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CORRESPONDENCE

Spikevax booster and delayed urticaria: a Swiss signal with diagnostic uncertainties due to a high proportion of direct patient reports

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Letter to the Editor

Shortly after the booster vaccination campaign began in Switzerland in December 2021, an increasing number of cases of delayed urticaria (defined as occurring from 4 h to several days after vaccine administration [1]) were reported in association with Spikevax® (elasomeran) to the Swiss Agency for Therapeutic Products (Swissmedic), which initiated a further evaluation. Up to February 8, 2022, 107 spontaneous reports of delayed urticaria following booster vaccination with Spikevax® have been recorded in the Swiss national pharmacovigilance database (out of 12,334 reports of suspected adverse reactions to COVID-19 vaccines by January 1, 2022, and 6,103,662 vaccinated people with at least one dose). To date, two case reports [2, 3] and a series of 21 patients from three Italian university hospitals [4] describing the onset of delayed urticaria following booster vaccination with Spikevax® have been reported in the literature. The present case series from the Swiss national pharmacovigilance database is the first to recognize this issue through a spontaneous reporting system. Out of 107 cases, 79 (73.8%) were reported by consumers/non-health professionals and 28 (26.2%) by health professionals (not further specified—information not collected within the Swiss national pharmacovigilance database). Women were more frequently involved (55, 51.4%), and the median age was 38 years (interquartile range, IQR, 34–44 years). Urticaria developed within a median of 10 days after booster vaccination with Spikevax® (IQR 9–11.5 days, minimum 5 days and maximum 21 days). In 55 (51.4%) reports, urticaria was the solely adverse event reported, while 52 (48.6%) cases reported additional adverse events including pruritus (27, 25.2%), angioedema (7, 6.5%), pyrexia (6, 5.6%), fatigue (4, 3.7%), headache (2, 1.9%), chills (1, 0.9%), adverse events at the injection site (5, 4.7%), and gastrointestinal adverse events (5, 4.7%). In 81 (75.7%) cases, delayed urticaria had no serious consequences, whereas in the remaining 26 (24.3%) reports, it either caused or prolonged hospitalization (4, 3.7%), was disabling/incapacitating (2, 1.9%), or determined other clinically relevant conditions not further specified (20, 18.7%). Except for one report mentioning additionally bilastine as suspected medicine, the booster vaccination with Spikevax® was the only suspected pharmacological trigger for urticaria in all the other reports. In 69 (64.5%) cases, urticaria was still persisting at the time of reporting, which occurred a median of 14 days after booster administration (IQR 6–21 days).

Similarly to delayed urticaria developed following COVID-19 mRNA primary vaccinations [5–8], delayed urticaria after booster vaccination with Spikevax® from the literature [2–4] and the present series of spontaneous reports was not accompanied by specific patterns of organ toxicity. By contrast, the present study highlighted that delayed urticaria developing after booster vaccination with Spikevax® appeared in most cases not self-limiting and with a prolonged course, which might warrant a follow-up system to continue monitoring their outcome.

Because of the delayed time to onset, delayed urticaria is unlikely to represent an immunoglobulin E (IgE)-mediated allergic reaction to vaccination [9]. Rather, this time course might correspond to the beginning of the normal immune/inflammatory response to vaccination, which may include the generation of cytokines or other factors that lead to non-IgE-mediated mast cell degranulation [10].

In summary, this case series indicates that booster vaccinations with Spikevax® might be a trigger for delayed urticaria, although the limitations of spontaneous reporting have to be considered. First, the temporal relationship between the booster vaccination with Spikevax® and the onset of delayed urticaria, albeit potentially suggestive for,

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does not prove causality. Second, information on medical and allergic history, clinical course, and treatment is frequently incomplete or missing in spontaneous reports, and thus, valid evaluation might be hampered. Third, with most of the spontaneous reports being from consumers/non-health professionals, it is unknown whether the reported delayed urticaria was medically confirmed with appropriate diagnostics.

However, even if the uncertainties about clinical diagnosis, duration, and clinical course of delayed urticaria following booster vaccination with Spikevax® are taken into account, based on previous findings on successfully treated delayed urticaria with COVID-19 mRNA primary and booster vaccinations [4–8], it is presumable that these reactions do not change the positive benefit-risk ratio of subsequent COVID-19 mRNA vaccinations, although further investigation is required. Meanwhile, the Swiss product information of Spikevax® was updated and other authorities, like the European Medicines Agency, are assessing urticaria currently [11].

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Declarations

Conflict of interest The authors declare no competing interests.

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