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LETTER

Outcomes of COVID-19 vaccination in 323 patients with clonal and non-clonal mast cell activation disorders

To the Editor,

SARS-CoV-2 vaccines are proven to be safe and effective.[1] The vaccines are overall well tolerated although hypersensitivity reactions have been reported, which are more frequent in females with atopy and those with a history of anaphylaxis.[2] The reports of anaphylaxis are of concern for patients with mast cell activation disorders (MCAD) and have created vaccine hesitancy. Preliminary data indicate a low risk for vaccination-induced hypersensitivity symptoms,[3–5] and in a recent study of 30 patients with clonal mast cell disorders who received H1- and H2-antihistamine premedication, none developed symptoms of mast cell activation.[6] The aim of this report was to provide outcomes of the safety and tolerability of COVID-19 vaccination in a large, international cohort of patients with mast cell disorders.

This was a retrospective study conducted across three institutions in the United States and Europe. The study was approved by an Institutional review board at each member institution. Adverse effects were considered "related to vaccine" if symptoms occurred within 2 h of vaccination. Patients with symptoms involving more than one organ system were scored according to the Brighton anaphylaxis scale.

A total of 323 patients received 666 vaccinations. Patients were stratified based on clonal or nonclonal disorder. As MCAS criteria described by Valent et al[7] were not applied to all patients, we refer to these patients as clonal or nonclonal symptomatic mast cell disorders. Our cohort included 276 patients with clonal mast cell disorders, 18 with nonclonal mast cell disorders, and 29 with hereditary alpha-tryptasemia. Table 1 describes patient demographics. All patients with hereditary alpha-tryptasemia underwent workup to exclude clonal mast cell disorders. Patients with clonal mast cell disorders did not routinely undergo tryptase genotyping (HαT testing). The majority received Pfizer (89.0%) vaccine, followed by Moderna (10.1%), Astra Zeneca (0.31%), and Johnson and Johnson (0.6%). Vaccines were overall well-tolerated with adverse symptoms occurring in 40/666 (6%). Cutaneous symptoms such as pruritus, urticaria, and flushing were most common (13/40, 32.5%), followed by gastrointestinal symptoms (11/40, 27.5%), pulmonary symptoms (7/40, 17.5%), and musculoskeletal (2/40, 5%). Figure 1 graphically depicts adverse reactions.

TABLE 1 Patient demographics ($n = 323$)

		Female sex	Age	Baseline tryptase	Vaccine (Moderna/Pfizer/J&J/AZ)	H_1-antihistamine premedication	Adverse reaction
Diagnosis, % (*n*)		**% *n***	**Mean ± SD**	**Mean ± SD**	***n***	**% (*n*)**	**% (*n*)**
Clonal MC disorders							
CM	7.1 (23)	52.2 (12)	48.1 ± 17.4	10.6 ± 13.9	4/19/0/0	47 (11)	8.5 (4)
ISM−	42.4 (137)	35.0 (48)	60.0 ± 11.9	30.9 ± 58.4	4/132/0/1	86.1 (118)	5.0 (14)
ISM+	30.3 (98)	62.2 (61)	53.3 ± 12.8	45.3 ± 54.2	10/88/0/0	86.1 (85)	5.6 (11)
AdvSM	4.6 (15)	40 (6)	66.3 ± 9.9	98.3 ± 124.4	2/12/0/0	60.0 (9)	12.1 (4)
Nonclonal disorders							
mMCD	0.9 (3)	66.7 (2)	49.0 ± 6.6	11.9 ± 4.8	0/3/0/0	33.3 (1)	0.0 (0)
Symptomatic MCA	5.6 (18)	61.1 (11)	56.4 ± 12.5	8.2 ± 5.4	2/16/0/0	83.3 (15)	10.8 (4)
Other disorders							
HaT	8.9 (29)	86.2 (25)	59.8 ± 13.3	17.1 ± 4.3	9/18/2/0	69.0 (20)	7.4 (5)

Abbreviations: CM, Cutaneous mastocytosis; ISM−, Indolent systemic mastocytosis without skin involvement; ISM+, Indolent systemic mastocytosis with skin involvement; mMCD, Monoclonal mast cell disorder; AdvSM, Advanced systemic mastocytosis; Symptomatic MCA, Mast cell activation disorder; HaT, Hereditary alpha-tryptasemia; J&J, Johnson and Johnson; AZ, Astra-Zeneca; n, number; MC, mast cell.

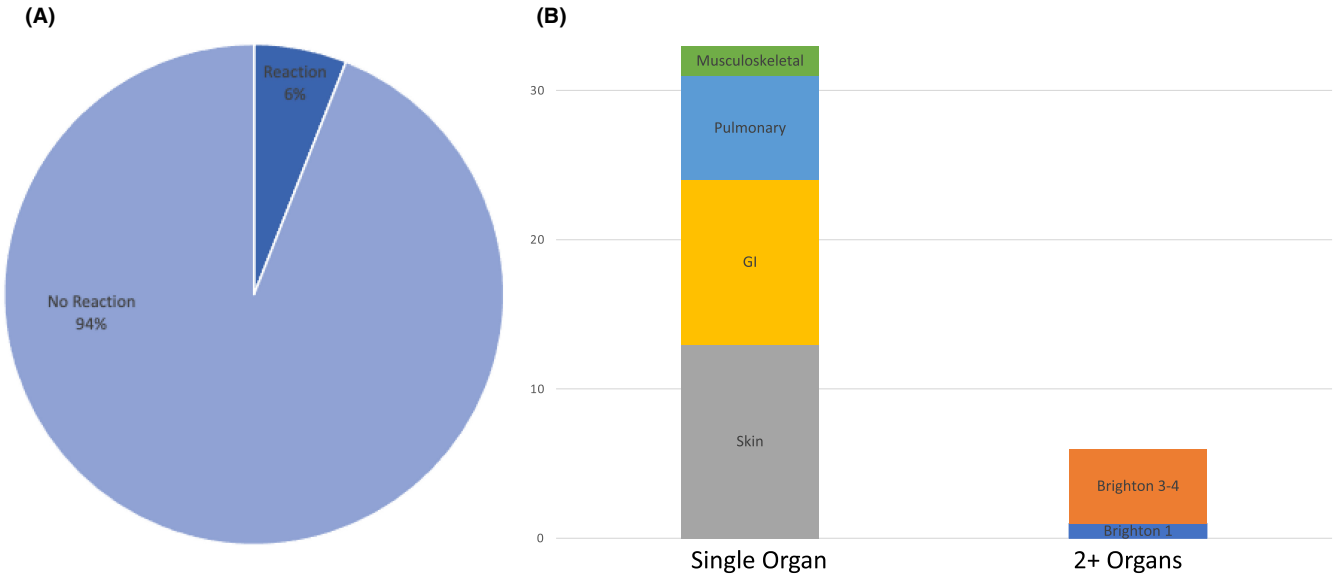

FIGURE 1 Characterization of adverse reactions to COVID-19 vaccination. (A) graphical depiction of percentage of patients with adverse reaction or no reaction. (B) Brighton Criteria scoring in adverse reactions to COVID-19 vaccination involving two or more organ systems.

Six patients reported symptoms involving more than one organ. Adverse reactions from this patient subset were scored according to Brighton criteria. One patient met criteria for anaphylaxis (Brighton level 1); the other 5 did not meet Brighton level 1/2 criteria. Most multi-system adverse reactions occurred after the first dose (5/6, 83%) and after the Pfizer vaccine (5/6, 83%). Two patients were administered epinephrine. One patient did not receive antihistamine premedications and was not taking scheduled H_1-antihistamines.

Most patients were premedicated prior to vaccination and 80.2% received H_1-antihistamines. Three patients were pretreated with systemic steroids. There was no statistically significant difference in adverse reaction rate between premedicated and non-premedicated patients ($p = .44$), although few patients were not premedicated. Many patients were also taking antihistamines at baseline for their ongoing mast cell activation disorders which was not considered premedication. With regard to patients with HαT, there were no statistically significant differences in adverse reactions based on genotype.

Outcomes of COVID-19 vaccines were favorable in most patients with mast cell disorders. There were no reported deaths, intubations, or ICU admissions. The rate of adverse reactions was higher as compared to the general population (6% vs. 2%, respectively), as well as higher than previous reports in clonal mast cell activation disorders. Most reactions were mild, involved a single-organ system, and did not require a higher level of care.

We also report a higher rate of anaphylaxis compared to the general population. Prior data indicate that anaphylaxis occurs in 0.011% of vaccines.[2] One patient fulfilled Brighton Level 1 criteria (1/666, 0.15%), and five additional patients fulfilled Brighton level 3/4 criteria. Of these patients, 5/6 (83%) were female. We did not detect any statistically significant differences in rate of adverse reactions between vaccine types (e.g., Pfizer vs. Moderna) nor were there statistically significant differences of adverse reaction due to disease type.

Although COVID-19 vaccination with mRNA and other vaccine platforms is safe and well-tolerated in patients with mast cell activation disorders, there is a relative increase in hypersensitivity and anaphylactic reactions. We recommended all patients carry epinephrine autoinjectors at the time of vaccination and consider receiving the vaccine at a center capable of responding to anaphylaxis and other severe adverse reactions.

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