that is used for injection into the skin to correct facial rhytids. Skin testing prior to HA use is not required, as it is for bovine collagen. HA skin fillers appear to offer distinct advantages compared with bovine collagen, in that they are not animal-based and provide increased durability with only rare allergic reactions. HA, however, can cause delayed inflammatory reactions.1-3

We report a case of a 57-year-old Hispanic woman who was skin tested for Restylane 8 weeks prior to injection and developed an acute hypersensitivity reaction immediately following Perlane injections into the oral commissures. The reaction resolved after appropriate treatment with no sequelae. We also report a case of delayed hypersensitivity to Restylane occurring several weeks after injection.

Case 1

A 57-year-old Hispanic woman received Perlane injections around her oral commissures and Botox injections in her upper face in December 2002. The patient had been receiving collagen injections since 1999. She had a past medical history of childhood asthma and disseminated actinic porokeratosis but no known drug allergies. Her supplements and medications included vitamins C and E, calcium, and Prempro. She was skin tested for Restylane in July 2002 and showed no positive reaction. Ten minutes after injection of 0.7 mL of Perlane, her oral commissures began to swell. She complained of a throbbing sensation and a lump inside her mouth. Pressure was immediately applied, as well as ice, for a presumed hematoma. She had been taking vitamin E regularly but denied taking any for the previous 2 weeks. The edema continued and became significantly worse. The patient became anxious and upset, and complained that the pulsating sensation was migrating into her lower lip and mouth. The skin was slightly violaceous and warm. Lorazepam, 1 mg PO, was administered for acute anxiety. She requested a second opinion and was seen by another dermatologist several hours later.

The second physician determined that the patient was experiencing acute angioedema from the Perlane injections. Prednisone, at 40 mg PO qd, was administered for 3 days, followed by 20 mg PO for 5 days. Two days after treatment, the patient noted that the swelling had decreased but stated she could still feel the product inside her mouth. Clarinex, 5 mg PO qd, was added. She had complete resolution of her reaction within the next 2 weeks. The patient was subsequently lost to follow-up and could not be later re-tested for Restylane.
Case 2

A 77-year-old Caucasian woman received Restylane injections limited to the nasolabial folds in August 2004. The patient had a past medical history of hypothyroidism and osteoporosis. Her medications included Ambien, Fosamax, Synthroid, and methylprednisolone.

Three weeks after receiving the injections, intermittent swelling and induration developed on the left upper lip, left cheek, chin, and nasolabial fold areas. She saw a dentist, who told her the swelling had nothing to do with her teeth. She was treated with 2 methylprednisolone packs, with some improvement. However, when the steroid treatment ended, the swelling reoccurred.

On physical examination, she had non-tender indurated edematous plaques on her left cheek, chin, nasolabial fold, and upper lip. There was no erythema, nodules, drainage, cysts or dermatitis. The induration and swelling improved with administration of intralesional kenalog injections, 2.5 mg/mL × 2 mL. The patient refused a skin biopsy. Despite multiple attempts to contact her, she never returned for follow-up appointments.

Discussion

Restylane is a non-animal stabilized hyaluronic acid product (NASHA) that is produced by microbiologic engineering techniques through bacterial fermentation of streptococci, which are then alcohol-precipitated, filtered, and dried. Streptococci are used because of their ability to produce a high yield of HA. NASHA products are produced with HA derived from bacterial cultures and are stabilized by a partial cross-linking method. The stabilization is a 2-step process: the addition of an epoxide results in a cross-link between a minor portion (<1%) of the disaccharides in the HA molecule. This allows the formation of a 3-dimensional network that is very elastic and stable. Neither chemical cross-linking nor stabilization changes the biocompatibility of the native polymer, preserving its inert nature.

The resulting product is a clear, colorless, and transparent gel that is packaged with sodium chloride and a phosphate buffer and comes preloaded in a 0.7-mL syringe. It is a viscous material (20 mg/mL), which is significantly more viscous than Hylaform gel (Inamed Aesthetics, Santa Barbara, CA) (6 mg/mL). Both products comprise the ground substance that binds to water molecules and is responsible for dermal hydration.

The bioengineering process used for the production of NASHA yields a highly pure form of HA. Because tissue pressure can sometimes vary to a higher or lower value as may occur, for example, with low fluid intake, small but significant changes of the material may take place. Edema is a common side effect of HA treatment, as the material can swell after injection.

There are uncommon reports of adverse events believed to be secondary to trace amounts of protein in the hyaluronic acid raw material. Hypersensitivity reactions have been reported as swelling and induration at the implant site, with edema of the surrounding tissues. These reactions have started shortly after injections or after a delay of a few weeks. The swelling can be more noticeable when treating the lip area. A recently published paper has documented intermittent swelling and severe granulomatous reactions lasting several months after injections. Raulin et al reported an exudative granulomatous reaction to HA. Histologic analysis of persistent lip nodules after HA injection revealed the presence of a granulomatous reaction surrounding a blue amorphous material with tinctorial features of HA. In one report, biopsy obtained in the nasolabial fold showed a moderate infiltrate of lymphocytes and plasma cells with a few macrophages containing hemosiderin pigment. No foreign-body giant cells or refractile material were seen in the lower dermis and subcutaneous fat.

A retrospective review of all adverse events data from Europe, Canada, Australia, South America, and Asia, including data from 144,000 patients treated in 1999, indicated that the major reaction to injectable HA was localized hypersensitivity reaction, occurring in approximately 1 of every 1400 patients treated. In 1999, there was an adverse event reported for 1 out of every 650 patients (0.15%) treated. These were temporary events that included redness, swelling, localized granulomatous reactions, bacterial infections, and acneiform and cystic lesions.

In 1999, the NASHA manufacturing process was modified to reduce the bacterial protein content. This has significantly lowered the incidence of adverse reactions from 0.15% to 0.06%. For the year 2000, there were an estimated 262,000 patients treated with HA gel. The total number of adverse events was 144, corresponding to 1 adverse event per 1800 patients. The major event was hypersensitivity, occurring in 1 out of every 5000 patients treated. This hypersensitivity was thought to be most likely due to impurities of bacterial fermentation. According to the Q-Med company, hypersensitivity reactions have been reported in 1 out of every 2000 patients treated. These reactions have been described as mild to moderate and self-limiting, with an average duration of 2 weeks.
In a retrospective study, surveys were sent to physicians in European countries, and a total of 12,344 syringes of HA were sold to these physicians from 1997 until 2001. During this period, 34 cases of hypersensitivity were reported: 16 cases of immediate hypersensitivity and 18 cases of delayed reaction.10 Immediate reactions resolved within less than 3 weeks. The risk of strong but transient delayed reaction was approximately 0.3%. Four resolved within less than 3 weeks. The risk of strong but transient delayed reaction was approximately 0.3%. Four cases of abscess were reported. They were all sterile. No bacterial infection or systemic reactions were found.10

The manufacturer states that since HA is chemically identical in all living organisms, it has no immunological properties. Therefore, it is not necessary to perform a skin test before treatment. Micheels et al11 reported positive IgG and IgE antibodies against hyaluronic acid. In a 6-year period, they reported 8 patients with adverse reactions to injectable HA and advocated intradermal testing before injections with HA. Lowe et al2 discussed their experience with Hylaform and Restylane fillers between September 1996 and September 2000. In this study, 709 patients were treated with HA and Restylane and were followed up clinically for 1 year. Three of these patients (0.42%) developed delayed skin reactions. Three other patients were referred for evaluation of their skin reactions from other physicians. Five of these 6 patients agreed to skin testing of their forearms. In the 5 patients tested, challenge intradermal skin testing was positive in 4 patients; the reactions started approximately 8 weeks after injection. Lowe et al suggested conducting further studies to establish the incidence of reactions in larger populations and the need for skin testing. According to Andre,10 HA is a safe filler product and skin testing does not seem necessary.

The literature suggests that skin testing is unlikely to predict which patients might experience acute reactions to HA, but would definitely be helpful in predicting which patients might be at risk for delayed, long-term reactions. Treatment of acute angioedema-like reactions to HA includes pressure and short courses of steroids and antihistamines. Delayed hypersensitivity reactions can be treated with interlesional and topical steroids, topical Tacrolimus ointment 0.1% BID, and short courses of oral steroids.

Conclusion

Although classified as inert, these HA fillers are clearly able to stimulate both clinically evident granulomatous (delayed) and acute reactions. Patients have thus far not been warned that such reactions may occur. Informed consent should be changed to reflect this new, albeit uncommon, adverse reaction. Physicians need to re-evaluate the need for skin testing before injecting patients with these NASHA materials, and be more aware that these types of reactions can occur.

References

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