

Hyaluronic acid skin fillers: Adverse reactions and skin testing

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Background: Hyaluronic acid (HA) fillers have been proposed as alternatives to other temporary skin fillers, such as bovine collagen, for treating facial skin lines and for providing lip augmentation. Several types of commercial HA fillers are now available in many countries. They include Restylane, which is produced by microbiologic engineering techniques, and Hylaform, which is HA extract derived from rooster combs. They have been approved for use in several countries, but not currently in the United States. There are no recommendations to perform pretreatment skin testing by the manufacturers.

Objective: Our purpose is to describe and comment on our experiences with Hylaform and Restylane fillers. Observation of any side effects and skin testing results were documented.

Methods: Between September 1996 and September 2000, 709 patients were treated with Hylaform and Restylane and were followed up clinically for at least 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 practitioners. Five of these 6 patients agreed to skin testing of their forearms.

Results: In the 5 patients tested, challenge intradermal skin testing was positive in 4 patients; the reactions started approximately 8 weeks after injection.

Conclusions: There was a slight incidence of delayed inflammatory skin reactions to two HA fillers. Both of these reactions occurred after the first and repeat injections. Challenge skin testing was positive in 4 of 5 tested patients. (*J Am Acad Dermatol* 2001;45:930-3.)

Some features of facial aging are the development of facial lines and reduction of lip volume. The treatment of these features has led to the development of several skin fillers over the past few years. These fillers include autologous fat,¹⁻³ bovine serum collagen,⁴⁻⁷ autologous and allogeneic human collagen,⁸ and expanded polytetrafluoroethylene.^{9,10} HA fillers have been proposed as alternatives to other temporary skin fillers for treating facial skin lines and for providing lip augmentation.¹¹⁻¹³

Skin reactions have been well documented for bovine serum collagen.^{14,15} Positive skin tests occur

in approximately 3.5% of patients; delayed hypersensitivity reactions occur in approximately 3% of patients.^{16,17} The importance of double skin testing before initiation of treatment with bovine serum collagen is recommended.¹⁸ More recently, other temporary fillers containing HA or its derivatives have been developed. They include Restylane¹⁹ (Q-Med, Uppsala, Sweden) and Hylaform²⁰ (Biomatrix, Inc, Ridgefield, NJ). Restylane is produced by microbiologic engineering techniques; Hylaform is extracted from rooster combs. These materials have been used for several years as intra-articular injections to treat osteoarthritis.²¹

The manufacturers and distributors of these products suggest that there is no need for skin testing because the products are either nonallergenic or have minimal allergy risk. However, both products contain varying amounts of hyaluronin-associated protein, and therefore a theoretic risk for sensitivity reactions exists.

One recent case report²² documented a cutaneous reaction to an HA filler but did not disclose the type of filler, and skin testing and skin biopsy information were not reported.

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The management of the aging face continues to be refined. The development and usage of safe filling agents, often used with other treatments such as skin resurfacing and botulinum toxin relaxation of hyperfunctional facial muscles, continue to be a priority for those involved in aesthetic surgery.

This article reviews experiences with HA as temporary fillers in the management of the aging face. We report our experience with delayed skin reactions, skin testing, and histopathologic features of the reactions.

PATIENTS, MATERIAL, AND METHODS

Seven hundred nine patients were treated at a private dermatology clinic in London, England, with two HA fillers. The patients were provided with information and consent forms before intradermal implantation with either of the two HA fillers. Four hundred thirty-eight patients were treated with Hylaform; 271 patients were treated with Restylane between 1996 and 2000. One hundred eighty of the Hylaform patients and 56 of the Restylane patients had more than one treatment session. Patients' ages ranged between 25 and 75 years. Treatment indications were nasolabial lines, glabellar lines, lip augmentation, and atrophic facial scars. Six hundred seventy-seven women and 32 men were treated. All patients provided written informed consent before treatment with HA fillers. Patients were treated without prior skin testing, as recommended by the manufacturers, with an intradermal, horizontal tunneling injection.

No abnormal skin reactions were observed at the time of injection other than mild transient erythema. Subsequently, in 3 of the 709 patients, delayed, inflammatory reactions developed at some of the injected sites of the HA fillers. In addition, 3 other patients treated elsewhere were referred for evaluation of delayed skin reactions to HA. These reactions began approximately 6 to 8 weeks after HA injection. Therefore a decision was made to perform retrospective skin testing on those patients who had developed inflammatory skin reactions. One patient agreed to a biopsy of the skin affected by a delayed HA reaction.

RESULTS

Skin testing

Following our initial observations of delayed inflammatory reactions in the 6 patients in mid 1998, skin testing was performed on 5 patients who developed these reactions (one patient declined skin testing). Aliquots (0.1 mL) of both fillers were injected intradermally into the forearm skin. The areas were then observed.



Fig 1. Skin-tested forearm 8 weeks after intradermal injection of HA filler (Hylaform) with severe grade III inflammatory reaction.

Four of the 5 patients tested developed discernible skin reactions ranging from mildly inflammatory nodules to inflammatory reactions with an abscess in one patient (Fig 1). The elapsed time until appearance of the reactions in the 5 patients was between 5 and 7 weeks.

Skin reactions

Both Hylaform and Restylane caused skin test reactions in 3 of the patients who had had previous reactions. Hylaform alone showed a reaction in one patient. One patient did not react upon testing to either product. The skin test reaction sites resolved between 2 and 12 weeks after appearance.

Skin reactions at sites injected with the HA fillers were noted on 6 patients (4 with Hylaform and 2 with Restylane) (Figs 2 and 3). The delayed reactions were of varying severity. Four patients (3 with Hylaform and 1 with Restylane) developed induration and inflammation at the injected sites. They all developed an abscess in the nasolabial region. On palpation, these areas were firm, tender, edematous, and erythematous. The duration until satisfactory resolution in these patients ranged from 6 to 24 weeks. Three of the patients required several intralesional triamcinolone injections (3 mg/mL) to reduce the induration and inflammation.

Eventually all lesions resolved. The patient with abscess formation had minimal scarring.

Histopathologic examination

A 3-mm punch biopsy specimen was obtained from one patient's nasolabial area affected by a reaction to Hylaform. The biopsy was performed about 6 weeks after the patient first noticed the reaction. The other affected patients declined skin biopsies.



Fig 2. Example of delayed inflammatory reaction to HA filler (Hylaform) occurring 8 weeks after implantation.



Fig 3. Another patient showing inflammatory skin reactions 7 weeks after implantation (Hylaform).

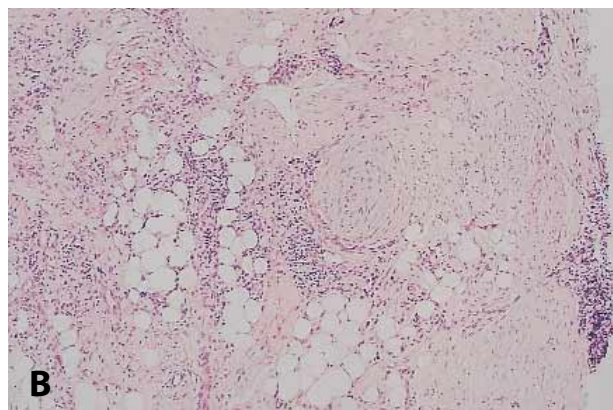
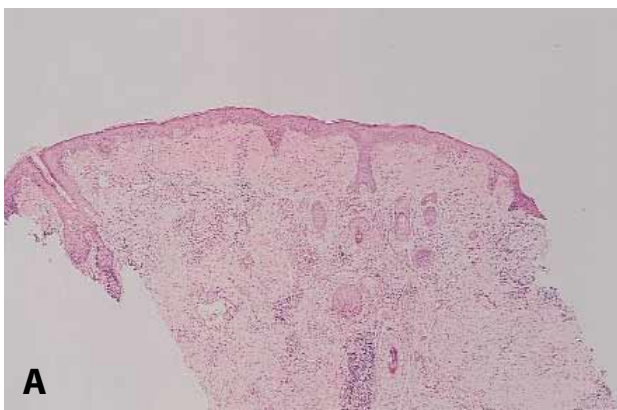


Fig 4. A and B, Histologic features of biopsy specimen taken from skin affected by inflammatory reaction (see text for description of features). A deep, predominantly lymphocytic and plasma cell infiltrate is seen (Hylaform).

The biopsy specimen was fixed in 10% neutral buffer formalin. After routine processing, sections were stained with hematoxylin and eosin and alcian blue at pH 2.5. Light microscopic examination of hematoxylin-eosin-stained section showed a normal epidermis with major changes confined to the dermis and subcutaneous fat. The upper dermis showed elastic degeneration, which was consistent with actinic damage. The mid and lower dermis showed a moderate infiltrate of lymphocytes and plasma cells with few scattered macrophages containing hemosiderin pigment. Eosinophils were not seen, and there were no foreign body giant cells. The changes were accompanied by organizing fibrosis that was most prominent in the lower dermis. Furthermore, all the aforementioned changes extended into the subcutaneous fat. There was no refractile material, and examination under polar-

ized light showed no foreign birefringent material. Alcian blue stains for HA mucins, with normal skin used as a control, showed no abnormal staining for such substance (Fig 4).

DISCUSSION

The HA fillers represent an alternative treatment option for the aging face, particularly for facial lines, for lip augmentation, and for treatment of distensible atrophic facial scarring.

From our observations, these agents are clearly potentially reactive to the skin. The precise nature of this reactivity requires further investigation. The delayed time responses after skin testing require additional study to examine the histopathologic and immunologic responses of the skin to HA products and incipients. Correspondence from both manufacturers and/or distributors of HA products stress min-

imal risk of allergy and do not suggest the need for pretreatment skin testing.

The incidence of allergy in our own treated patients appears much lower (ie, 3/709, 0.42%) than that reported for bovine-derived collagen, which has been reported as being between 3% and 4%.¹⁸

In 3 of the patients who reacted to HA fillers, there was no previous history of injection of these agents. These patients showed reactions to both Hylaform and Restylane, which implies causes other than an avian-protein reactivity that would be expected only with Hylaform.

The histopathologic features of the dermal reaction in the only patient who agreed to undergo skin biopsy showed a delayed, nonacute reaction with the presence of predominantly lymphocytic and plasma cell infiltrates. These types of infiltrates contrast with the mild acute inflammatory infiltrates reported in the animal studies with HA (unreported data on file, Collagen Corp and Biomatix). Hylaform and Restylane have been approved for use in many countries including Canada, Australia, and those in Europe. They are currently not approved for use in the United States, but clinical studies are planned.

Recently several other temporary and permanent dermal fillers have become available in Europe; these include Achyal, New-Fill, DermaLive, and Artecoll. Fascian and Cymetra have also been recently approved for use in the United States.

Several of these products have had limited human testing before marketing; because they are classified as medical devices, they are not required to have the same degree of scrutiny by the Food and Drug Administration that is required for new drugs. In view of the observations in our report, perhaps human testing in larger patient populations is desirable before approval of new skin fillers. Further controlled double-blind studies are required to provide additional information about comparative duration of HA and other fillers.

CONCLUSION

HA fillers are useful for the management of facial lines, lip augmentation, and distensible acne scars. Patients' acceptability appears to be good, although the successful placement of HA fillers in the high subdermal plane is clearly dependent on the skill of the practitioner.

The issue of skin testing needs to be further explored. These agents clearly have the potential for delayed, inflammatory skin reactions, albeit in a smaller percentage of patients than reported for bovine collagen fillers. Further research is needed to investigate the incipients that cause these reactions, to establish the incidence of reactions in a larger patient

population, and to determine the need for intradermal skin testing before initiation of HA filler therapy.

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