

Postmarket Safety Surveillance of Delayed Complications for Recent FDA-Approved Hyaluronic Acid Dermal Fillers

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OBJECTIVE To review postmarketing data for delayed (≥ 14 days post-treatment) adverse events (AEs) of interest (inflammatory and noninflammatory nodules, hypersensitivity, granulomas) for newer hyaluronic acid (HA) fillers FDA-approved within the last 5 years (2016–2020).

METHODS Reports from the Manufacturer and User Facility Device Experience (MAUDE) database were extracted for HA_{REF}, HA_{DEF}, HA_{KYS}, HA_{VER}, HA_{VLR}, HA_{VOB}, HA_{RH2}, HA_{RH3}, and HA_{RH4} from January 2016 to January 2021. Keywords from event narratives were used to identify and categorize AEs and then verified through inclusion/exclusion criteria. Percentages are based on the total combined events of interest to provide an overall perspective of the events reported during the search period.

RESULTS Of 585 MAUDE reports, there were 195 (33.3%) delayed AEs of interest. Of those, 71.8% were nodules (42.1% inflammatory and 29.7% noninflammatory), 21.5% hypersensitivity, and 6.7% granulomas. The combined total events of interest, ordered by frequency reported, were HA_{VLR} (74.4%), HA_{VOB} (12.3%), HA_{DEF} (5.1%), HA_{RH4} (3.6%), HA_{REF} (2.6%), and HA_{RH2} (2.1%), with no reports for HA_{RH3}, HA_{VER}, and HA_{KYS}.

CONCLUSION Although delayed nodules and inflammatory events are rare, reports for these events were extracted from the MAUDE database from 2016 to 2020 for HA_{VLR}, HA_{VOB}, HA_{DEF}, HA_{RH4}, HA_{REF}, and HA_{RH2} (most to least frequent).

The most popular aesthetic fillers are derived from hyaluronic acid (HA) due to their safety profile.¹ However, adverse events (AEs) still occur and are generally categorized as early-onset or delayed-onset. Early-onset (<14 days post-treatment) AEs (e.g., bruising, swelling, lumps/bumps) are more likely related to injection technique (e.g., superficial placement, rapid injection/flow rates, higher volumes).² Delayed-onset (≥ 14 days post-treatment) events are more likely to be product related and concerning for providers because they can appear months to years after the treatment.^{3,4} Delayed-onset

nodules and inflammatory events are of special interest to aesthetic providers because they are often immune mediated (noninfectious) and typically require removal of the product.^{3,4}

In contrast to the older generation, the long-term safety profile of the newer generation HA fillers is not well-established. Thus, more recently FDA-approved HA fillers (2016–2020) are of interest in this review: Juvederm Volbella (HA_{VOB}; Allergan plc), Restylane Refyne (HA_{REF}; Galderma SA), and Restylane Defyne (HA_{DEF}; Galderma SA), all approved in 2016; Juvederm Vollure (HA_{VLR}; Allergan plc), Teosyal RHA2/3/4 (HA_{RH2/3/4}; Teoxane SA), and Revanesse Versa (HA_{VER}; Prolenium Medical Technologies), approved in 2017; and Restylane Kysse (HA_{KYS}; Galderma SA) approved in 2020. Although the FDA approved HA_{RH2/3/4} in 2017 and available in Europe since 2015, they were not available in the United States until mid 2020.

Each product uses various manufacturing technologies, providing them with unique properties that maximize versatility. HA_{VOB} and HA_{VLR} use Vycross technology, which combines low- molecular-weight and high-molecular-weight HA to improve the crosslinking efficiency of the HA chains⁵; HA_{RH2/3/4} use Preserved Network technology, designed with reduced synthetic crosslinking due to preserved natural HA polymers⁶; HA_{VER} uses Thixofix technology, designed to maximize the effectiveness of the crosslinked HA chains present in the gel⁷; and HA_{REF}, HA_{DEF}, and HA_{KYS} use XpresHAN technology, which has varying degrees of crosslinking to provide different levels of

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flexibility and support while maintaining natural movement in areas of dynamic expression.^{8–11}

Several clinical trials have established the efficacy and safety of each product.^{12–20} Additionally, each product has postmarketing surveillance (PMS) data available in the Manufacturer and User Facility Device Experience (MAUDE) FDA database.

Although safety reviews with the MAUDE database have been conducted to understand events reported for older HA fillers,^{21–23} these analyses were not inclusive of those more recently approved. The aim of this safety review was to summarize delayed events of interest reported in the MAUDE database from January 2016 to January 2021 for FDA-approved HA fillers 2016 to 2020. The events of special interest in this review include hypersensitivity reactions, nodules (both inflammatory and non-inflammatory), and granulomas.

Methods

The MAUDE database compiles PMS data submitted to the FDA of potential device-related safety issues that are derived from mandatory reports (manufacturer) and voluntary reports (health care professionals [HCP] and consumers).²⁴ This includes events assessed as related to the product and/or procedure collected from spontaneous reports, the literature, and health authorities (including ex-US data). The "Event Text" field in the reports contain information, such as the treatment date, time of event onset and duration, event description, and any interventions. This information can be incomplete for individual reports due to patient privacy, the reporter, or reporter follow-up.

The MAUDE database was queried for complications related to injection of HA_{REF}, HA_{DEF}, HA_{KYS}, HA_{VER}, HA_{VLR}, HA_{VOB}, HA_{RH2}, HA_{RH3}, and HA_{RH4} from January 1, 2016 to January 31, 2021. Duplicated reports under multiple report numbers were consolidated into single representative reports.

Keywords summarized in Table 1 were generated to search and categorize events of interest from each report. Categorizations were based on the "lay terms" most used to describe the events of interest. Because MAUDE does not classify the type of event in each report, the "event text" (narrative) section was queried for the keywords. Once events were categorized, event descriptions were used as a basis to either include or exclude event reports consistent with the criteria below. This ensures consistency of results across all products analyzed. Note that individual event reports may contain multiple AEs of interest.

Inclusion criteria were as follows: manufacturer or HCP reports, "delayed AE" identified by HCP or reported as ≥14 days after treatment, and verified events of interest (hypersensitivity, nodules [inflammatory or noninflammatory], and granulomas) based on descriptions.^{3,4} Hypersensitivity was confirmed if the description included HCP-reported hypersensitivity, diffuse facial swelling/inflammation, and persistent facial swelling. Nodules were confirmed if the description included palpable lumps/bumps or specifically identified them as nodules. Inflammatory nodules were differentiated from noninflammatory nodules if the description included tenderness, erythema, swelling/inflammation, pain, or irritation. Granulomas were confirmed if a biopsy demonstrated a "granulomatous" or "foreign body reaction"; otherwise, they were reclassified as the "other events of interest" if they met the criteria described.

Exclusion criteria were as follows: early-onset AE (<14 days) or no confirmation of a delayed event, patient or consumer reports with no HCP confirmation, and events that may have been caused by a different product or a combination of products based on narrative.

For the purposes of reporting relative frequencies, percentages were based on the total combined events of interest identified. The nodules reported by injection site were analyzed relative to the combined total number of nodules identified.

Results

Between 2016 and 2020, there were a combined total of 585 MAUDE reports extracted for each HA filler. Of these, there were 195 (33.3%) confirmed delayed AEs of interest; 71.8% were nodules (42.1% inflammatory and 29.7% noninflammatory), followed by hypersensitivity (21.5%), and granulomas (6.7%). Ordered by frequency, these were with HA_{VLR} (74.4%), HA_{VOB} (12.3%), HA_{DEF} (5.1%), HA_{RH4} (3.6%), HA_{REF} (2.6%), and HA_{RH2} (2.1%), with no reports for HA_{RH3}, HA_{VER}, and HA_{KYS} (Figure 1 and See, Supplemental Digital Content 1, Table S1, <http://links.lww.com/DSS/A972> displaying the total number of events and percentages relative to the total combined events of interest identified for each product).

Of the 140 reports of nodules, 41.4% occurred in the lips, followed by nasolabial folds (NLFs; 23.6%), marionette lines (MLs; 22.1%), perioral areas (19.3%), tear troughs (12.1%), chin (5.7%), cheeks (4.3%), and prejowl (3.6%) (Figure 2). Note that nodules reported in multiple sites per patient counted as one event.

TABLE 1. Keywords Used to Identify and Categorize Delayed Events From MAUDE Reports	
Event	Extracted "Keywords"
Nodules	Nodule, papule, mass, lump, bump, induration
Granuloma	Granuloma, foreign body
Hypersensitivity	Hypersensitivity, swelling/inflammation

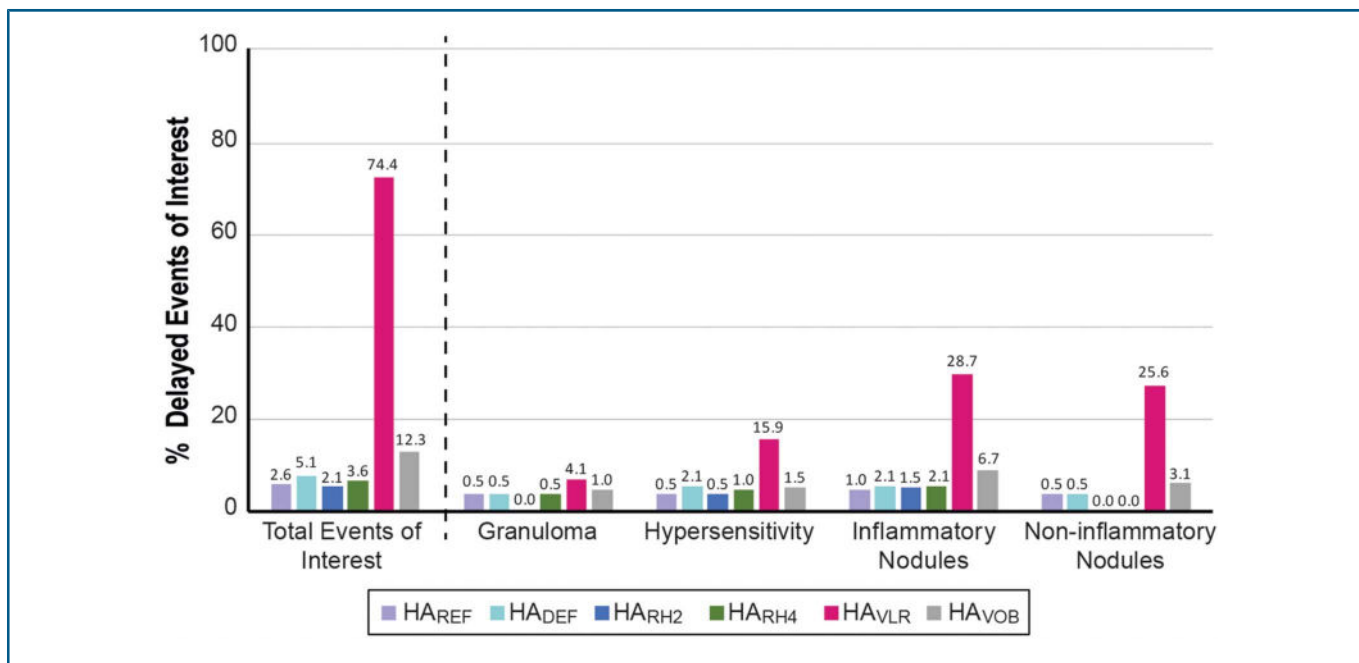


Figure 1. Percentage of delayed events of interest relative to the combined total for all HA fillers.

XpresHAN Technology

Of the total events of interest, there was 1 (0.5%) report of granuloma and noninflammatory nodules for both HA_{DEF} and HA_{REF}. HA_{REF} had 1 (0.5%) report of hypersensitivity reaction and 2 (1.0%) inflammatory nodules, whereas HA_{DEF} had 4 (2.1%) hypersensitivity reactions and inflammatory nodules each (Figure 1). There were no events of interest reported for HA_{KYS} during the search period.

Events had a time of onset ranging from 2 weeks to 4.5 months, with a median of 2 months. Nodules were reported in the lips and MLs for both products and in the chin, prejowl sulcus, and cheeks with HA_{DEF}.

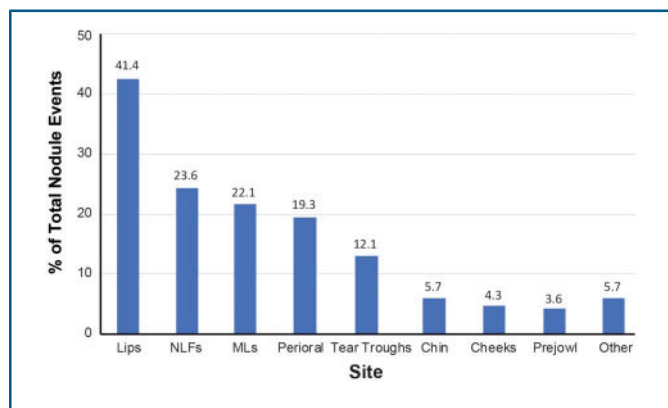


Figure 2. Location of nodules relative to total number of nodule events identified. Other includes neck, glabella, forehead, temple, nose, ear, and full face. One event equals one report. Nodules could be in multiple locations per event. MLs, mario-nette lines; NLFs, nasolabial folds.

Vycross Technology

Of the total events of interest, there were 56 (28.7%) reports of inflammatory nodules, 50 (25.6%) noninflammatory nodules, 31 (15.9%) hypersensitivity reactions, and 8 (4.1%) granulomas for HA_{VLR} (Figure 1). For HA_{VOB}, there were 13 (6.7%) reports of inflammatory nodules, 6 (3.1%) noninflammatory nodules, 3 (1.5%) hypersensitivity reactions, and 2 (1.0%) granulomas (Figure 1).

Events had a time of onset ranging from 2 weeks to 19 months after injection, with a median of 3 months. Of note, there was one report of inflammatory nodules with hypersensitivity (same patient) with a time of onset of 19 months, and 2 events of noninflammatory nodules with a time of onset of ≥ 1 year after injection of HA_{VLR}. Nodules were most reported in the lips, followed by NLFs and MLs for HA_{VLR}, and in the lips and perioral areas for HA_{VOB}.

Preserved Network Technology

Of the total events of interest, HA_{RH2} had 3 (1.5%) reports of inflammatory nodules and 1 (0.5%) hypersensitivity reaction, and HA_{RH4} had 4 (2.1%) reports of inflammatory nodules, 2 (1.0%) hypersensitivity reactions, and 1 (0.5%) granuloma (Figure 1). There were no events of interest reported for HA_{RH3} during the MAUDE search period. Report dates ranged from 2018 to 2020. Although not explicitly stated in reports for the other HA fillers, it was specified in the "event text" field that all but one occurred outside of the United States.

Events had a time of onset after injection ranging from 1 to 8 months, with a median of 3.5 months. Nodules were reported in the lips, chin, and nose for HA_{RH4} and in the lips, chin, NLFs, MLs, and glabella for HA_{RH2}.

Treatment

With limited information in each report, documented treatments for the AEs of interest were generalized. Non-inflammatory nodules were treated with hyaluronidase, and inflammatory nodules were treated with some combination of hyaluronidase, antihistamines, corticosteroids, anti-inflammatories, and antibiotics. Hypersensitivity was treated with some combination of corticosteroids, antihistamines, and anti-inflammatories, whereas granulomas were treated with antibiotics and corticosteroids.

Discussion

The US HA filler market continues to expand with 9 new FDA approvals within the past 5 years. Each product uses various manufacturing technologies, providing them with unique characteristics, which maximize versatility and aesthetic outcomes. Clinical trials have established the safety and efficacy of the fillers in this review^{12–20}; however, AEs occur in clinical practice for all medical devices, and thus, there is a need for postmarketing safety surveillance to establish a long-term safety profile.

Delayed-onset nodules and inflammatory events were the focus of this analysis due to the likelihood of these events being product related.^{2,3} These events can appear months to years after treatment, and because they are usually immune mediated (noninfectious), treatment is difficult and may even require product removal.^{3,4}

The estimated incidence of delayed nodules and inflammatory reactions in the literature generally ranges from 0.02% to 4.0%.^{25–29} Delayed inflammatory reactions with HA fillers are likely due to a Type IV hypersensitivity reaction and are typically treated with antihistamines, corticosteroids, and anti-inflammatory drugs.^{3,4,28} Inflammatory nodules are frequently reported as granulomas because they are treated similarly; however, biopsies are rarely taken to confirm diagnosis.^{3,4} Consequently, the incidence of true granulomas is estimated to be less than nodules.^{3,4,29}

In this PMS retrospective review, nodules were the most frequently reported delayed event, of which, most were inflammatory in nature. Hypersensitivity reactions and granulomas were the second and third most frequently reported delayed event, respectively. Most of these events had a time of onset of 2 to 4 months, and documented treatments were consistent with consensus guidelines.³⁰

Interestingly, nodules were most reported in the lips, and the relative frequencies were consistent with previously published literature, suggesting that the lips appear to be more prone to developing nodules.²⁶

Of the delayed events identified in the MAUDE database during the 5-year search period, there were more reports for HA_{VLR} and HA_{VOB} (Vycross) overall (12.3%–74.4%), and most were noninflammatory (3.1%–25.6%) and inflammatory (6.7%–28.7%) nodules. Consistent with these findings, other published literature suggests that Vycross technology has been associated with higher rates of delayed-onset nodules in clinical practice (0.5%–4.25%).^{25,31,32} There were fewer reports for other HA fillers overall (2.1%–5.1%) and

for nodules (0.5% noninflammatory; 1.0%–2.1% inflammatory). No events were found for newer agents, HA_{VER} (Thixofix), HA_{KYS} (XpresHAN), and HA_{RH3} (Preserved Network). A likely explanation is that these products were not available in the United States for as long as others (after December 2017), thus limiting the number of total AEs reported.

The number of events of interest for each HA filler is likely influenced by the frequency of use (information not available) and the length of time available. It is also important to note that these events have been identified solely from the event description field in the MAUDE reports, which is often limited in nature. For this reason, strict inclusion and exclusion criteria were developed to help characterize events in the reports to the best of the authors' ability.

Importantly, because the MAUDE database is a passive surveillance system and heavily reliant on voluntary reporting, the true number of events is likely significantly larger than reported.³³ For instance, the American Society of Plastic Surgeons reported more than 8 million dermal filler procedures in the United States from 2016 to 2019.³⁴ Based on this and the estimated rates of delayed-onset AEs in the literature, more events are expected in clinical practice than seen in these databases. Therefore, the number of reports cannot be used to determine national incidence, and no definitive conclusions regarding the relative frequency of AEs between specific products can be made.

Despite the limitations of the current methodology, the MAUDE database is one of the few large data sources available for postmarket surveillance of HA dermal fillers. This review is meant to provide visibility on the most frequent delayed-onset events linked to HA fillers reported in this database. Similar methodology has been used to provide information about the relative number of events reported each year and the types of events being reported more frequently.^{21–23}

For example, a 10-year retrospective analysis (January 2007–July 2017) of the MAUDE database reports that the most common complication reported for aesthetic dermal filler use was nodule formation.²¹ These included both early-onset and delayed-onset nodules. Of the total MAUDE reports extracted for overall AEs ($N = 5,204$), 20.9% were for Juvederm Voluma XC (HA_{VOL}), 2.9% HA_{VOB}, 0.8% HA_{VLR}, 0.06% HA_{DEF}, and 0.03% HA_{REF}.

A 21-year retrospective MAUDE analysis (June 1993–August 2014) found that the most frequently reported AEs associated with injectables were lumps (39.2%), infection (12.9%), and swelling (10.2%).²² Of the total MAUDE reports extracted ($N = 3,782$), the Juvederm brand had 517 reports (13.7%) and the Restylane brand had 236 reports (6.2%).

Finally, a 2-year retrospective MAUDE analysis (January 2014–December 2016) found that the most common complications associated with HA-based fillers were swelling, infection, nodules, and pain.²³ Of the total MAUDE reports extracted ($N = 1,748$); 839 (48.0%) for HA_{VOL}, 633 (36.2%) for Juvederm, and 128 for Restylane (7.3%).

Postmarketing safety surveillance can provide information on real-world use of products in patient populations normally excluded or not studied during clinical trials, as well as providing insight into less common and/or rare AEs

not observed during clinical trials.³⁵ This allows for a better understanding of the events that are occurring. Comparisons of delayed nodules and inflammatory events reported for both older and newer HA fillers would be useful for clinicians and are of interest for future analyses.

Conclusion

Although delayed-onset nodules and inflammatory events may be relatively uncommon in clinical practice, this retrospective database review from 2016 to 2020 demonstrates that they do occur for HA fillers with XpresHAN, Vycross, and Preserved Network technologies, with the most common being nodules. This review benefits the practicing clinician by providing visibility on the most frequent delayed-onset events linked to HA fillers reported in the MAUDE database and how these events were treated in practice.

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