Vaxzevria® (COVID-19 vaccine AstraZeneca) and dermal filler reactions

Introduction

Vaxzevria®, produced by AstraZeneca (AZ), is a monovalent vaccine composed of a recombinant and replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the spike glycoprotein of Sars-CoV-2, *indicated for immunisation against Sars-CoV-2 virus causing COVID-19*. Following intramuscular administration the spike glycoprotein is expressed locally, stimulating antibody and cellular immune response (1). In The Netherlands, Vaxzevria® has been used since February 2021, mainly used for immunisation of healthcare workers and people aged 60-65 and on demand for people >65 years (2).

Dermal fillers, also known as injectable implants, are used to help create a smoother and/or fuller appearance in the face, including nasolabial folds, cheeks, chin, lips and also in the back of the hands (3). The FDA categorizes dermal fillers into four different types based on the material of the filler (4). Hyaluronic acid (HA) fillers are biodegradable fillers that are reabsorbed by the body quickly, which means that their cosmetic effect is relatively short-lived. Hyaluronic acids are linear polymeric dimers of N-acetyl glucosamine and glucuronic acid (5). HA is found naturally in the body, with the highest concentrations in the skin, joints and eyes. It binds water and can act as a lubricant and shock absorber in the joints (6). When people age it can lead to a decrease in production of hyaluronic acid and collagen in the skin. HA fillers work by boosting the skin's supply of HA, which leads to attraction of water and thus replacing the lost volume to the skin. In additions to this, HA fillers have also been shown to increase collagen production (7). HA fillers are the most used biodegradable fillers in both Europe and the USA (5).
Calcium hydroxylapatite (CaHA) fillers consist of synthetic, biodegradable, CaHA microspheres suspended in a carrier gel. CaHA fillers stimulate the body to produce its own collagen. These fillers have a longer duration effect than HA fillers (5).
Poly-L-lactic acid (PLLA) fillers work in a similar way as the CaHA fillers. PLLA is a synthetic polymer that provides soft tissue augmentation through stimulation of an inflammatory tissue response with subsequent collagen deposition (5).
The last category of dermal fillers are the fillers with collagen, made of highly purified cow or human collagen and nonabsorbable microspheres. Collagen is a naturally-occuring protein found in bones, cartilage, tendons and skin. Collagen-boosting dermal fillers are stimulating the body's natural production of collagen. These fillers are nonbiodegradable (5,8).

All types of fillers mentioned above are associated with a risk of complications and adverse reactions. These can be both short-duration and long-duration complications or reactions. Some reactions occur immediately after treatment, while other reactions may have a delayed onset (5). The most common side effects are bruising, redness, swelling, pain and itching on the injections site (4,5). Other less common side effects are infections, lumps and bumps and skin discoloration or changes in pigmentation. Rare but serious side effects include hypersensitivity reactions and scarring, blurred vision, partial vision loss, blindness, tissue necrosis and stroke if the dermal filler is injected into a blood vessel (4,5).

Reports

In the period from February 2021 until October 20th, 2021 the Netherlands Pharmacovigilance Centre Lareb received 6 reports on dermal filler reactions associated with administration of Vaxzevria® (table 1).

Table 1. Reports of dermal filler reactions associated with Vaxzevria®.

No.	ID, sex, age, primary source	Drug, administration dose	Implant type: brand	Filler reaction, latency time	Other reactions	Time between dermal filler injection and filler reaction
1	NL-LRB-00549576, female, 60-70 years, Consumer or other non health professional	AstraZeneca, 1st dose	Hyaluronic acid filler: Restylane	Implant site inflammation, latency unknown	Headache, pyrexia, myalgia	Unknown
2	NL-LRB-00509626, female, 60-70 years, Consumer or other non health professional	AstraZeneca, 1st dose	Filler: unknown	Implant site mass, nodule subcutaneous, 1 week	None	3 months
3	NL-LRB-00534347, female, 60-70 years, Consumer or other non health professional	AstraZeneca, 1st dose	Filler: unknown	Implant site dermatitis, 11 days	Tinnitus, chills, headache, nausea, myalgia, generalized joint pain, malaise, body temperature increased	7 months
4	NL-LRB-00543387, female, 60-70 years, Consumer or other non health professional	AstraZeneca, 1st dose	Hyaluronic acid filler: unknown	Implant site induration, 20 days	None	6 months
5	NL-LRB-00631726, female, 40-50 years, Consumer or other non health professional	AstraZeneca, 2nd dose	Filler: unknown	Implant site rash, implant site scar, 10 days for implant site rash, unknown for implant site scar	None	2 days
6	NL-LRB-COVID-00481761, female, 30-40 years, Other health professional	Astrazeneca, 1st dose	Filler: unknown	Implant site swelling, lip swelling, latency of hours	injection site inflammation, pyrexia, chills, headache, fatigue, secondary dysmenorrhea	Unknown

Additional information on the cases:

1. The patient experienced an inflammation reaction in her neck, where Restylane fillers are present, after her first COVID-19 vaccination (unknown latency time). After her second COVID-19 vaccination patient experienced pain at her right breast implant.
2. The patient has received fillers around her mouth 3 months before vaccination. A week after vaccination patient started to notice subcutaneous nodules (accumulation of filler) in her chin where the filler was injected. Patient is recovering a month after vaccination.
3. The patient experienced redness, inflammation and a burning sensation in her neck, where the filler was injected, 11 days after vaccination. The patient has recovered from the dermal filler reaction with a duration of 12 days. The fillers had been injected 7 months before.
4. The patient has had hyaluronic acid fillers in her face 6 months prior to vaccination. Twenty days after vaccination patient experienced induration where the filler was injected. The patient recovered in 7 days.
5. The patient describes getting little bumps on her skin 11 days after vaccination. She was treated with prednisone and antihistamine by her general practitioner. The reaction worsened. An ultrasound confirmed the development of scar tissue. Dermal fillers had been injected two days before the second vaccination. The patient has not recovered at the time of reporting.

6. The patient experienced swelling of her upper lip, where fillers had been administered, a couple of hours after vaccination. She recovered within a day.

Other sources of information

SmpC

The SmPC of Vaxzevria® does not mention dermal filler reactions as an adverse reaction (1).
The SmPCs of Comirnaty® and Spikevax® mention facial swelling in patients with a history of injection of dermal fillers (9,10).

Databases:

On 15-11-2021 the number of reports in Vigilyze for Vaxzevria® was 653,364 (11). In table 2 the number of reports of implant site reactions associated with administration of Vaxzevria® are listed. It should be noted that the implant site reactions mentioned in this table can also be implant site reactions in association with other implants, as no narratives are available to verify upon the type of implant. None of the associations in table 2 were statistically disproportional.

Table 2. Reports of implant site reactions associated with administration of Vaxzevria® in Vigilyze (11).

Vaccine Brand	MedDRA PT name	Number of reports
Vaxzevria® *COVID-19 vaccine NRVV Ad (ChAdOx1 nCOV-19)*	Implant site pain	8
	Implant site swelling	4
	Implant site rash	2
	Implant site dermatitis	1
	Implant site induration	1
	Implant site scar	1
	Implant site inflammation	1
	Implant site mass	1
	Implant site pruritus	1

On 23-11-2021 there were 29 implant site reactions associated with administration of Vaxzevria® reported in Eudravigilance. In only 5 of these 29 reports it was mentioned in the narrative that the implant site reaction was associated with dermal fillers. These five reports were from the Netherlands and can be seen in more detail in table 1. In the other 24 reports it was either associated with another implant or unknown. It even appears that most of the implant site reactions that are coded are actually injection site reactions (16).

Literature and mechanism

Dermal filler reactions have been described in case reports associated with Covid-19 vaccination with mRNA vaccines from Pfizer (12,13) and Moderna (14). No case reports of dermal filler reactions after vaccination with Vaxzevria® were found in the literature.

The dermal filler reactions might be a delayed hypersensitivity reaction following the introduction of an immunologic trimmer, and have been previously noted after other viral illnesses and influenza vaccines (12,15). There have also been cases where people had a dermal filler reaction post COVID-19 infection (17,18). Delayed (or type IV) hypersensitivity reactions can take place from 24 hours to months after allergen contact. Delayed-type hypersensitivity reactions to dermal fillers is a very rare complication and is usually presented as a tender, erythematous swelling. It is a cell-mediated hypersensitivity reaction caused by T-lymphocytes (12,13), but the etiology of dermal fillers reactions is not yet known but likely to be multifactorial. Various etiologic factors have been suggested, including filler properties, injection technique, and previous trauma or infection in the area of injection (12,15).

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received six reports of dermal filler reactions after administration of Vaxzevria®. Filler injections were administered from two days till seven months prior to vaccination. Filler reactions occurred from hours (e.g. swelling) to twenty days (in case of induration) after vaccination. Recovery, if known, took place one day till one month after the start of the reaction. Until now, no case reports of dermal filler reactions in the literature were found in association with Vaxzevria®, but these are seen after other COVID-19 vaccinations (Comirnaty® and

Spikevax®) and influenza vaccines. The dermal filler reactions might be a delayed hypersensitivity reaction.

Based on the reports of dermal filler reactions and the mechanism of dermal filler reactions, a causal relationship for dermal filler reactions with Vaxzevria® is considered plausible.

References

1. EMA. Summary of Product Characteristics (SmPC) Vaxzevria. [cited 2021 October 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar- product-information_en.pdf
2. Rijksoverheid. Mensen die AstraZeneca-vaccin krijgen eerder volledig gevaccineerd. [cited 2021 October 20]. Available from: https://www.rijksoverheid.nl/actueel/nieuws/2021/05/21/mensen-die-astrazeneca-vaccin-krijgen-eerder-volledig-gevaccineerd
3. U.S. Food & Drug Administration. Dermal fillers (Soft tissue fillers). [cited 2021 November 9]. Available from: https://www.fda.gov/medical-devices/aesthetic-cosmetic-devices/dermal-fillers-soft-tissue-fillers
4. U.S. Food & Drug Administration. Filling in Wrinkles Safely. What to know about FDA-approved injectable dermal fillers. [cited 2021 November 9]. Available from: https://www.fda.gov/consumers/consumer-updates/filling-wrinkles-safely
5. Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. Clin Cosmet Investig Dermatol. 2013 Dec 12;6:295-316.
6. American Society for Dermatologic Surgery. Injectable Hyaluronic Acid. [cited 2021 November 9]. Available from: https://www.asds.net/skin-experts/skin-treatments/injectables/injectable-hyaluronic-acid
7. Walker K, Basehore BM, Goyal A, et al. Hyaluronic Acid. [Updated 2021 Jul 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482440/
8. Attenello NH, Maas CS. Injectable fillers: review of material and properties. Facial Plast Surg. 2015 Feb;31(1):29-34.
9. EMA. Summary of Product Characteristics (SmPC) Comirnaty. [cited 2021 October 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf
10. EMA. Summary of Product Characteristics (SmPC) Spikevax. [cited 2021 October 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf
11. WHO database Vigilyze [cited 2021 November 15]. Available from: https:// https://vigilyze.who-umc.org/
12. Savva D, Battineni G, Amenta F, Nittari G. Hypersensitivity reaction to hyaluronic acid dermal filler after the Pfizer vaccination against SARS-CoV-2 virus. Int J Infect Dis. 2021 Sep 28;S1201-9712(21)00773-6.
13. Michon A. Hyaluronic acid soft tissue filler delayed inflammatory reaction following COVID-19 vaccination - A case report. J Cosmet Dermatol. 2021 Sep;20(9):2684-2690.
14. Osmond A, Kenny B. Reaction to dermal filler following COVID-19 vaccination. J Cosmet Dermatol. 2021 Oct 27.
15. McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, Desai SR, French LE, Lim HW, Thiers BH, Hruza GJ, Blumenthal KG, Fox LP, Freeman EE. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. J Am Acad Dermatol. 2021 Jul;85(1):46-55.
16. Eudravigilance database. (version date: 2021, access date: 22-11-2021) http://bi.eudra.org (access restricted).
17. Rowland-Warmann MJ. Hypersensitivity reaction to Hyaluronic Acid Dermal filler following novel Coronavirus infection - a case report. J Cosmet Dermatol. 2021 May;20(5):1557-1562.
18. Shome D, Doshi K, Vadera S, Kapoor R. Delayed hypersensitivity reaction to hyaluronic acid dermal filler post-COVID-19 viral infection. J Cosmet Dermatol. 2021 May;20(5):1549-1550.

This signal has been raised on December 23, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl