Localised swelling at sites of dermal filler injections following administration of Covid-19 vaccines: a systematic review

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Abstract

Introduction: Localised swelling at sites of filler injections has been reported in the Moderna mRNA-1273 coronavirus disease 2019 (COVID-19) vaccine trial.

Methods: We conducted a review of the existing data and literature on the potential pathophysiology for this adverse event and its potential management.

Results: Data from the Moderna and Pfizer COVID-19 vaccine Phase 3 trial and one case series were available. Three out of 30,400 subjects developed possible filler reaction in the Moderna trial. Two other cases were reported after emergency use authorisation. Reactions occurred at a mean of 1.4 days post-vaccination. Fillers were injected at a mean of 14.1 months before vaccination. Areas involved included lips, infraorbital areas and tear troughs. Treatment included observation, corticosteroids, antihistamine, hyaluronidase and 5-fluorouracil.

Conclusion: Rare, self-limiting adverse reactions to dermal fillers have been reported following COVID-19 vaccination. Clinicians should be aware of this clinical phenomenon and its management, as vaccination is carried out globally.

Keywords: Dermal fillers, COVID-19, local swelling, vaccination

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an ongoing global pandemic caused by the causative pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] A Coordinated Global Research Roadmap was published by the World Health Organization (WHO) to guide research efforts and vaccine development.[2] Several COVID-19 vaccines have been authorised for administration to humans. The United States Federal Drug Administration (FDA) has given emergency use authorisation (EUA) for Pfizer-BioNTech (Pfizer) (New York, NY, USA and Mainz, Germany) and Moderna (Cambridge, MA, USA) vaccines.[3,4]

The release of data submitted by Moderna to the FDA on 30 November 2020 from an ongoing Phase 3 randomised, double-blinded and placebo-controlled trial of its mRNA-1273 vaccine in approximately 30,400 study participants revealed a serious adverse event of localised facial swelling in two patients and a medically significant event of lip angioedema in one patient who had previous dermal filler injections in the treatment group.[4] While both the Moderna and Pfizer COVID-19 vaccines are mRNA-based vaccines, Pfizer did not report adverse events related to dermal fillers in the data submitted to the FDA.[5]

In light of this new development, we conducted a review of the existing data and literature on the potential pathophysiology for this adverse event and the potential management options.

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METHODS

A systematic literature review was performed for information and articles on COVID-19- and COVID-19 vaccine-related dermal filler swelling/oedema and facial swelling/oedema; and vaccine-, viral- and drug-related dermal filler swelling/oedema, oedema and facial swelling/oedema. Our search strategy was as follows: first, we conducted a search within the FDA, Centers for Disease Prevention and Control (CDC) and National Institute of Allergy and Infectious Diseases (NIAID) websites for information on vaccine trial data; then, we searched the databases, Medline, Embase, CINAHL, Web of Science and Scopus, for relevant literature. We did not include cutaneous reactions that were not explicitly associated with dermal filler injections.

RESULTS

Table 1 summarises the cases of dermal filler reactions from COVID-19 vaccination. The information was gleaned from Phase 3 trial data on the Moderna mRNA-1273 vaccine,[5] as well as a case series that reported two other patients who developed filler reactions post-EUA.[6]

In the Moderna Phase 3 trial data, adverse events of facial swelling had been reported in three patients with previous dermal filler injections.[5] Two patients reported swelling on the face, without further mention of specific subsites of the face. In the remaining patient, the swelling was described as lip angioedema without mention of whether the upper, lower or both lips were involved. However, the document reported the resolution of facial swelling in all three subjects.

After EUA was given by the FDA, there were two other reported cases of localised facial swelling at sites of previous hyaluronic acid (HA) filler injection after COVID-19 vaccination. One had received the Moderna mRNA vaccine, and the other had received the Pfizer mRNA vaccine.[6]

Based on the information provided, filler reactions occurred at a mean of 1.4 days post-vaccination. The fillers were injected at a mean duration of 14.1 months before vaccination.

DISCUSSION

Facial swelling post-COVID vaccination is likely a form of delayed-type hypersensitivity (DH) initiated by T lymphocytes and mediated by $CD4^+$ T cells.[7] This is rare and occurs in an estimated 0.02% of treatments.[8]

This form of DH has been associated with vaccinations, trauma and infections[7,9,10] (influenza, herpes simplex, post-gastroenteritis, COVID-19) and occurs in association with certain drugs, especially biologics that upregulate the immune system.[11] These cases of DH occurred across various brands and subtypes of HA fillers with varying degrees of cross-linkages.[12] The time to onset of symptoms from the date of last filler injection ranged from 3 to 10 months.[12] Delayed-type hypersensitivity to non-HA fillers such as calcium hydroxyapatite has not been reported at the time of manuscript submission. As such, our postulated triggers are limited to HA fillers.

Hyaluronic acid *per se* is not immunogenic because it is a naturally occurring glycosaminoglycan in human skin, connective tissues and organs.[13] However, non-HA components in fillers, such as cross-linkers, for example, 1,4-butanediol diglycidyl ether (BDDE),[14] protein impurities from the bacterial fermentation process used in HA production and other molecules can be immunogenic.[15] While HA fillers as a temporary filler generally degrade within 12 months, the volumising effects of HA fillers have been reported to be 24 months or longer, suggesting that product molecules may persist for 24 months or longer.[16] In addition, trauma, drugs, infections and vaccinations may introduce antigens that exhibit biomimicry to HA fillers and/or upregulate the innate and adaptive immune responses, bringing about DH to fillers.[17] Evidence suggests that this happens in genetically predisposed individuals with certain human leukocyte antigen haplotypes.[18] One recent study postulated that the binding of SARS-CoV-2 spike protein to dermal angiotensin-converting enzyme 2 (ACE2) receptors may trigger a pro-inflammatory TH1 immune cascade, leading to a cutaneous inflammatory response.[4] Given that DH to fillers has been reported in both COVID-19 infection[6,19] and COVID-19 mRNA vaccination, this suggests that the trigger could possibly be present in both the virus and the protein expressed from translation of the mRNA vaccines. Figure 1 summarises the possible triggers and predisposing factors for delayed filler reactions.

While it is distressing to patients, late-onset or delayed reaction to fillers from COVID vaccinations are generally temporary

Table 1. Characteristics of patients with dermal filler reactions after COVID-19 vaccination.

Age (yr)	Gender	Vaccine company	Site	Time of filler injection before vaccination	Onset after the last dose of vaccine	Resolution
46	Female	Moderna (trial data)[5]	Face swelling	6 months	1 day	Resolved
51	Female	Moderna (trial data)[5]	Face swelling	2 weeks	1 day	Resolved
29	Female	Moderna (trial data)[5]	Lip angioedema	Unknown	2 days	Resolved
36	Female	Moderna (post-EUA)[6]	Bilateral infraorbital, tear trough and lip swelling	20 months	2 days	Resolved
43	Female	Pfizer (post-EUA)[6]	Bilateral infraorbital swelling	2.5 years	1 day	Resolved

COVID-19: coronavirus disease 2019, EUA: emergency use authorisation

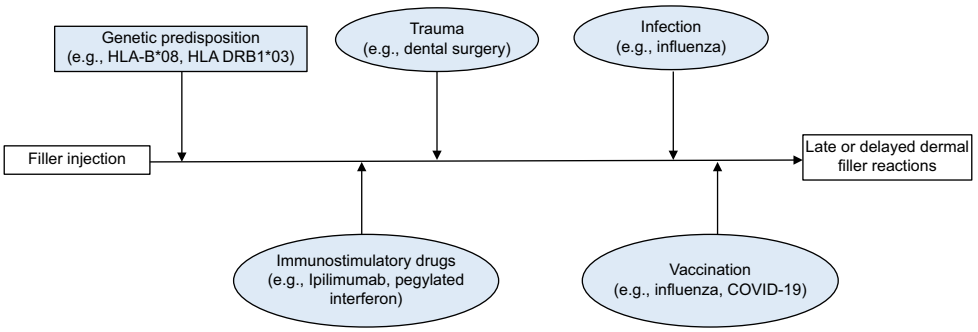

Figure 1: Diagram shows the possible triggers and predisposing factors for delayed filler reactions. HLA: human leukocyte antigen

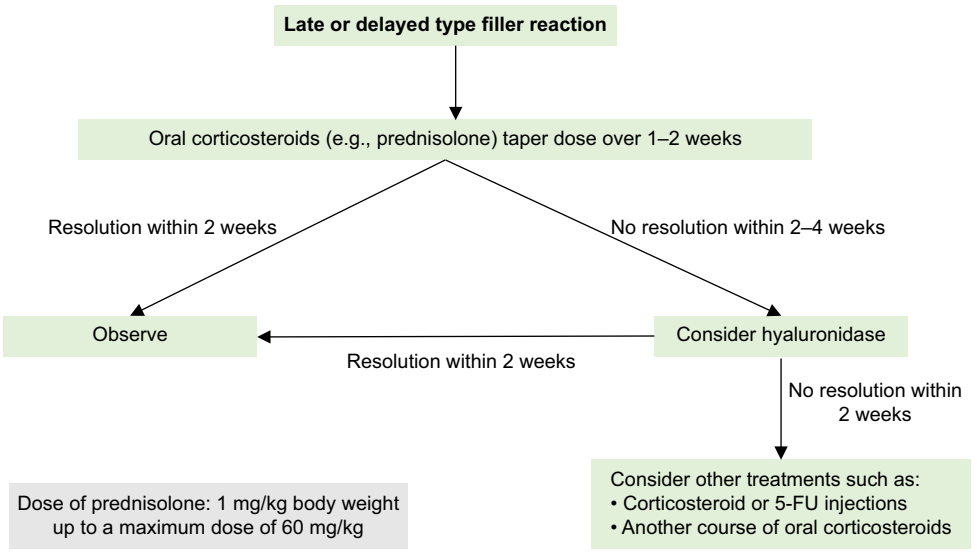

Figure 2: Diagram shows the suggested algorithm for the management of delayed-type hypersensitivity reactions to fillers.

and self-limiting. Treatment options are summarised in Figure 2. First-line treatment is usually in the form of oral corticosteroids gradually tapered over a few days. If there is residual swelling, intralesional hyaluronidase injections should be attempted. Other treatment options include intralesional 5-fluorouracil, intralesional corticosteroids and radiofrequency treatments.[6,19-21] The American Society for Dermatologic Surgery and the Society of Aesthetic Medicine (Singapore) have issued statements on the administration of systemic corticosteroids and intralesional hyaluronidase injections and have also stated that patients with dermal fillers should not be precluded from receiving COVID-19 mRNA vaccinations.[20,21]

In conclusion, adverse reaction to dermal fillers following vaccination or viral infections is not a new phenomenon. Pre-EUA, the Moderna mRNA-1273 vaccine trial reported three cases of facial swelling in subjects who had previously received dermal fillers. However, delayed reactions to dermal fillers have now been reported post-EUA of both the Moderna and Pfizer vaccines. There is limited information on this specific condition, and therefore, limited conclusions can be drawn. Clinicians should be cognisant of the potential for reactions to dermal fillers following COVID-19 vaccination and should report to the relevant health authorities and in case reports or series when such reactions are encountered.

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Conflicts of interest

Ng CL is a member of the SMJ Editorial Board, and was thus not involved in the peer review and publication decisions of this article.

REFERENCES

1. World Health Organization. Coronavirus Disease (COVID-19) Pandemic. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance. [Last accessed on 2021 Sep 06].
2. World Health Organization. A Coordinated Global Research Roadmap: 2019 Novel Coronavirus; 2020. Available from: https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap. [Last accessed on 2021 Sep 06].
3. Fact Sheet for Recipients and Caregivers-Emergency Use Authorization of the Pfizer-Biontech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 in Individuals 16 Years of Age and Older. U.S. Food and Drug Administration; 2020. Available from: https://www.fda.gov/media/144638/download.
4. FDA Briefing Document on Moderna COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting. U.S. Food

and Drug Administration; 2020. Available from: https://www.fda.gov/media/144434/download.
5. FDA Briefing Document on Pfizer-BioNTech COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting. U.S. Food and Drug Administration. December 10, 2020.
6. Munavalli GG, Guthridge R, Knutsen-Larson S, Brodsky A, Matthew E, Landau M. COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: A challenging clinical conundrum in diagnosis and treatment. Arch Dermatol Res 2022;314:1-15.
7. Turkmani MG, De Boulle K, Philipp-Dormston WG. Delayed hypersensitivity reaction to hyaluronic acid dermal filler following influenza-like illness. Clin Cosmet Investig Dermatol 2019;12:277-83.
8. 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.
9. Bhojani-Lynch T. Late-onset inflammatory response to hyaluronic acid dermal fillers. Plast Recon Surg Glob Open 2017;5:e1532.
10. Urdiales-Galvez F, Delgado NE, Figueiredo V, Lajo-Plaza JV, Mira M, Moreno A, *et al*. Treatment of soft tissue filler complications: Expert consensus recommendations. Aesth Plast Surg 2018;42:498-510.
11. Bisschop C, Bruijn MS, Stenekes MW, Diercks GFH, Hospers GAP. Foreign body reaction triggered by CTLA-4 blockade 25 years after dermal filler injection, a case report. Br J Dermatol 2016;175:1351-3.
12. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: Review. Dermatol Surg 2005;31:1616-25.
13. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K. Hyaluronic acid skin fillers: Adverse reactions and skin testing. J Am Acad Dermatol 2001;45:930-3.
14. Keizers PHJ, Vanhee C, van den Elzen EMW, de Jong WH, Venhuis BJ, Hodemaekers HM, *et al*. A high crosslinking grade of hyaluronic acid found in a dermal filler causing adverse effects. J Pharm Biomed Anal 2018;159:173-8.
15. Pinheiro MV, Bagatin E, Hassun KM, Talarico S. Adverse effect of soft tissue augmentation with hyaluronic acid. J Cosmet Dermatol 2005;4:184-6.
16. Glasser DA, Kenkel JM, Paradkar-Mitragotri D, Murphy DK, Romagnano L, Drinkwater A. Duration of effect by injection volume and facial subunit for a volumizing hyaluronic acid filler in treating midface volume deficit. Dermatol Surg 2015;41:942-9.
17. Alijotas-Reig J, Fernandez-Figueras MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. Semin Arthritis Rheum 2013;43:241-58.
18. Decates TS, Velthius PJ, Schelke LW, Lardy N, Palou E, Schwartz S, *et al*. Increased risk of late-onset, immune-mediated, adverse reactions related to dermal fillers in patients bearing HLA-B*08 and DRB1*03 haplotypes. Dermatol Ther 2021;34:e14644.
19. 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;20:1549-50.
20. Guidance Regarding SARS-CoV-2 mRNA Vaccine Side Effects in Dermal Filler Patients. American Society of Dermatologic Surgery; 2020. Available from: https://www.asds.net/skin-experts/news-room/press-releases/asds-provides-guidance-regarding-sars-cov-2-mrna-vaccine-side-effects-in-dermal-filler-patients.
21. Guidance on adverse reactions in dermal filler patients following SARS-CoV-2 vaccines. The Society of Aesthetic Medicine Singapore. 2021.