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BRIEF REPORT

Delayed Injection Site Reaction After mRNA-1273 Vaccination in Japan: A Retrospective, Cross-Sectional Study

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The incidence of delayed injection site reaction after the first dose of mRNA-1273 vaccine was 12.5% among females and 1.5% among males in a cohort of primarily elderly Japanese. After the second dose, 48.4% of those who could be contacted reported recurrence. The reaction may be relatively common among Asian females.

Keywords. COVID arm; COVID-19; delayed hypersensitivity; Moderna arm; mRNA.

Vaccination against coronavirus disease 2019 (COVID-19) has become a global priority in containing the pandemic. mRNA-1273, the messenger RNA (mRNA) vaccine manufactured by Moderna, was granted approval in Japan and vaccination started at designated mass vaccination centers in the country at the end of May 2021. mRNA-1273 has been associated with delayed injection site reactions, which is thought to represent a delayed hypersensitivity reaction and was coined "Moderna arm" or, more recently, "COVID arm" as it may also occur with the other mRNA vaccine BNT162b2, albeit with lower incidence [1–4]. The incidence of this reaction has been estimated to be 1.1% in a cohort of female health care workers in the United States and 2.0% in the subgroup of female recipients aged 31–45 years based on self-reporting to a hospital hotline [1]. The report did not specify race or ethnicity of the recipients. As the recipients of the first mRNA-1273 dose started to return for the second dose at our vaccination center, we noticed that many reported having experienced delayed injection site reaction several days after the first dose. We therefore conducted a 1-day cross-sectional survey of mRNA-1273 recipients in early July 2021 upon their presentation for the second dose to estimate the incidence of delayed injection site reaction in this population.

The survey was conducted at a mass vaccination center operated by a university hospital in Japan, which was 1 of the first 4 sites that started administering mRNA-1273 in the country. All vaccine recipients are routinely interviewed by a physician for eligibility screening and consent prior to receiving a vaccine by local regulation. On the day of the survey, we additionally asked whether they had any injection site reaction after receiving the first dose. If a recipient reported any reactions, they were interviewed further for their nature, timing, and duration, and any treatment administered if any. We defined delayed skin reaction as erythema occurring around the cutaneous injection site with onset occurring at least 2 days after vaccination [1]. With permission from the recipients, we also contacted them by phone approximately 2 weeks after receipt of the second dose to determine whether the reaction recurred. Injection site reactions were summarized by numbers and percentages, and the duration of erythema by median and range. The proportions of injection site reaction were compared by sex and age group using Fisher exact test, and the durations of erythema after the first and second doses were compared by Wilcoxon signed-rank test. The survey was conducted as part of routine clinical care, and reporting of the data was approved by the institutional review board of Fujita Health University.

On the day of the survey, 1098 persons received the second dose of mRNA-1273. Given the national vaccination prioritization schedule at the time, 963 of them (87.7%) were local residents ≥64 years of age who qualified for early vaccination. The rest were essential workers including health care and law enforcement personnel. All of them had received the first dose at the same vaccination center in early June 2021.

The recipients were all Asian and included 551 females (median age, 68 years [range, 18–98 years]) and 547 males (median age, 70 years [range, 18–93 years]). Delayed injection site reaction after the first dose was reported in 69 (12.5% [95% confidence interval {CI}, 9.8%–15.3%]) of the female recipients (age range, 18–88 years) and 8 (1.5% [95% CI, 0.5%–2.5%]) of the male recipients (age range, 31–78 years), and the difference between the sexes was statistically significant ($P < .001$). In terms of age groups, the incidence rates of the reaction were 7.2% (69/963) of those ≥64 years of age and 5.9% (8/135) of those <64 years of age, with no statistically significant difference ($P = .72$).

The median time from vaccination to onset was 7 days (range, 2–15 days) and the median duration of symptoms was 7 days (range, 2–21 days). The specific symptoms are summarized in

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Table 1. The self-reported major axis of erythema was ≥10 cm in 33 of 77 recipients. Pain or tenderness was reported by 20, swelling by 46, and pruritus by 56 of the 77 recipients, respectively. Twelve recipients reported using topical anti-itch cream, but none used oral medications. Overall, the recipients described the reaction as minor transient discomfort, and all 77 recipients proceeded with the second dose.

Of the 77 recipients who reported delayed injection site reaction after the first dose, 64 could be reached by phone between 2 and 3 weeks after the second dose. In total, 31 recipients reported erythema at the injection site (48.4% [95% CI, 36.2%–60.1%]) at any point after the dose. Twenty-eight of 31 recipients were female, the median age was 70 years (range, 18–86 years), and the median time from vaccination to onset was 1 day (range, 0–3 days). The median duration of erythema was 5 days (range, 2–10 days), which was significantly shorter than after the first dose (median, 7 days [range, 2–21 days]; $P = .003$). The self-reported major axis of the skin involvement after the second dose was ≥10 cm in 8 of 31 recipients. Pain or tenderness was reported by 19, swelling by 20, and pruritus by 24 of the 31 recipients, respectively (Table 1). Only 10 recipients (15.6% [95% CI, 6.7%–24.5%]) met the definition of delayed injection site reaction used for the first dose, that is, erythema with onset ≥2 days after the dose. In this subgroup, the median duration of erythema was 4 days (range, 2–10 days).

In a survey of health care workers in the United States, delayed injection site reaction was reported by 1.1% of females who received mRNA-1273, all of which except 1 occurred after the first dose, whereas none of the males reported the reaction. It is possible that the incidence was underestimated due to reliance on self-reporting. In that survey, only 5 of 13 individuals who had a delayed reaction to the first dose had a reaction to the second dose, which started 2–3 days after injection and tended to be less severe [1]. Our findings confirm the preponderance of this reaction in females, but the incidence after the first dose was much higher (12.5% in females and 1.5% in males) in our cohort that consisted primarily of elderly Asian individuals. While the reason for delayed injection site reaction triggered by mRNA-1273 is unknown, the histology is reportedly compatible with a hypersensitivity reaction [5], and the specific polyethylene glycol used as an excipient in the vaccine (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG]) has been suggested as a possible trigger [2]. It is reassuring, nonetheless, that none of the recipients who had this reaction after the first dose declined the second dose, and that less than half of them reported erythema after the second dose, which was shorter in duration and generally milder in nature as has been previously reported [6], even when defined broadly. When we used the strict definition with onset ≥2 days after the dose, only 15.6% of those who had the reaction after the first dose experienced recurrence. However, it was more difficult to clearly distinguish immediate vs delayed injection site reaction after the second dose, since symptoms that were consistent with delayed injection site reaction (ie, erythema accompanied by pruritus) often occurred within 2 days after the dose.

Table 1. Symptoms of Delayed Injection Site Reaction After Receiving mRNA-1273 Vaccine

Symptom	After First Dose[a] (n=77)	After Second Dose[b] (n=31)	After Second Dose[a] (n=10)
Erythema			
≥10 cm	33 (42.9)	8 (25.8)	4 (40)
<10 cm	44 (57.1)	23 (74.2)	6 (60)
Pain			
Present	20 (26.0)	19 (61.3)	5 (50)
Absent	57 (74.0)	12 (38.7)	5 (50)
Pruritus			
Present	56 (72.7)	24 (77.4)	7 (70)
Absent	21 (27.3)	7 (22.6)	3 (30)
Swelling			
≥10 cm	11 (14.3)	2 (6.5)	0 (0)
<10 cm	35 (45.4)	18 (58.1)	5 (50)
Absent	16 (20.8)	11 (35.5)	5 (50)
Unknown	15 (19.5)	0 (0)	0 (0)

Data are presented as No. (%).

[a]Defined as erythema with onset ≥2 days after the dose.

[b]Defined as erythema with onset any time after the dose.

This study has several limitations. Since it was a retrospective survey, recall bias by the recipients cannot be excluded, and the information was self-reported including variables such as the size of erythema. Also, those who experienced the reaction only after the second dose could not be captured. Earlier reports, however, suggest that onset of this reaction after the second dose of mRNA-1273 is generally uncommon [1, 3]. Finally, younger age groups were underrepresented due to limited eligibility for vaccination at the time of the survey.

In summary, the incidence of delayed injection site reactions following mRNA-1273 vaccination was high and occurred disproportionately in females in a cohort consisting primarily of elderly Japanese persons. The finding suggests that the vaccine-related reaction may be relatively common among Asian females. Importantly, the reactions were self-limiting, and all recipients who experienced it after the first dose proceeded with the second dose. As vaccination with mRNA-1273 expands to countries and populations that differ in demographics from where the vaccine underwent clinical trials and was rolled out initially, surveillance of vaccination-related reactions in specific settings will be important in maintaining and boosting confidence in the vaccine as well as vaccination programs.

Notes

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Patient consent. The study was reviewed by the Institutional Review Board at Fujita Health University and was designated "opt-out" with waiver of consent based on the retrospective, noninterventional nature of the study.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Jacobson MA, Zakaria A, Maung Z, et al. Incidence and characteristics of delayed injection site reaction to the mRNA-1273 SARS-CoV2 vaccine (Moderna) in a cohort of hospital employees [manuscript published online ahead of print 4 June 2021]. Clin Infect Dis **2021**. doi:10.1093/cid/ciab518.
2. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. N Engl J Med **2021**; 384:1273–7.
3. Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series. JAMA Dermatol **2021**; 157:716–20.
4. Fernandez-Nieto D, Hammerle J, Fernandez-Escribano M, et al. Skin manifestations of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers. 'COVID-arm': a clinical and histological characterization. J Eur Acad Dermatol Venereol **2021**; 35:e425–7.
5. Kempf W, Kettelhack N, Kind F, et al. "COVID arm"—histological features of a delayed-type hypersensitivity reaction to Moderna mRNA-1273 SARS-CoV2 vaccine [manuscript published online ahead of print 9 July 2021]. J Eur Acad Dermatol Venereol **2021**. doi:10.1111/jdv.17506.
6. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. J Am Acad Dermatol **2021**; 85:46–55.