The author recommends that, contrary to currently accepted protocol, patients undergo skin testing before receiving injectable hyaluronic acid (HA) gel fillers. The risk of hypersensitivity to HA gel fillers, although low compared with bovine collagen, is a factor to consider. As larger volumes of fillers are injected, more extensive and vigorous reactions may be seen. (Aesthetic Surg J 2005;25:403-405.)

The popularity of minimally-invasive cosmetic procedures is continuing to grow. As part of this phenomenon, various types of fillers are increasing in popularity. Currently, fillers are used for depressed nasolabial and melolabial folds, lip augmentation, and scar reduction and, in larger quantities, for structural augmentation along the cheek bones and jaw line. Hyaluronic acid (HA) gel fillers have become increasingly popular because the correction achieved with HA lasts longer than the correction achieved with traditional collagen products.

Much of the original enthusiasm for HA gel fillers was because of their low antigenicity when compared with bovine collagen.1,2 In fact, the package insert for both Hylaform (INAMED Aesthetics, Santa Barbara, CA) and Restylane (Q-Med, Uppsala, Sweden), the 2 Food and Drug Administration (FDA)–approved HA gel fillers, states that they do not require skin testing.

However, over the last 8 years, I have become aware of several significant localized hypersensitivity reactions caused by Hylaform and Restylane. Although not FDA-approved during much of this time period, these products were widely used in Canada and Europe.

The first reported reactions to Hylaform and Restylane were in 2000. Both reactions occurred on repeat-injection cycles: (1) Following Hylaform administration, a granulomatous reaction occurred that peaked at days 4 to 6 and resolved spontaneously over 6 weeks.3 (2) An acute hypersensitivity reaction to Restylane occurred 2 weeks after the third treatment, manifesting as erythematous indurated nodules in the treatment area. The condition resolved with oral and topical treatment.4

Between 2001 and 2002, an increasing number of hypersensitivity reactions were reported, prompting some to consider the advisability of skin-testing before injecting HA, as is done before collagen treatments.5-7 It was postulated that the cause of hypersensitivity reactions was residual protein impurities in the materials. These concerns prompted a large retrospective review of adverse events associated with Restylane based on the data available from the manufacturer.8 The study revealed that a 0.15% adverse event incidence in 1999 was reduced to 0.06% in 2000. This decrease was attributed to the introduction of a more purified HA raw material in the Restylane product.

Despite the improved product introduced by Q-Med in 2000, reactions to HA products have continued to be reported.9,10 Most recently, in a retrospective study examining adverse reactions to Restylane in Europe from 1997 to 2001, the authors concluded that since 2000 the overall incidence of hypersensitivity reactions was about 0.6%. About half of these reactions occurred immediately and resolved over a 3-week period; the other half were delayed reactions. Four abscesses were also reported in this group.11

Because bovine collagen is estimated to have a 3% to 5% risk of causing a hypersensitivity reaction, it has been recommended that patients undergo 2 skin tests before it is administered.12-14 The risk of hypersensitivity to HA gel fillers, although low compared with bovine collagen, is still a factor. I, personally, have seen 5 patients with hypersensitivity reactions to HA gel fillers. It is notable that 2 of these patients also had hypersensitivity reactions to injected bovine collagen. All of these reactions appeared several weeks after the material was injected and appeared as erythematous indurated papules. Fortunately, all the reactions, except for one, resolved without sequelae.

**Second Thoughts**

Karyn L. Grossman, MD, Santa Monica, CA, is a board-certified dermatologist.
The most recent reaction I have seen was in a patient who was treated by another physician and then presented to me for treatment advice. Her reaction, which occurred several weeks after the injections, continued to persist as an isolated papule 6 weeks into treatment with intraleisional injections of triamcinolone (Figure).

Because of the hypersensitivity reactions I have seen and those reported in the literature, it is my practice to have patients skin-tested before treatment with HA gel fillers. Although the risk of reaction is lower than with bovine collagen, I tell my patients that a reaction is possible. As larger volumes of fillers are being injected, more extensive and vigorous reactions may be seen.

Although there are currently no reports of scarring from HA hypersensitivity reactions, I have seen 3 patients with scarring from intense reactions to bovine collagen. Further, because one of the patients reported to have an HA hypersensitivity reaction required surgical drainage of the sterile abscess formed by the reaction, I have concern that a future patient may develop scarring from a vigorous reaction. Patients undergoing voluntary cosmetic procedures, especially those they believe to be low-risk, may have little tolerance for adverse reactions.

Before initiating treatment with HA gel fillers, I administer an intradermal skin test, as is my practice with collagen, and then follow up 4 weeks later. I label the test syringe with the patient’s name and later use this as the treatment syringe. In one patient the skin test became erythematous and indurated during the testing period, and consequently I did not perform the treatment. While the skin test may not demonstrate every possible delayed reaction, it will at least reveal the more immediate hypersensitivity reactions. Interestingly, since 2001, I have had only one patient with a new positive skin test for bovine collagen.

I occasionally have a patient who refuses skin testing, pointing out that it is not required by the manufacturer. Thus, as part of my informed consent, I have a detailed section on the risk of allergic reaction. Skin testing and extensive informed consent on all of the potential risks of HA gel fillers have added an extra layer of safety to this procedure.

The quest for the perfect filler continues as injectable procedures gain popularity. Captique (Genzyme Corp, Cambridge, MA), a new non–animal-derived HA gel filler, has just been approved in the United States, and Juvederm (Inamed, Santa Barbara, CA) is undergoing clinical trials. More HA gel fillers are in the pipeline. I anticipate that the popularity of these products will grow, because many other types of fillers have not fulfilled practitioner expectations.

**References**


Reprint requests: Karyn L. Grossman, MD, 1301 20th Street, Suite 350, Santa Monica, CA 90404.

Copyright © 2005 by The American Society for Aesthetic Plastic Surgery, Inc.

1090-820X/$30.00
doi:10.1016/j.asj.2005.00.000