Letters to the Editor

Hyaluronic Acid: A Common Thread

To the Editor:

The scientific basis for the application of substances for soft tissue augmentation is critical. It is used to support the cosmetic application of an agent and define the adverse event profile. Unfortunately, the scientific literature concerning these agents is often confusing.

In particular, many articles have attributed reactions to hyaluronic acid (HA) fillers to hypersensitivity. Recently, Dr. Karyn Grossman discussed such cases. Nevertheless, on close inspection, the literature fails to identify allergy as the etiology.

Hyaluronic acid is a common thread, and identical, among all vertebrates. It is produced from enzymes in the cell membrane contained in what has been theorized to be a specific organelle. Commercial HA products have a molecular weight between 1 and 10 million. In the human body they have a very fast turnover, except in the eye. Their usefulness for aesthetic indications requires cross-linking or other modifications to increase residence time in tissues.

These agents are produced by tissue extraction or biosynthesis from a non-animal source (NASHA). These cross-linked hylan gel derivatives of hyaluronan retain the biocompatibility and biological properties of the natural hyaluronan and are non-immunogenic. Studies in mice, rabbits, primates (owl monkeys), and guinea pigs in various tissue compartments (intramuscular, intravitreal, intraperitoneal, intradermal, subcutaneous) did not produce symptoms of sensitization or immune response. If there is any immunologic response to these products, it is most likely a response to protein contaminants rather than to the HA itself.

As noted by Dr. Grossman, there have in fact been reports of hypersensitivity to HA in the literature. However, this is likely due to the original protein load. In 1999, Restylane (Medicis, Scottsdale, AZ) was reformulated with a resultant 6-fold reduction of protein load in the final product. This reduction has resulted in concomitant reduction in occurrences of suspected hypersensitivity reactions reported to the World Health Organization (WHO) international database.

Recently, there have been a series of reports on theorized hypersensitivity reactions, which are more likely a treatment-associated response to hyaluronans. One article attributed extreme angioedema of the lips to hypersensitivity. A true allergic reaction would not resolve within a week. A treatment-associated response is generally avoidable by injecting the NASHA slowly and gently. No antibody tests were run in this case to support the author’s claim of hypersensitivity of the reaction. If it were believed that this patient had an allergic reaction, why were no antibody tests run?

Dr. Grossman’s reference to the article by Micheels is misleading. Micheels reported that IgG and IgE responses to HA can occur and are responsible for hypersensitivity to these HAs. In his article, the specificity to HA of these antibodies was not confirmed, and the re-challenge of one of the reported allergic patients elicited no positive skin response. Finally, skin tests in the Micheel’s article were performed after the HA fillers were digested with hyaluronidase, which leaves no HA. Therefore, these skin tests are void of HA. Lowe no longer supports the conclusions of his article on HA allergy as valid based on his observations over the past 4 years (personal oral communication, July 2005).

Another recent article reported a granulomatous reaction to NASHA and suggested, without evidence, that the possible mechanism of the reaction was allergic in nature. These authors also did not perform antibody studies and again cited Micheels. The Micheels article is often referenced by those who think every adverse response to HA is allergic in nature. Furthermore, the availability of hyaluronidase (Vitrase, ISTA Pharmaceuticals, Irvine, CA) now makes treating lumps or misplaced HAs very simple. The lumps themselves, as described by Grossman, are not caused by adverse reactions but are actually misplaced filler. Nevertheless, when physicians are referred a case of supposed long-standing allergy to HA, they should confirm that the agent used was actually an HA, in that silicone or other fillers have been found to be the responsible agent in situations in which HA was the purported product causing
an allergic reaction\textsuperscript{10,11}(Wortzman M, personal oral communication, February 2005).

At a time when we are seeing agents such as Sculptra (Dermik, Berwyn, PA) used in an off-label manner in immune-competent individuals, as well as assuming all HA products are equal, let us not forget the importance of a scientific basis for our assumptions and clinical decisions.

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\textbf{References}


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