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ORIGINAL RESEARCH

Good scientific practice of using worldwide post-marketing surveillance data to ensure safety with HA_{ALI} BDDE cross-linked hyaluronic acid fillers

Hema Sundaram[1,2], Beatriz Molina[3], Editta Buttura da Prato[4], Gabriel Siquier-Dameto[5,6], Michela Zazzaron[7], Clara Cigni[8], Franco Grimolizzi[8]

[1]Private Practice, Rockville, Maryland; Private Practice, Fairfax, Virginia, USA; [2]Division of Musculoskeletal and Skin Diseases, University of Manchester, Manchester, UK; [3]Medikas Clinic, Somerset, Bristol, UK; [4]Private Practice, Verona, Italy; [5]Dameto Clinics International, Campanet, Spain; [6]Research Group of Clinical Anatomy, Embryology and Neuroscience (NEOMA), Department of Medical Sciences, University of Girona, Girona, Spain; [7]Private Practice, Roncade, Treviso, Italy; [8]IBSA Farmaceutici Italia Srl, Lodi, Italy

Abstract

Background: Aliaxin fillers (HA_{ALI}), produced by IBSA Farmaceutici Italia SrL (Italy), are biodegradable, non-pyrogenic, 1,4-butanediol diglycidyl ether cross-linked hyaluronic acid (HA) hydrogels. The formulations are tailored for different clinical indications, ensuring precise and natural outcomes. Their cohesivity and tissue integration capabilities are associated with relatively few adverse events (AEs), supporting their widespread use in aesthetic treatments. This article examines the real-world safety profile of HA_{ALI} fillers derived from worldwide post-marketing surveillance data.

Methods: Post-marketing surveillance was registered by the manufacturer from January 2018 to September 2023. During this period, product complaints were globally gathered from healthcare practitioners and consumers, relating to technical issues or safety and product-related adverse events.

Results: No discernible trend or substantial escalation in AEs across the entire product range were observed during the surveillance period ($p>0.05$). No statistically significant increases ($p>0.05$) in the frequency or severity of safety incidents and AEs were observed. The most frequently observed AEs were oedema (26%) and swelling (19%).

Conclusion: The analysed data further support and confirm the high safety profile of the HA_{ALI} fillers for different approaches in aesthetic medicine. This evaluation also highlights the importance of post-marketing analysis by continuing to foster a robust understanding of products currently used in daily clinical practice.

Keywords: BDDE cross-linked dermal filler, filler complications, hyaluronic acid, injectable safety, post-marketing surveillance, safety.

Citation

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Introduction

Hyaluronic acid (HA)-based cross-linked fillers are valuable tools in aesthetic medicine to achieve durable volumetric correction and skin texture improvement. They are preferred by many injectors and patients for their tissue biocompatibility, safety and natural-looking results.[1,2]

With the steadily increasing number of HA filler procedures performed worldwide, broader clinical indications, and the advent of sequential treatments over years and decades, there is also an expected escalation in reports of complications. It is a fundamental principle of ethics and patient safety for all filler manufacturers to objectively collate and publish pharmacovigilance data for procedures performed using their products. A number of

variables have been implicated in the onset of adverse events (AEs) subsequent to HA filler injections,[3–8] including patient history, product characteristics and the injection technique used to administer the product.

The most common AEs associated with HA fillers include oedema, bruising, granulomas (often without histopathological confirmation), inflammatory nodules, angioedema, skin induration and delayed swelling, lumps or nodules.[7,8] These adverse reactions are typically mild and transient, with swelling being the most frequently reported complication.[9–11] Foreign body granuloma has also been reported as an AE, though histopathological and other confirmation that this is due to the HA filler rather than contaminant microbes or non-filler foreign bodies introduced during injection would be required for definitive diagnosis.[5,12] With these caveats, the reported rate of granuloma following HA filler treatment is between 0.02% and 0.4%, although there have been recent reports of a higher incidence since the COVID-19 pandemic.[5,13,14]

The range of Aliaxin HA (HA_{ALI}) fillers (IBSA Farmaceutici Italia Srl, Italy) evaluated in this report are biodegradable medical devices composed of a sterile, HA hydrogel cross-linked with 1,4-butanediol diglycidyl ether (BDDE). Investigations regarding the safety of BDDE cross-linking have focused on the presence of residual, unreacted BDDE-containing epoxide groups, after the filler cross-linking reaction is completed (Figure 1). However, it is reported that the epoxide groups can be easily hydrolysed to non-toxic chains.[15] No direct evidence of a potential toxic or carcinogenic effect of BDDE-cross-linked HA fillers has been found in mice nor in humans over three decades. This has also been confirmed by different reviews and meta-analyses evaluating AEs reported over the last 15 years of several BDDE-cross-linked fillers.[16–18] In these reports, no toxic or carcinogenic effects derived from the use of BDDE-cross-linked fillers have been declared and none of the existing AEs has been directly associated with the use of BDDE.

BDDE-cross-linked HA fillers can be prepared as different formulations and their rheological properties can be optimized, such as the elastic (storage) modulus (G′) and tan delta (tan δ), with the goal of achieving results that are patient-tailored and individualized for the intended clinical indication.[19,20] The evaluation of the rheological parameters, such as G′ and cohesivity, are fundamental as they describe the behaviour of the hydrogels once injected into the tissues. Therefore, they represent critical parameters in the choice of the right filler for each patient and application in the daily clinical practice. Moreover, it has been reported that high G′ fillers are more likely to cause nodules if placed in thin-skinned and/or mobile areas such as the lips or the tear trough region.[21] The range in G′ of HA_{ALI} filler products evaluated in this report from 39 Pa (A_{SR}) to 295 Pa (A_{SV}) reflects an understanding of the appropriate rheological parameters for each treatment area, with the aim of ensuring safe and efficacious patient outcomes. To evaluate the best and safest treatment approaches, it is then crucial for healthcare practitioners (HCPs) to be able to compare the parameters of commercially available fillers. When comparing products, the different laboratory settings used must be considered. An effective and simple method, such as the Gavard–Sundaram scale,[22] can be used to evaluate filler cohesivity, defined as the force between particles of the same substance that acts to unite them.[23,24] HA_{ALI} fillers exhibit high cohesivity scores of 5/5 on the Gavard–Sundaram scale,[25] which is generally associated with an optimal degree of tissue integration. This characteristic helps minimize the incidence of nodules and inflammatory reactions.[24–27]

Following clinical studies on HA_{ALI} fillers,[26,28] the primary aim of this report is to elucidate findings from a 5-year post-market surveillance analysis of this product range. The secondary aim is to compare the product characteristics (HA concentration, G′ and cohesivity) of different HA fillers.

Methods

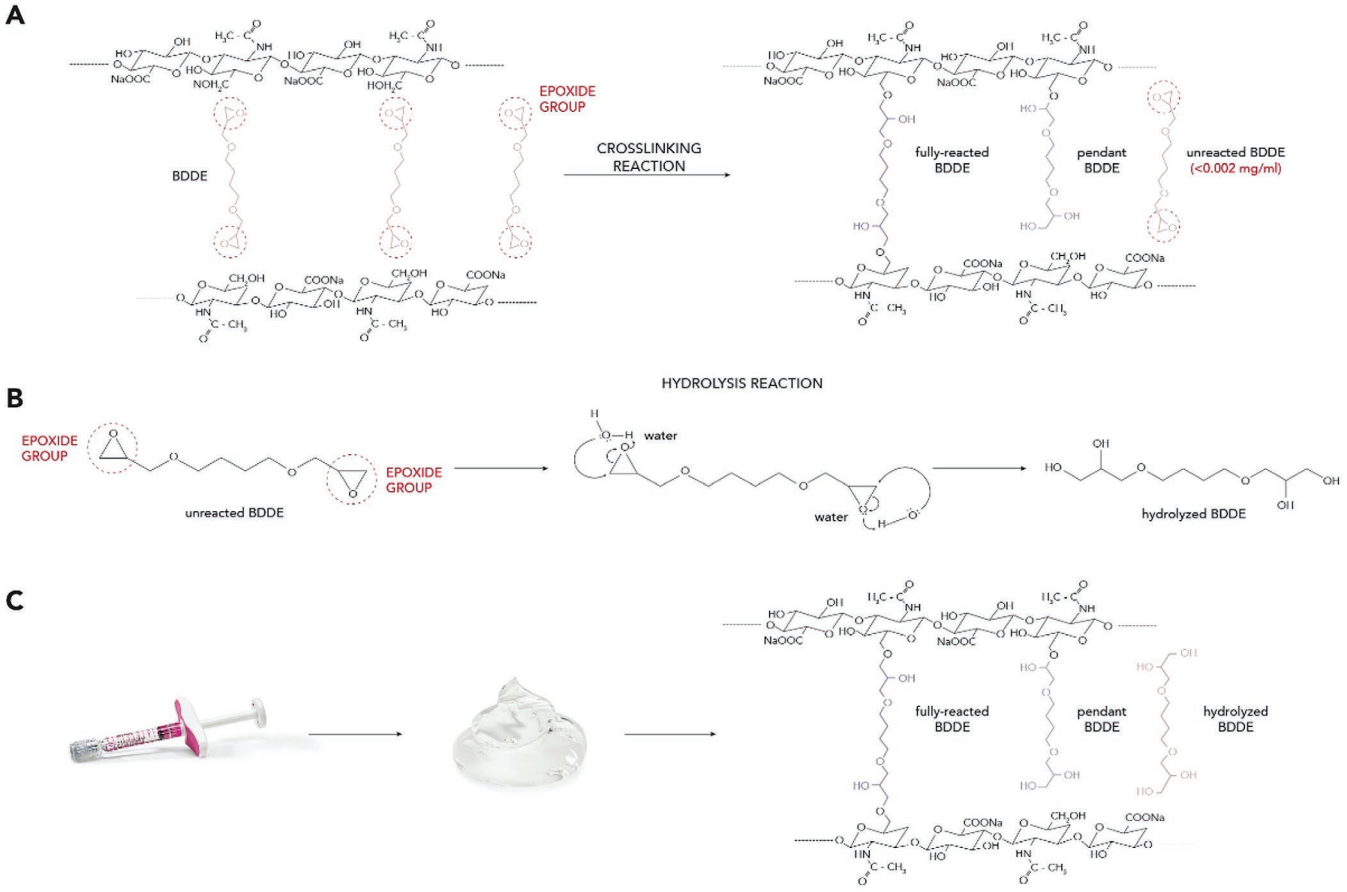
Data collection

From 1 January 2018 to 30 September 2023, IBSA Farmaceutici Italia Srl (Italy) systematically gathered global reports from physicians and consumers who used HA_{ALI} fillers for aesthetic treatment, including facial volume restoration, wrinkle correction, and skin hydration. HA_{ALI} fillers comprise six formulations: Aliaxin Essential Volume (A_{EV}), Aliaxin Fine Lines (A_{FL}), Aliaxin Global Performance (A_{GP}), Aliaxin Lips Volume (A_{LV}), Aliaxin Shape and Restore (A_{SR}), and Aliaxin Superior Volume (A_{SV}).

These treatments were performed using needles or cannulas, depending on HCP preference and the specific requirements of the procedure. Complaints were categorized either as technical, covering quality concerns related to technical or manufacturing issues, or as related to safety, which were associated with AEs. Only safety complaints are considered herein, and these were analysed and further categorized according to the AEs reported.

A comprehensive qualitative and quantitative analysis was conducted on AEs reported with the use of the evaluated HA_{ALI} fillers. Safety-related feedback and complaints were reviewed and categorized to identify and assess their nature, frequency and severity. This provided valuable insights into the safety profile and potential AEs associated with the use of presented HA dermal fillers.

Figure 1. 1,4-Butanediol diglycidyl ether (BDDE) metabolism after cross-linking reaction. A) BDDE is present in different chemical states at the end of the cross-linking reaction: the fully reacted crosslinker, the pendant crosslinker and unreacted BDDE. B) Hydrolysis reaction transforms epoxide groups in the unreacted BDDE, creating non-toxic metabolites. C) Hyaluronic acid fillers commonly used for aesthetic treatments are typically composed of cross-linked hydrogels containing fully reacted crosslinker, pendant crosslinker and residual hydrolysed crosslinker.



In adherence to ethical standards and privacy regulations, all data utilized in this study were anonymized to remove personally identifiable information before analysis. The analysis was conducted in accordance with the Declaration of Helsinki.

Cohesivity score

Fourteen BDDE-cross-linked HA dermal fillers were evaluated for their cohesivity: A_{SV}, A_{SR}, A_{GP}, A_{FL}, A_{LV} and A_{EV} (IBSA Farmaceutici, Italy); B1, B2 and B3 (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany); J1, J2 and J3 (Allergan Aesthetics, an AbbVie Company, USA); and R1, R2 and R3 (Galderma, Uppsala, Sweden).

Cohesivity was evaluated following the Gavard–Sundaram scale specifications.[22] Technically, 10 µL of toluidine blue (0.1% w/w in phosphate buffer, pH 7.4) were added to 1 g of each filler gel, with subsequent mixing and centrifugation to obtain a homogenous staining. The gel samples were then carefully drawn into 1-mL syringes and extruded under standardized conditions. Immediately after extrusion, magnetic stirring commenced and video and images were recorded up to 90 seconds after extrusion. Cohesivity was evaluated independently by four raters that assigned, for each sample at each time point, a value of cohesivity (from 1 to 5) referring to the Gavard–Sundaram Cohesivity Scale.[22] Results were reported as the mean score ± SD.

Statistical analysis

The safety data were evaluated on an annual basis in relation to worldwide sales data for the products. The number of sold syringes was obtained from sales data and used to estimate patient exposure. The recommended dosing regimen for the evaluated HA dermal fillers is that treatment may be repeated periodically, every 6–12 months as needed, to maintain the desired results. Accordingly, two syringes for a year-long cycle of treatment for each patient were assumed, with the maximum number of patients exposed being calculated

as the number of syringes sold divided by 2. The complaint rate for exposed patients was also estimated and expressed as a percentage, that is ([number of AEs/number of exposed patients] ×100).

All graphs, calculations and statistical analyses were performed using GraphPad Prism software version 10.2.0 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Trend analysis of sales data *versus* AEs

During the years spanning 2018–2023, a discernible increase was observed in both the quantity of syringe sales and the incidence of registered total complaints. However, only a small percentage (18.5%) of the total complaints during 2018–2023 were related to AEs, with the majority being technical complaints. For the purposes of this investigation, only safety complaints related to AEs were analysed. The total number of AEs received for each year are summarized in Table 1.

According to the product Instructions for Use (IFU), an estimation of two syringes for a year-long cycle of treatment for each patient was assumed to calculate the number of exposed patients. However, this calculation clearly represents an approximation, as some patients would probably have received more than two syringes, leading to a potential overestimation of patient exposure.

A subsequent linear regression trend analysis failed to reveal any statistically significant correlation in the proportion of AEs relative to time and number of patients exposed (p=0.9676; R^2 < 0). Although the number of syringes sold and patients exposed increased over the analysed years, the percentage complaint rate related to AEs remained notably low and, interestingly, decreased from 2018 to 2023 (Table 1).

Adverse events

Twelve categories of AEs, for a total of 31 AEs in the period 2018–2023, were reported, including swelling/itching (n=8), oedema (n=6), nodules (n=5), hypersensitivity (n=3), infection (n=2), bruise (n=1), wheal formation (n=1), pallor on hands (n=1), rosacea (n=1), redness (n=1), bleeding (n=1) and ischaemia (n=1) (Table 2). Amongst these AEs, swelling or oedema (26% and 19% out of total events, respectively) and nodule formations (16% out of total events) were the most common. The total AEs in the analysed period (2018–2023) corresponded to 0.0025% of estimated patients exposed to injections. Statistical analysis and comparison of the AEs revealed no significant temporal variation in the frequency of safety-related complaints across the surveyed years, nor was there any significant difference identifiable amongst the various symptoms reported (p≥0.05). These data suggest a consistent safety profile with no particular AE trend over time.

Aetiology of registered complaints

Aetiological factors contributing to the registered complaints were classified into five categories: procedural technicalities with injection (injection site conditions), idiopathic origins (unknown), factors unrelated to the therapeutic intervention (not related), sun exposure, and patient-specific attributes (patient characteristics) (Figure 2). Technical complications associated with the injection administration procedure accounted for the majority of complaints (76%). Individual patient characteristics were identified as the second most prevalent cause (12%). This analysis underscores the imperative for enhanced technical precision during the injection

Table 1. Sales data for period from 2018 to 2023 referring to the number of syringes sold, estimated number of patients exposed, number of reported adverse effects (AEs) and the relative estimated proportion of exposed patients with an AE.

Year	No. syringes sold	No. patients exposed[a]	AEs	Estimated proportion (%) of exposed patients with an AE
2018	187,368	93,684	4	0.0040
2019	251,428	125,714	7	0.0055
2020	296,274	148,137	7	0.0047
2021	484,522	242,261	5	0.0015
2022	649,224	324,612	5	0.0015
2023	597,744	298,872	3	0.0010

[a]Patient exposure was estimated by assuming that the highest number of syringes that could be used by a patient for a year-long cycle of treatment was two, as per the Instructions for Use. Therefore, the number of patients exposed = number of syringes sold/2.

Table 2. Total adverse events and estimated proportion of exposed patients with an adverse event (AE) for the evaluated hyaluronic acid dermal fillers by AEs Main categories from 2018 to 2023.

Year	AE categories	No. of total events	Estimated proportion (%) of exposed patients with an AE[a]
2018	Oedema	3	0.0032
	Bruising	1	0.0010
2019	Swelling	3	0.0032
	Oedema	1	0.0008
	Infection	1	0.0008
	Redness	1	0.0008
	Hypersensitivity	1	0.0008
2020	Swelling	2	0.0014
	Nodules	2	0.0014
	Wheals	1	0.0007
	Bleeding	1	0.0007
	Oedema	1	0.0007
2021	Hypersensitivity	2	0.0008
	Oedema	1	0.0004
	Infection	1	0.0004
	Swelling	1	0.0004
2022	Nodules	2	0.0006
	Swelling	1	0.0003
	Hands pallor	1	0.0003
	Rosacea	1	0.0003
2023	Swelling	1	0.0003
	Nodule	1	0.0003
	Ischaemia	1	0.0003
2018–2023	Total	31	0.0025

[a]Proportion of exposed patients experiencing an AE was estimated and expressed as a percentage, i.e. ([number of AEs/ number of exposed patients]×100).

process and a tailored approach considering known patient-specific factors to mitigate the incidence of complications.

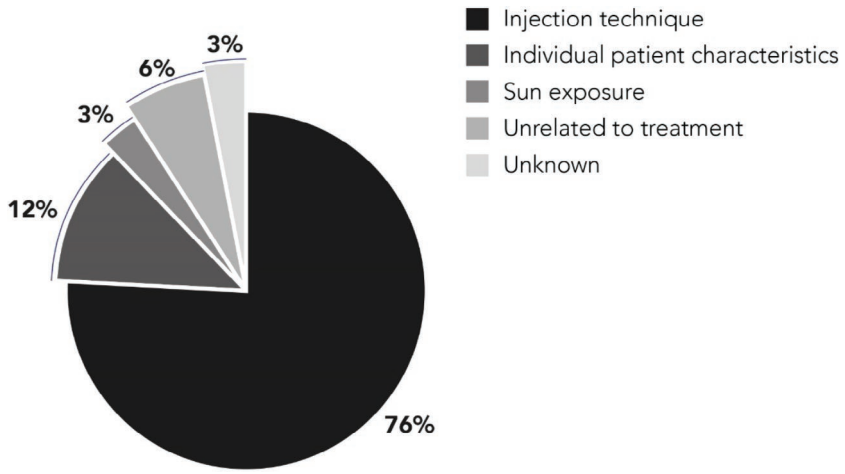
Comparison of cohesivity scores and rheological parameters

The Sundaram–Gavard scale was used to evaluate and compare the gel cohesivity of nine commercially available HA fillers up to 90 seconds. The cohesivity scores and the comparative HA concentration and rheological parameters (G′) retrieved from the scientific literature are provided in Table 3. Results demonstrated that the evaluated HA dermal fillers have a cohesivity score from highly (A_{SV} = grade 4) to fully (A_{SR}, A_{GP}, A_{FL}, A_{LV}, A_{EV} = grade 5) cohesive. Two of the other analysed HA fillers (B1, B2) also displayed a highly or fully cohesive score. The other six fillers showed low to medium cohesivity scores; interestingly, almost all these products also had high G′ values (>340 Pa). No correlation was found between cohesivity scores and HA concentration.

Discussion

The analysis of post-market surveillance data pertaining to HA_{ALI} dermal fillers over a 5-year period offers a nuanced insight into the product's safety profile in clinical practice. Despite the observed increase in both syringe sales and registered complaints, the trend analysis presented herein shows no statistically significant correlation between the incidence of complaints and the passage of time.

Figure 2. Aetiological classification of complaints associated with the evaluated hyaluronic acid dermal fillers.



The low complaint rate observed in this study further supports a high safety profile for the studied HA fillers. However, a limitation of this study is the method used to calculate patient exposure, which assumes that each patient received two syringes per year. This approximation, whilst the only current estimation method, may lead to an overestimation of patient exposure as some patients might require a different number of syringes for their treatment. Consequently, the actual number of patients exposed could be lower than estimated, potentially impacting the accuracy of the complaint rate calculations although the percentage of AEs relative to syringes sold would be the same.

Moreover, a potential underreporting of AEs from HCPs and patients can also occur and may represent a limitation. This effect can especially affect mild and expected AEs, as they can be considered not severe enough by patients to be reported to the HCPs or they are considered as normal side-effects, as indicated in the product leaflet. On the other hand, some AEs may be considered as a consequence of inadequate injection technique and consequently not reported.

Overall, these limitations should be considered when interpreting the observed complaint rate and highlight the importance of continually performing post-marketing surveillance and real-world data analysis and examinations on different populations.

The safety data reveal that oedema and swelling were the predominant AEs reported, yet no significant temporal trend was discernible in the frequency of these or any other AEs. Such consistency in the safety profile year-over-year, despite increased product distribution, indicates that these AEs are not becoming more common with wider usage and reflects a stable safety profile for the studied HA dermal fillers. The post-treatment oedema reported in this study is consistent with known side-effects of other HA fillers and does not deviate from the expected results. For example, a systematic review conducted by Stojanovič et al. analysed the efficacy and safety profiles of various HA fillers;[1] AEs reported were principally localized reactions at the site of injection, predominantly oedema and swelling. These outcomes are in-line with those observed for the evaluated HA fillers, with oedema typically featuring as a self-limited side-effect.

Granuloma formation represents a protracted inflammatory response to a foreign substance[5] that has been reported for patients complaining of palpable nodules under the skin. It is also of note that granuloma is a histopathological diagnosis, whereas inflammatory or non-inflammatory nodules are appropriate clinical designations. Direct association of HA fillers with these events requires complete elimination of other potential causes, including contamination with microbes or other foreign bodies such as make-up particles introduced before, during or after the injection process. Despite reports showing an increase in the rate of delayed filler granulomas since the COVID-19 pandemic,[13,29,30] the post-surveillance safety analysis here reported presents a contrasting narrative. Throughout the duration of this surveillance period, there was no documented instance of granuloma formation as an AE amongst patients treated with these products.

The articles recently published[5,13] on granulomas or nodule formation also highlight the need for clinicians

Table 3. Comparison between nine different commercially available hyaluronic acid (HA) fillers based on HA concentration and rheological parameters. HA concentration and G′ was obtained from the scientific literature (references shown in table), whilst cohesivity score were evaluated using the Gavard–Sundaram scale.[22]

HA hydrogel	Total HA (mg/mL)	G′ (Pa)[a]	Cohesivity	Refs.
A_{EV}	25	162	5	26,27
A_{FL}	25	45	5	26,27
A_{GP}	25	95	5	26,27
A_{LV}	25	107	5	26,32
A_{SR}	25	39	5	26,27
A_{SV}	25	295	4	2,27
B1	22.5	128	5	34
B2	25.5	255	4	31,33
B3	26	438	3	31,33
J1	20	398	1	34
J2	17.5	340	1	33,34
J3	15	271	1	34
R1	20	864	1	34
R2	20	977	1	34

[a]G′ (Pa) are reported as declared by manufacturers and have been calculated at 1.59 Hz frequency (A_{SV}, A_{SR}, A_{GP}, A_{FL}, A_{LV}, A_{EV}) and at 5 Hz frequency (B1, B2, B3, J1, J2, J3, R1, R2).

to have a comprehensive knowledge of product characteristics, including with respect to rheology. The data in this report indicated that A_{SV}, A_{SR}, A_{GP}, A_{FL}, A_{LV} and A_{EV} fillers displayed high cohesivity score based on the Gavard–Sundaram scale, whereas the other tested products with higher G′ (>340 Pa) showed lower cohesivity scores.[18,29] Cohesivity may be of value in achieving natural-looking outcomes with the face at rest and in animation by maintaining gel integrity and reducing the risk of contour irregularities.[23,24]

Technical issues related to the injection procedure were the principal cause of complaints, accounting for 76% of the total. This finding underlines the critical need for ongoing evaluation of injection techniques and their outcomes, and the importance of comprehensive training for practitioners. The 12% of complaints attributed to individual patient characteristics point to the necessity of personalized patient assessments before treatment, and the need for greater understanding of patient-specific risk factors for filler complications. Given the multifaceted nature of filler complaints, this discussion posits that, whilst the evaluated HA dermal fillers exhibit a consistent safety profile, the technical skill of the practitioner and individual patient characteristics play a significant role in the aetiology of AEs. To this end, ongoing education and training for HCPs, along with patient-specific evaluations, emerge as crucial components in the effort to uphold the high safety standards associated with HA fillers.[31] In this context, it will be of crucial importance for HCPs to perform a correct anamnesis of the patients, excluding individuals with known hypersensitivity or history of inflammatory or autoimmune reactions. Moreover, the results of the current analysis also show the importance of selecting the right filler using the correct injection technique, avoiding, for example, placement of high G′ products in sensitive areas such as temples and lips.[32,33] Finally, the choice of the right injection technique must be correctly performed avoiding the risk of vascular complications; for example, the choice of the cannula is considered advisable in the treatment of areas like temples, forehead and preauricular area.[34] Overall, good clinical practice is required to ensure an ethical and safe approach for the patients.[35]

Future studies could benefit from a longitudinal design that includes a larger sample size and diverse demographics to explore the potential cumulative effects of repeated filler injections over time. The establishment of standardized protocols for injection techniques could help to prevent the most common technically related complications observed. By continuing to foster a robust understanding of both products and user techniques, and by advancing evidence-based methods of complications reporting the appropriate balance between technological innovation and patient welfare can be maintained.[36] A key step in achieving this goal would be for pharmacovigilance data for all fillers currently used in clinical practice to be published, available for reference, and periodically updated.

Conclusion

The investigation into the real-world safety data of the studied HA dermal fillers (IBSA Farmaceutici, Italy) highlights a low incidence of AEs, with the majority expected and self-limited and others related to injection techniques. Comprehensive temporal trend analysis revealed no discernible trends or significant increases in safety complaints across the product range. Statistical analysis showing no rise in the frequency or severity of either serious or self-limited/expected

AEs, despite the significant rise in product sales and treatments worldwide, reinforces the conclusion that the evaluated HA dermal fillers maintain a favourable safety profile. The findings suggest that, with appropriate use and adherence to manufacturer guidelines, BDDE fillers remain a safe option within their intended clinical applications. The overall risk-benefit assessment supports the reliability, predictability, and safety of HA dermal fillers in clinical settings.

Contributions: H.S., B.M., E.B.d.P., G.S.-D. and M.Z. collected the data, performed the statistical analysis and contributed to the data interpretation. H.S., B.M., E.B.d.P., G.S.-D., M.Z., C.C. and F.G. have contributed to manuscript writing, editing and reviewing. All authors have read and agreed to the published version of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Correspondence: Franco Grimolizzi, IBSA Farmaceutici Italia Srl, Lodi, Italy. Email: franco.grimolizzi@ibsa.it

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References

1. Stojanovič L, Majdic N. Effectiveness and safety of hyaluronic acid fillers used to enhance overall lip fullness: a systematic review of clinical studies. *J Cosmet Dermatol*. 2019;18(2):436–443. https://doi.org/10.1111/jocd.12861
2. La Gatta A, Salzillo R, Catalano C, et al. Hyaluronan-based hydrogels as dermal fillers: the biophysical properties that translate into a "Volumetric" effect. *PLoS One*. 2019;14(6):e0218287. https://doi.org/10.1371/journal.pone.0218287
3. Lafaille P, Benedetto A. Fillers: contraindications, side effects and precautions. *J Cutan Aesthet Surg*. 2010;3(1):16–19. https://doi.org/10.4103/0974-2077.63222
4. Philipp-Dormston WG, Bergfeld D, Sommer BM, et al. Consensus statement on prevention and management of adverse effects following rejuvenation procedures with hyaluronic acid-based fillers. *J Eur Acad Dermatol Venereol*. 2017;31(7):1088–1095. https://doi.org/10.1111/jdv.14295
5. Lee JM, Kim YJ. Foreign body granulomas after the use of dermal fillers: pathophysiology, clinical appearance, histologic features, and treatment. *Arch Plast Surg*. 2015;42(2):232–239. https://doi.org/10.5999/aps.2015.42.2.232
6. Abdelmohsen MA. Injectable fillers: imaging features and related complications. *Egypt J Radiol Nucl Med*. 2020;51(1):129. https://doi.org/10.1186/s43055-020-00249-4
7. Ghareeb FM, Hassan MSA, Nahas MAE, et al. Complicated facial fillers: management algorithm. *Plast Reconstr Surg Glob Open*. 2022;10(7):e4445. https://doi.org/10.1097/GOX.0000000000004445
8. Povolotskiy R, Oleck NC, Hatzis C, Paskhover B. Adverse events associated with aesthetic dermal fillers: a 10-year retrospective study of FDA data. *Am J Cosmet Surg*. 2018;35(3):143–151. https://doi.org/10.1177/0748806818757123
9. Cohen JL, Patel M, Hicks J. Ten-year global postmarket safety surveillance of delayed complications with a flexible cheek filler. *Dermatol Surg*. 2022;48:1126–1127. https://doi.org/10.1097/DSS.0000000000003587
10. Corduff N, Juniarti L, Lim T, et al. Current practices in hyaluronic acid dermal filler treatment in Asia Pacific and practical approaches to achieving safe and natural-looking results. *Clin Cosmet Investig Dermatol*. 2022;15:1213–1223. https://doi.org/10.2147/CCID.S363583
11. Kaufman-Janette J, Taylor SC, Cox SE, et al. Efficacy and safety of a new resilient hyaluronic acid dermal filler, in the correction of moderate-to-severe nasolabial folds: a 64-week, prospective, multicenter, controlled, randomized, double-blind and within-subject study. *J Cosmet Dermatol*. 2019; 18(5):1244–1253. https://doi.org/10.1111/jocd.13100
12. Saad A, Iyengar KP, Davies AM, et al. A rare case of migration of hyaluronic acid gluteal injection to the medial thigh presenting as a soft lump. *Indian J Radiol Imaging*. 2023;33:253–256. https://doi.org/10.1055/s-0042-1760364
13. Michel JC, Perenack JD, Chapple AG, et al. Are delayed dermal filler granulomas more common since COVID-19? *J Oral Maxillofac Surg*. 2023;81(1):42–48. https://doi.org/10.1016/j.joms.2022.09.011
14. Rzany B, Converset-Viethel S, Hartmann M, et al. Efficacy and safety of 3 new resilient hyaluronic acid fillers, crosslinked with decreased BDDE, for the treatment of dynamic wrinkles: results of an 18-month, randomized controlled trial versus already available comparators. *Dermatol Surg*. 2019;45(10):1304–1314. https://doi.org/10.1097/DSS.0000000000001971
15. De Boulle K, Glogau R, Kono T, et al. A review of the metabolism of 1,4-butanediol diglycidyl ether-crosslinked hyaluronic acid dermal fillers. *Dermatol Surg*. 2013;39(12):1758–1766. https://doi.org/10.1111/dsu.12301
16. Faivre J, Pigweh AI, Iehl J, Maffert P, Goekjian P, Bourdon F. Crosslinking hyaluronic acid soft-tissue fillers: current status and perspectives from an industrial point of view. *Expert Rev Med Devices*. 2021;18(12):1175–1187. https://doi.org/10.1080/17434440.2021.2014320
17. Colon J, Mirkin S, Hardigan P, Elias MJ, Jacobs RJ. Adverse events reported from hyaluronic acid dermal filler injections to the facial region: a systematic review and meta-analysis. *Cureus*. 2023;15(4):e38286. https://doi.org/10.7759/cureus.38286
18. Molina B, Romano D, Zazzaron M, et al. Full face tailored treatments using hyaluronan dermal fillers: biophysical characterization for safe and effective approaches. *Cosmetics*. 2024;11:144. https://doi.org/10.3390/cosmetics11040144
19. Furtado GRD, Dametto AC, Barbosa KL, et al. Rheological properties of hyaluronic acid-based fillers for facial cosmetic aesthetics. *Res Soc Dev*. 2023;12(1):e22012139676. https://doi.org/10.33448/rsd-v12i1.39676

20. Fagien S, Bertucci V, Grote Ev, et al. Rheologic and physicochemical properties used to differentiate injectable hyaluronic acid filler products. *Plast Reconstr Surg*. 2019;143(4):707e–720e. https://doi.org/10.1097/PRS.0000000000005429
21. Diwan Z, Trikha S, Etemad-Shahidi S, Parrish N, Rennie C. Evaluation of current literature on complications secondary to lip augmentation following dermal filler injection. *J Clin Aesthet Dermatol*. 2023;16(7):26–33.
22. Sundaram H, Rohrich RJ, Liew S, et al. Cohesivity of hyaluronic acid fillers: development and clinical implications of a novel assay, pilot validation with a five-point grading scale, and evaluation of six U.S. Food and Drug Administration-Approved Fillers. *Plast Reconstr Surg*. 2015;136(4):678–686. https://doi.org/10.1097/PRS.0000000000001638
23. Kleine-Börger L, Kalies A, Meyer RSA, et al. Physicochemical properties of injectable hyaluronic acid: skin quality boosters. *Macromol Mater Eng*. 2021;306(8):2100134. https://doi.org/10.1002/mame.202100134
24. Tran C, Carraux P, Micheels P, et al. In vivo bio-integration of three hyaluronic acid fillers in human skin: a histological study. *Dermatology*. 2014;228(1):47–54. https://doi.org/10.1159/000354384
25. Sundaram H, Cassuto D. Biophysical characteristics of hyaluronic acid soft-tissue fillers and their relevance to aesthetic applications. *Plast Reconstr Surg*. 2013;132:5S–21S. https://doi.org/10.1097/PRS.0b013e31829d1d40
26. La Gatta A, Schiraldi C, Zaccaria G, et al. Hyaluronan dermal fillers: efforts towards a wider biophysical characterization and the correlation of the biophysical parameters to the clinical outcome. *Clin Cosmet Investig Dermatol*. 2020;13:87–97. https://doi.org/10.2147/CCID.S220227
27. La Gatta A, Rosa MD, Frezza MA, et al. Biophysical and biological characterization of a new line of hyaluronan-based dermal fillers: a scientific rationale to specific clinical indications. *Mater Sci Eng C*. 2016;68:565–572. https://doi.org/10.1016/j.msec.2016.06.008
28. Iannitti T, Morales-Medina JC, Coacci A, et al. Experimental and clinical efficacy of two hyaluronic acid-based compounds of different cross-linkage and composition in the rejuvenation of the skin. *Pharm Res*. 2016;33(12):2879–2890. https://doi.org/10.1007/s11095-014-1354-y
29. Michel JC, Perenack JD, Chapple AG, Christensen BJ. Are delayed dermal filler granulomas more common since COVID-19? *J Oral Maxillofac Surg*. 2023;81(1):42–48. https://doi.org/10.1016/j.joms.2022.09.011
30. Bachour, Y. An update and overview of the literature on late inflammatory reactions (LIRs) in soft tissue fillers after SARS-CoV-2 infection and vaccination. *Eur J Plast Surg*. 2023;46:855–864. https://doi.org/10.1007/s00238-023-02121-w
31. Prasetyo AD, Prager W, Rubin MG, Moretti EA, Nikolis A. Hyaluronic acid fillers with cohesive polydensified matrix for soft-tissue augmentation and rejuvenation: a literature review. *Clin Cosmet Investig Dermatol*. 2016;9:257–280. https://doi.org/10.2147/CCID.S106551
32. Zazzaron M, Musella D. Esperienze Dermatologiche – Dermatological Experiences Case Report. Real-life experience of a new crosslinked hyaluronic acid lip filler. *Esperienze Dermatologiche*. 2020;22:45–48. https://doi.org/10.23736/S1128-9155.20.00509-9
33. Bravo BSF, Calvacante T, Silveira C, Bravo LG, Zafra MC, Elias MC. Resolve and dissolve—An ultrasound-guided investigation on the effects of hyaluronidase on different soft tissue fillers. *J Cosmet Dermatol*. 2024;23:3173–3181. https://doi.org/10.1111/jocd.16393
34. Soares DJ. Bridging a century-old problem: the pathophysiology and molecular mechanisms of HA filler-induced vascular occlusion (FIVO)—implications for therapeutic interventions. *Molecules*. 2022;27:5398. https://doi.org/10.3390/molecules27175398
35. da Prato EB, Cartier H, Margara A, et al. The ethical foundations of patient-centered care in aesthetic medicine. *Philos Ethics Humanit Med*. 2024;19:1. https://doi.org/10.1186/s13010-024-00151-1
36. Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al. Preventing the complications associated with the use of dermal fillers in facial aesthetic procedures: an expert group consensus report. *Aesthetic Plast Surg*. 2017;41:667–677. https://doi.org/10.1007/s00266-017-0798-y