Resistant and Recurrent Late Reaction to Hyaluronic Acid–Based Gel

Ofir Artzi, MD,* Christoforos Loizides, MD,* Ines Verner, MD,† and Marina Landau, MD‡

BACKGROUND Late reactions to hyaluronic acid (HA)-based fillers have a recorded rate of 0.02%. The recent experience with a newly introduced filler in the tear trough area and the lips showed higher rate of reactions with a tendency to persistency and recurrences.

OBJECTIVE To delineate the features of reactions to this newly introduced filler.

MATERIALS AND METHODS Medical records of 400 patients (360 women and 40 men; average age = 49.6 years) were examined in this retrospective study. Juvéderm Volbella (HA-Vb) filler was injected only into the tear trough area or lips. Other HA-based products were used in other areas of the face.

RESULTS Seventeen patients (4.25%) developed prolonged (up to 11 months) and recurrent (average: 3.17 episodes) late (average onset: 8.41 weeks after the injection) inflammatory cutaneous reactions.

CONCLUSION The incidence of late reactions to HA-based fillers varies between products. The authors are reporting an exceptionally high rate of cutaneous reactions for this newly introduced filler. In the authors' experience, broad-spectrum antibiotics in conjunction with repeated high-dose hyaluronidase injections into the inflammatory nodules were effective treatments.

The authors have indicated no significant interest with commercial supporters.

Delayed reactions to hyaluronic acid (HA)-based fillers are estimated to occur in approximately 0.02% of the treatments.[1] In this study, the authors describe a cohort of 400 patients; of whom, 4.25% developed late and persistent reactions to a new filler injected in the tear trough area and lips. These data suggest that this new product may be associated with more frequent late-onset cutaneous reaction than previously reported for other products.

Objective

To delineate the features of reactions to a newly introduced filler.

Materials and Methods

The authors collected clinical data for all patients treated with Juvéderm Volbella (HA-Vb) injectable gel at four medical centers in Israel. Patients who were treated with non-HA fillers were excluded from this study. All injections were performed by two physicians, between February 2014 and June 2014 (Physician 1) and between September 2013 and February 2014 (Physician 2). After treatment, patients were instructed not to apply make-up for 12 hours. Data were collected from patient charts and through phone call interviews. Recorded data included age, sex, medical history (including autoimmune disorders),

Tel Aviv Sourasky Medical Center, Department of Dermatology, The Sackler School of Medicine, Tel Aviv, Israel; †Dr. Verner Clinic of Dermatology & Aesthetics, Kiriat Ono, Israel; ‡Wolfson Medical Center, The Sackler School of Medicine, Tel Aviv, Israel

ISSN: 1076-0512 • Dermatol Surg 2016;42:31–37 • DOI: 10.1097/DSS.0000000000000562

medications, previously injected products, amount of injected new filler and other HA fillers, number of different fillers injected at each treatment session, injection sites, injection methods, time lag between injection and the first reaction, the course of the reaction, histology results when available, treatments, and outcomes.

Results

The authors ascertained a total of 400 patients (360 women [90%]; average age = 49.6 years [range: 28–70]) who were treated with HA-Vb injectable gel. The filler was injected in the tear trough area of 350 patients (Physician 1) and in the lips and tear trough area of 49 patients and 1 patient, respectively (Physician 2). No other products were injected in the lips and tear trough area other than HA-Vb. All patients were injected with additional HA-based products into other facial areas. The average number of different products injected to the same patient, in two consecutive sessions, was 2.6 (range: 1–4). The average amount of fillers injected to the same patient in two consecutive sessions was 3.2 mL. The interval between two sessions ranged from 6 weeks to 6 months. In all 400 patients, both cannulas and needles were used.

Of 400 patients, 17 (4.25%) developed a cutaneous reaction to the examined filler. Affected individuals were generally healthy and without a history of autoimmune disease or former injections of permanent filler (silicone or others). Of 17 patients, 2 had hyperlipidemia treated with simvastatin, 2 had hypothyroidism treated with levothyroxine, and 1 had hypertension treated with ramipril.

In addition to HA-Vb, 8 of 17 patients (47%) were treated with 1 additional product, 4 (23%) were treated with 2 additional products, and 5 (29%) with 3 additional products (Table 1).

In 11 patients (64%), all products were injected at the same time (during the same treatment session), whereas in 6 patients (36%), HA-Vb filler was injected 6 to 8 weeks up to 6 months after a first treatment with different fillers.

The cutaneous reaction was observed 8.41 weeks after the injection of HA-Vb (range: 5–12) and initially manifested with purplish to brownish discoloration of the skin surrounding the injection site. In the cases of tear trough correction, the change of color appeared mostly bilaterally, below the eyes, and was referred to by many patients as a "sad-clown" look (Figure 1). Subsequent to color changes, the injected area became tender, warm, and indurated (2–7 days), up to the formation of a deep nodule (Figures 2A and 3).

All affected individuals were first treated with oral ciprofloxacin (500–750 mg twice a day) for a period of 3 to 4 weeks. In 6 of these patients, all symptoms and signs receded and did not recur. The 11 remaining patients developed recurrent episodes of inflammatory reactions. Three patients had only 1 recurrence, 2 patients had 2 recurrences, 2 patients had 3 recurrences, 1 patient had 4 recurrences, 1 patient had 5 recurrences, and 2 patients had 8 recurrences. Relapses were not always seen at the initial reaction site. They resolved and recurred in different facial areas, where other HA fillers were previously injected (Figure 2B). Recurrent episodes were treated successfully with repeated courses of broad-spectrum antibiotics (ciprofloxacin or rifampicin for a minimum of 3 weeks) in conjunction with multiple intralesional injections of hyaluronidase (30–100 unit per mass or nodule). Oral, intramuscular, and intralesional administration of corticosteroids was less effective.

The overall period of the reaction (period from first episode to the resolution of the last episode) was between 1.5 and 11 months (average 4.59 months). Patients experienced an average of 3.17 recurrences (range: 1–9). Most recurrent episodes lasted an average of 2 to 4 weeks when treated and relapsed 2 weeks after cessation of therapy (Table 1). A biopsy obtained from patient 11 (Table 1) revealed a florid granulomatous dermatitis (Figure 4). Fungal, bacterial, and mycobacterial culture and a polymerase chain reaction (PCR) assay, taken before any treatment, were unrevealing in this patient.

A retrospective comparative study performed at Physician 1 site revealed that in contrast with the rate of

TABLE 1. The Features of the Recurrent Reaction

	No	Patient Initials	Date of Volbella Injection	Number of Other HA-Based Gel Injected	Other Material Injected in Addition to Volbella	All Material Injected at the Same Time	Total Amount Injected in All Sessions (mL)	Time to First Reaction After Volbella Injection (Weeks)	Number of Episodes Till Full Resolution	Time Till Full Resolution (Months)
Physician 1, injections in the tear trough area	1	MC	May 8, 2014	2	SubQ; Perlane	No	4	5	1	2
	2	RL	Feburary 10, 2014	2	SubQ; Restylane	Yes	4	9	2	4
	3	BH	May 15, 2014	3	SubQ; Restylane; Voluma	Yes	5	5	4	6
	4	MB	Feburary 27, 2014	1	Perlane	No	2	12	1	1.5
	5	RN	April 15, 2014	1	Restylane	Yes	4	8	4	5
	6	VB	July 1, 2014	1	Perlane	Yes	1	10	1	1
	7	OB	May 1, 2014	3	SubQ; Restylane; Voluma	Yes	6	9	9	11
	8	AH	July 11, 2014	3	SubQ; Restylane; Voluma	Yes	5	7	6	9
	9	ID	May 15, 2014	1	Perlane	No	2	7	3	4
	10	SK	March 11, 2014	1	Perlane	Yes	2	9	1	1
	11	LB	May 8, 2014	3	SubQ; Restylane; Voluma	Yes	7	10	9	11
	12	GF	Feburary 10, 2014	3	SubQ; Restylane; Voluma	No	6	11	3	4.5
	13	EM	March 11, 2014	1	Perlane	No	3	7	2	2.5
Physician 2, injections in the lips	14	ZZ	October 15, 2013	2	Voluma; Stylage L	Yes	4	12	1	3
	15	HT	October 21, 2013	1	Stylage L	Yes	2	9	2	3
	16	MA	September 17, 2013	1	Voluma	Yes	4	9	4	6
	17	KD	October 11, 2013	2	Juvéderm 2; Juvéderm 4	No	3	4	1	1.5

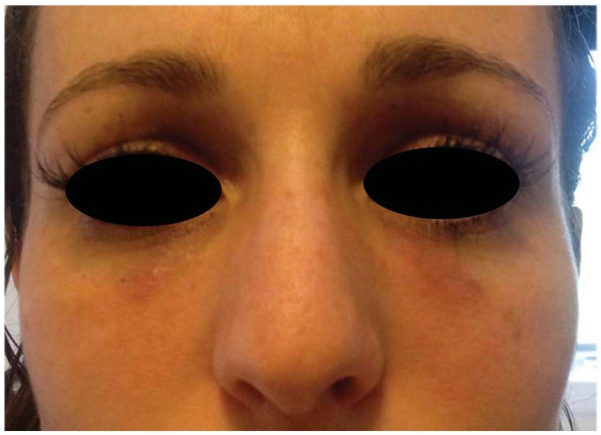

Figure 1. Sad-clown look described by patients.

late-onset reactions observed in this study, of 302 patients injected in the tear trough area with HA-based fillers between February 2013 and June 2013, only 1 developed a mild late reaction (0.3%). Of note, the average number of products, the total material volume per patient, and injection techniques and cleansing methods did not significantly vary between the 2 periods. The only change was the use of HA-Vb for treating the tear trough area in 2014, as compared with the usage of other HA-based filler in the tear trough area in 2013.

In attempt to identify factors predicting a skin reaction to HA-Vb, the authors attempted to correlate three parameters: number of different products injected, total volume of material injected, and whether the fillers were injected at the same time or at separate sessions.

A strong positive association was found between the number of products injected and the time of full resolution (Spearman correlation, r = 0.6; $p = .01$). When injecting three or more products, the median time of resolution was 4.5 months as compared with 2.75 months, when injecting two fillers (Wilcoxon test, $p = .11$). Furthermore, when comparing the injection of multiple products simultaneously to injections made at consecutive sessions, a tendency for more resistant course of the reaction with more numerous recurrences was noted.

The total volume of injected material also correlated with time until resolution (Spearman correlation, r = 0.81; $p \leq .0001$). When more than 1 mL of filler was injected during a session, the median time until resolution was 4.75 months when compared with 1.5 months, when only 1 mL was injected ($p = .02$). Moreover, when injecting more than 1 mL during the same session, the posttreatment reaction required a significantly longer time for resolution (median time until resolution of 6 months), compared with injecting the same amount of volume during two consecutive treatments (2.25 months, Kruskal–Wallis test, $p = .01$).

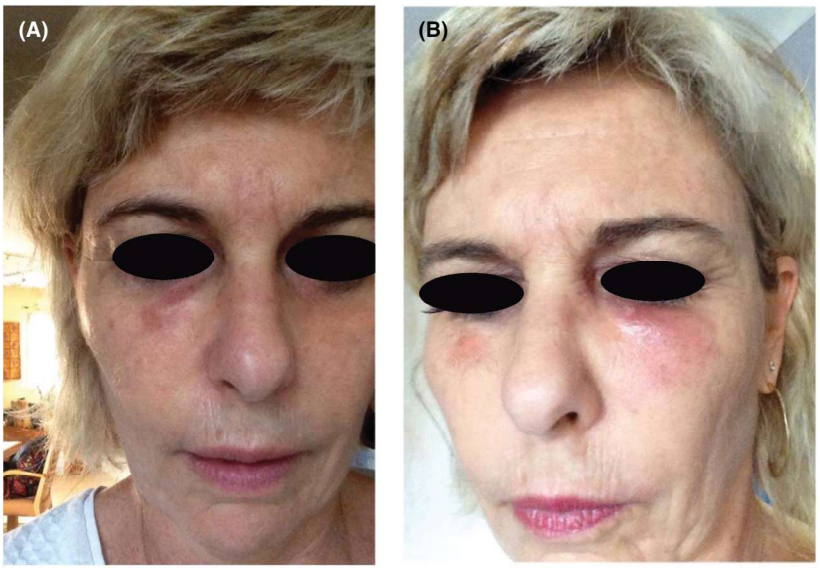

Figure 2. (A) Painful inflammatory nodules appearing 9 weeks after tear trough injection (first episode) and (B) fourth episode of the reaction—an observed "swing" from side to side.

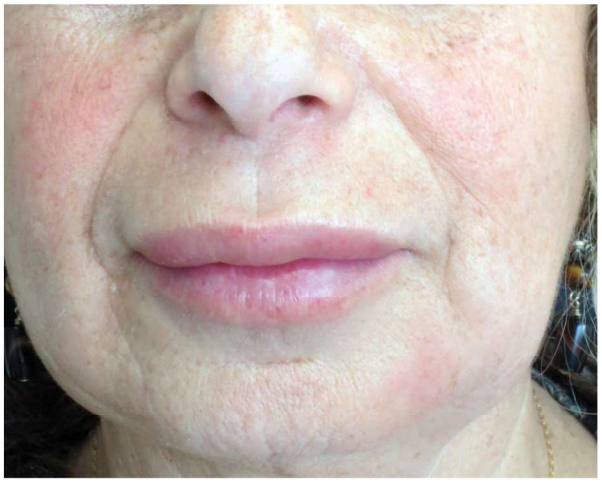

Figure 3. Painful inflammatory nodules appearing 9 weeks after lips injection.

Discussion

Injectable HA has been commonly used in the management of aging skin and other esthetic procedures. In its natural state, HA is unusable, because of its very short half-life before enzymatic degradation in the connective tissue.[2,3] Proprietary technologies are therefore used to optimize filler in-tissue viability and durability, which vary from one product to the other.

A review of the literature published after 2000 reveals several reports of delayed reactions to HA-based filler injections.[1,4–18] Before 1999, the reported rate of delayed reactions to HA fillers was 0.07%. The introduction of highly purified products decreased the incidence of such side effects to 0.02%,[1] which is now the accepted safety threshold for HA-based products. The details of the various stabilizing technologies used have mostly remained undisclosed, making it impossible to determine the factors favoring HA-based filler-associated cutaneous side effects. Juvéderm Volbella (HA-Vb; Allergan Inc., Santa Barbara, CA), an HA-based filler still not approved by the Food and Drug Administration, is specifically indicated for the treatment of fine lines, medium-sized skin depressions and lip enhancement. It is used off label for the correction of the tear trough area. It is based on the patented Vycross technology, incorporating short chain HAs together with long chain HAs to provide a more efficient cross-linking. The Vycross technology products include Juvéderm Voluma and Juvéderm Volift. The Juvéderm Voluma has shown an excellent safety profile since its approval in Europe in 2005 and in the United States in 2013. In a 12-month prospective, multicenter, open-label study using HA-Vb for lip enhancement in 60 patients, only 1 event of an injection site mass was observed (1/60).[19]

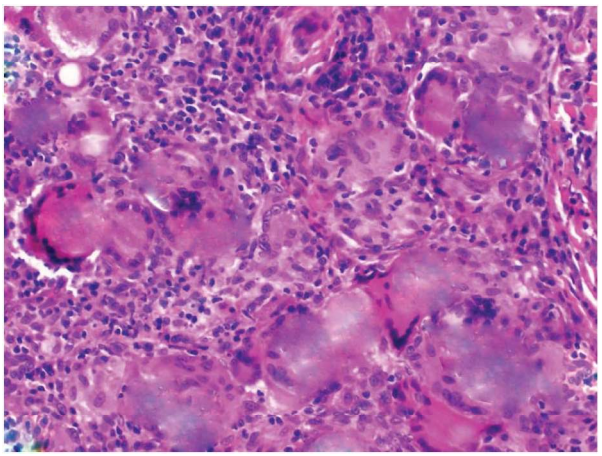

Figure 4. Biopsy from patient 11 demonstrated dermal nodular granulomatous dermatitis composed of epithelioid histiocytic granulomas, numerous multinucleated foreign body–type giant cells surrounding amorphous material.

In this study, the authors presented 17 patients who developed a delayed reaction to HA-Vb. The reaction rate was higher (17 of 400 [4.25%]) than the accepted safety threshold of 0.02% for HA-based fillers and much higher than previously experienced by the authors in previous years.

The tear trough area and lips are considered more challenging for adequate cosmetic corrections as they require accuracy and experience, and are more prone to complications if mistreated. Overcorrection and Tyndall phenomenon in the tear trough area and lumps, late macrocheilia, asymmetries, or chronic swelling episodes in the lips after HA injection are not uncommon. Nevertheless, inflammatory reactions are not reported to be more common in these areas compared with other areas of injection. This is in agreement with the general experience of tear trough correction and lip augmentation procedures with other HA-based fillers.

Delayed reactions after injections of HA-based products are believed to be mediated by macrophages and T-cell interactions.[3] These reactions are clinically

manifested as inflammatory painful nodules or masses.[4,5] The cause of these reactions still remains unclear, although several different etiologies have been suggested: circulating antibodies against HA,[20] protein impurities from the bacterial fermentation process,[21] and reactions to breakdown products from cross-linking during filler degradation.[22] Recently, the role of biofilms (accumulation of microorganisms within a self-developed matrix) has also been added as a possible cause for the delayed appearance of inflammatory nodules.[23–25] Biofilms are usually not identifiable by culture and may appear as sterile abscesses or cause a chronic inflammatory response.[26,27] Histologically, inflammatory reactions to HA injection have shown both lymphoplasmacytic and lymphocytic-macrophage infiltrates with foreign-body granulomas.[6]

The appearance of inflammatory nodules in areas located at some distance from the injection site, the course of the reaction (waxing and waning), the resistance of lesions to long-term antibiotic treatment, and the negative bacterial culture and PCR assay (in 1 patient, before antibiotic treatment) are less compatible with biofilm formation and favor an immunogenic reaction as the mechanism underlying reaction to HA-Vb. This hypothesis is consistent with the fact that reactions subsided under treatment with anti-inflammatory agents and relapsed approximately 2 weeks after cessation of therapy, responded to multiple hyaluronidase injections, and also with the fact that injection of larger volume[10] and higher number of different fillers at the same sessions was associated with a more resistant reaction and more recurrences, as previously reported.

Conclusion

Although the incidence of late-onset reactions to HA-based fillers is reportedly low, the authors believe that prevalence of such reactions is higher and is influenced by several parameters, including the number and volume of HA-based gel injections, the nature of the product injected, and possibly individual factors. Different products are associated with different rate of late-onset reactions. The authors believed HA-Vb to be more immunogenic than other HA-based gels and at the same time more resistant to degradation by hyaluronidase.

When facing late-onset or delayed reaction related to HA-Vb, the first-line treatment should be a 4-to-6 week course of broad-spectrum antibiotics (eg, ciprofloxacin 500–750 mg bid), as biofilm formation is a possible cause for the inflammatory reaction. The oral antibiotic treatment should be provided in conjunction with repeated high-dose hyaluronidase injections into the inflammatory nodules (30–100 IU into any solitary nodule). In case of severe inflammation or swelling, short-term systemic steroids can be considered to alleviate the reaction.

Limitations

Limitations include the retrospective design of this study and the medium-sized cohort of patients studied.

References

1. Friedman PM, Mafong EA, Kauvar AN, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. Dermatol Surg 2002;28:491–4.
2. Arron ST, Neuhaus IM. Persistent delayed-type hypersensitivity reaction to injectable non-animal-stabilized hyaluronic acid. J Cosmet Dermatol 2007;6:167–71.
3. Tezel A, Fredrickson GH. The science of hyaluronic acid dermal fillers. J Cosmet Laser Ther 2008;10:35–42.
4. Bardazzi F, Ruffato A, Antonucci A, Balestri R, et al. Cutaneous granulomatous reaction to injectable hyaluronic acid gel: another case. J Dermatol Treat 2007;18:59–62.
5. Park TH, Seo SW, Kim JK, Chang CH. Clinical experience with hyaluronic acid-filler complications. J Plast Reconstr Aesthet Surg 2011; 64:892–6.
6. Andre P, Lowe NJ, Parc A, Clerici TH, et al. Adverse reactions to dermal fillers: a review of European experiences. J Cosmet Laser Ther 2005;7:171–6.
7. Ghislanzoni M, Bianchi F, Barbareschi M, Alessi E. Cutaneous granulomatous reaction to injectable hyaluronic acid gel. Br J Dermatol 2006;154:755–8.
8. Fernández-Aceñero MJ, Zamora E, Borbujo J. Granulomatous foreign body reaction against hyaluronic acid: report of a case after lip augmentation. Dermatol Surg 2003;29:1225–6.
9. Rongioletti F, Cattarini G, Sottofattori E, Rebora A. Granulomatous reaction after intradermal injections of hyaluronic acid gel. Arch Dermatol 2003;139:815–6.
10. Grossman KL. Hyaluronic acid gel fillers: hypersensitivity reactions. Aesthetic Surg J 2005;25:403–5.
11. Edwards PC, Fantasia JE, Iovino R. Foreign body reaction to hyaluronic acid (Restylane): an adverse outcome of lip augmentation. J Oral Maxillofac Surg 2006;64:1296–9.
12. Patel VJ, Bruck MC, Katz BE. Hypersensitivity reaction to hyaluronic acid with negative skin testing. Plast Reconstr Surg 2006;117:92e–4e.

13. Al-Shraim M, Jaragh M, Geddie W. Granulomatous reaction to injectable hyaluronic acid (Restylane) diagnosed by fine needle biopsy. J Clin Pathol 2007;60:1060–1.

14. Mamelak AJ, Katz TM, Goldberg LH, Graves JJ, et al. Foreign body reaction to hyaluronic acid filler injection: in search of an etiology. Dermatol Surg 2009;35:1701–3.

15. Sage RJ, Chaffins ML, Kouba DJ. Granulomatous foreign body reaction to hyaluronic acid: report of a case after melolabial fold augmentation and review of management. Dermatol Surg 2009;35: 1696–700.

16. Sanchis-Bielsa JM, Bagán JV, Poveda R, Salvador I. Foreign body granulomatous reactions to cosmetic fillers: a clinical study of 15 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:237–41.

17. Hatcher JL, Goldman ND. Recognition and treatment of non-infectious hyaluronic acid reactions. J Dermatolog Treat 2014;25:513–5.

18. O'Reilly P, Malhotra R. Delayed hypersensitivity reaction to Restylane®SubQ. Orbit 2011;30:54–7.

19. Eccleston D, Murphy DK. Juvéderm® Volbella™ in the perioral area: a 12-month prospective, multicenter, open-label study. Clin Cosmet Investig Dermatol 2012;5:167–72.

20. Micheels P. Human anti-hyaluronic acid antibodies: is it possible? Dermatol Surg 2001;27:185–91.

21. Pinheiro MV, Bagatin E, Hassun KM, Talarico S. Adverse effect of soft tissue augmentation with hyaluronic acid. J Cosmet Dermatol 2005;4:184–6.

22. Coleman SR. Cross-linked hyaluronic acid fillers. Plast Reconstr Surg 2006;117:661–5.

23. Ozturk CN, Li Y, Tung R, Parker L, et al. Complications following injection of soft-tissue fillers. Aesthet Surg J 2013;33:862–77.

24. Daines SM, Williams EF. Complications associated with injectable soft-tissue fillers: a 5-year retrospective review. JAMA Facial Plast Surg 2013;15:226–31.

25. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, et al. Soft-tissue filler complications: the important role of biofilms. Plast Reconstr Surg 2010; 125:1250–6.

26. Dayan SH, Arkins JP, Brindise R. Soft tissue fillers and biofilms. Facial Plast Surg 2011;27:23–8.

27. Bjarnsholt T, Tolker-Nielsen T, Givskov M, Janssen M, et al. Detection of bacteria by fluorescence in situ hybridization in culture-negative soft tissue filler lesions. Dermatol Surg 2009;35:1620–4.

Address correspondence and reprint requests to: Ofir Artzi, MD, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel-Aviv 64239, Israel, or e-mail: ofira@tlvmc.gov.il