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Safety of COVID-19 vaccination in patients with clonal mast cell disorders

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Clinical Implications

In our series, COVID-19 vaccination in patients with clonal mast cell disease who received antihistamine before vaccination turned out to be safe, and the rate of adverse reactions was comparable to that of the general population.

Mast cell activation syndromes (MCAS) encompass a heterogeneous group of pathologies characterized by the presence of symptoms resulting from the release of mast cell (MC) mediators. The presenting symptomatology may vary from mild to severe symptoms, including anaphylaxis.[1] Mast cell activation syndromes are classified as secondary (to allergy or owing to other underlying diseases), idiopathic, and primary. The latter may be also divided into (1) clonal or monoclonal MCAS, is a condition that courses with systemic symptoms owing to the release of MC mediators and the presence of clonal MCs (the expression of CD25 and/or KIT mutation) although complete diagnostic criteria for systemic mastocytosis (SM) are not met; and (2) SM, a disease characterized by the proliferation and accumulation of neoplastic MCs in extracutaneous organs, with well-defined diagnostic criteria.[1] It is widely known that patients with clonal MC diseases (MCDs) have a permanent risk for several MC-release symptoms evoked by different triggers, such as viral infections or vaccine administration.

During the coronavirus pandemic (COVID-19) and subsequent severe acute respiratory syndrome (SARS-CoV-2), many questions have arisen about how infection with this virus could affect patients with SM. Some of these questions have already been answered by experts in the field.[2] It was reported that in SM patients infected with SARS-CoV-2, symptoms, severity, and mortality rates were comparable to those in the general population.[2]

At the beginning of the worldwide COVID-19 vaccination campaign, several reports indicated an increased incidence of anaphylaxis (0.2 and 1.2/100,000 doses for Moderna [Spikevax, Cambridge, MA] and Pfizer-BioNTech [Comirnaty, New York, NY and Maguncia, Mainz, Germany], respectively) that was up to 10 times higher than for other vaccines.[3] The European Competence Network on Mastocytosis (ECNM) and the Spanish Network on Mastocytosis (REMA) offered several recommendations including maintenance of MC-mediator blocking drugs during COVID-19 infections and before the administration of COVID-19 vaccines as an effective and preventive measure previously known regarding safety with other vaccines.[3,4] Furthermore, they urged these patients to get the corresponding doses in a hospital environment capable of treating serious reactions.[3] To date, three different case reports with a total of 44 cases of vaccinated SM or MC disorder patients were reported, all of which were well-tolerated.[5-7]

The goal of this multicenter study carried out in two Spanish tertiary hospitals was to evaluate the safety of administering COVID-19 vaccines in a large series of patients diagnosed with clonal MCD. For that purpose, we included a total of 119 patients with a diagnosis of monoclonal MCAS or SM after a complete bone marrow study according to the World Health Organization 2016 proposed criteria,[1] including bone marrow mastocytosis cytology, histology, and immunochemistry; flow cytometry immunophenotyping; and the study of KIT mutation. We performed a retrospective review of all patients with a diagnosis of a clonal MCD observed at the Ramon y Cajal Hospital, Madrid, and Hospital Clinic, Barcelona. We contacted all of these patients by phone call within 1 week after the end of the vaccination campaign to confirm whether they took an antihistamine before vaccination and to evaluate any MC release symptoms or adverse reactions (ARs) after COVID-19 vaccination. The study was approved by the local ethical committee and enrolled patients gave their consent to participate. We included only patients who had received the full vaccination schedule (two doses or a single dose for the Janssen vaccine). Thus, five patients were excluded from the main patient cohort (n = 124) because they had received a single vaccine dose (except those who received the Janssen vaccine); they were considered immunologically protected because they suffered COVID-19 infection in the previous 6 months. According to the recommendation of ECNM/REMA, patients took an antihistamine 1 hour before administration of the vaccine and remained under observation for at least 45 minutes. The demographic characteristics, type of clonal MCD, vaccines administered, and related reactions are detailed in Table I and Table E1 (in this article's Online Repository at www.jaci-inpractice.org).

A total of 119 patients were included. Of these, 49 (41.2%) had an atopy background and 27 (22.7%) had a history of anaphylaxis (Tables I and E1). Four patients (3.5%) had experienced COVID-19 infection more than 6 months before receiving the corresponding COVID-19 vaccine, so they received the full vaccination schedule. Moreover, 101 patients (84.9%) took an antihistamine as premedication between 30 minutes and 1 hour before the administration of each dose of vaccine. In addition, 101 (84.9%) were vaccinated in a hospital setting and the remaining 18 (15.1%) were vaccinated in a health care center (n = 9) or in one of the national facilities centers authorized for the safe administration of COVID-19 vaccine (n = 9).

No recruited patients had significant MC-release symptoms or exacerbations of clonal MCD after administration of the vaccine, as defined by the World Health Organization,[8] AR was observed in 26 patients (21%). Only one (0.8%) reacted to both doses and had fever both times. The remaining 25 patients had a reaction only after one dose (nine after the first dose and 16 after the second one). Among the 16 patients with a local reaction, 11 (69%) had received Spikevax (Moderna) and all but one were premedicated (Tables I and E1). All ARs occurred within the first 48 hours, but none took place in the first hour after administration of the vaccine.

TABLE I. Demographic characteristics of patients, type of clonal mast cell disease, vaccines administered, and reactions presented after administration

Variable	Total number of patients (n = 119)	Patients with AR after vaccine (n = 26)
Sex		
Female	66 (55.5)	15 (57.7)
Male	53 (44.5)	6 (23.1)
Age, y		
Mean (range)	54.7 (20-86)	50.8 (30-73)
Allergy background†	49 (41.2)	9 (34.6)
Anaphylaxis	27 (22.7)‡	4 (15.3)§
Drug allergy	19 (16)	3 (11.5)
Food allergy	16 (13.4)	4 (15.3)
Hymenoptera venom allergy	11 (9.2)	2 (7.7)
Respiratory allergy	14 (11.8)	3 (11.5)
Skin allergy	3 (2.5)	0 (0)
Clonal mast cell disorder type		
Monoclonal mast cell activation syndrome	2 (1.7)	0 (0)
Bone marrow mastocytosis	35 (29.4)	0 (0)
Indolent systemic mastocytosis	79 (66.4)	25 (96.2)
Smoldering systemic mastocytosis	1 (0.8)	0 (0)
Systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease*	2 (1.7)	1 (3.8)
Type of COVID-19 vaccine		
Comirnaty (Pfizer-BioNTech)	62 (52.1)	10 (38.5)
Spikevax (Moderna)	37 (31.1)	12 (46.1)
Vaxzevria (AstraZeneca)	18 (15.1)	4 (15.4)
Janssen (Johnson & Johnson)	2 (1.7)	0 (0)
Characteristics of ARs to vaccine‖		
Local reaction¶	NA	14 (11.3)
Fever	NA	10 (8)
Local reaction and fever	NA	1 (0.8)
Local reaction, fever, and lymphadenopathy	NA	1 (0.8)

Results are expressed as the number of patients per total patients studied (percentage).
AR, adverse reaction; *NA*; not applicable.
*One of patient presented with acute myeloid leukemia, and the other with mucosa-associated lymphoid tissue—type lymphoma.
†Patients may have more than one allergic pathology and may be placed in more than one of the disease groups in the table.
‡Causes of anaphylaxis in patients were drug allergy (10), food allergy (seven), hymenoptera venom allergy (nine), and idiopathic (one). More details may be found in Table E1.
§Causes of anaphylaxis in the population with adverse reactions to vaccine were food allergy (two) and hymenoptera venom allergy (two). More details may be found in Table E1.
‖We considered an adverse reaction, as defined by the World Health Organization, to be "any noxious and unintended response to the administration of the vaccine, which occurs at doses normally used in man. In other words, an AR is harm directly caused by the medicine at normal doses, during normal use." All ARs reported in our series appeared within 48 hours after administration of the vaccine.
¶A local or injection-site reaction was considered to be any pain, swelling, rash, bleeding, or redness that occurred at the site of injection.

We observed a comparable rate of AR to COVID-19 vaccine in patients compared to data provided by the Spanish Agency for Drugs and Health Products for the general population, in which local reactions were observed in 5% to 18% of patients and fever in 35% to 51%, with a variable frequency depending on the type of vaccine.[9]

All but four patients who had an AR had been medicated before administration of the vaccine. Of 26 patients, 21 were vaccinated at a hospital center (81%), four in a national facilities center authorized for the safe administration of COVID-19 vaccine (15%), and one in a health care center (4%).

In line with these results, COVID-19 vaccination in patients with clonal MCD in this series turned out to be safe, and the rate of AR was comparable to that in the general population. A limitation of this study is the recall bias, because it was impossible to ensure compliance with measures recommended by the ECNM/REMA and because the time between the phone call and the vaccination was not the same in all patients. Thus, further prospective studies are needed. However, the proposed approach appears to be an effective preventive measure for managing patients with SM in the context of COVID-19 vaccination.

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REFERENCES

1. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140:349-55.
2. Valent P, Akin C, Bonadonna P, Brockow N, Niedoszytko M, Butterfield J, et al. Risk and management of patients with mastocytosis and MCAS in the SARS-CoV-2 (COVID-19) pandemic: expert opinions. J Allergy Clin Immunol 2020;146:300-6.
3. Rama TA, Álvarez-Twose I. Delving into COVID-19 vaccination-induced anaphylaxis: are mRNA vaccines safe in mast cell disorders? J Investig Allergol Clin Immunol 2021;31:193-5.
4. Bonadonna P, Brockow K, Niedoszytko M, Elberink HO, Akin C, Nedoszytko B, et al. COVID-19 vaccination in mastocytosis: Recommendations of the European Competence Network on Mastocytosis (ECNM) and American Initiative in Mast Cell Diseases (AIM). J Allergy Clin Immunol Pract 2021;9:2139-44.
5. Rama TA, Moreira A, Castells M. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. J Allergy Clin Immunol 2021;147:877-8.
6. Rosman Y, Lavi N, Meir-Shafrir K, Lachover-Roth I, Cohen-Engler A, Mekori YA, et al. Safety of BNT162b2 mRNA COVID-19 vaccine in patients with mast cell disorders. J Allergy Clin Immunol Pract 2021;9:3487-9.
7. Kaakati R, Khokhar D, Akin C. Safety of COVID-19 vaccination in patients with mastocytosis and monoclonal mast cell activation syndrome. J Allergy Clin Immunol Pract 2021;9:3198-9.
8. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255-9.
9. Spanish Agency for Drugs and Health Products. 8th National Pharmacovigilance Report on COVID-19 Vaccines. Accessed October 19, 2021. https://www.aemps.gob.es/informa/boletines-aemps/boletin-fv/2021-boletin-fv/8o-informe-de-farmacovigilancia-sobre-vacunas-covid-19/?lang=en

ONLINE REPOSITORY

TABLE E1. Demographic data and characteristics of patients

Patient ID	Sex	Age, y	Allergy background	Clonal mast cell disorder type	COVID-19 vaccine	Vaccine doses received, n	Adverse reaction to vaccine		H1 blocker premedication
							Reactive dose	Symptoms	
1	Male	50	None	ISM	Johnson & Johnson	1	NA	None	Yes
2	Male	66	FA‡	BMM	Vaxzevria	2	NA	None	Yes
3	Female	28	None	ISM	Comirnaty	2	NA	None	Yes
4	Female	70	HA‡	BMM	Comirnaty	2	NA	None	Yes
5	Female	73	DA	ISM	Comirnaty	2	NA	None	Yes
6	Female	39	None	ISM	Comirnaty	2	NA	None	Yes
7	Male	69	HA‡	BMM	Comirnaty	2	NA	None	Yes
8	Male	43	SA	ISM	Vaxzevria	2	NA	None	Yes
9	Male	73	None	ISM	Comirnaty	2	NA	None	Yes
10	Male	40	FA, HA‡	BMM	Vaxzevria	2	NA	None	Yes
11	Female	66	DA	ISM	Vaxzevria	2	NA	None	Yes
12	Female	63	DA	ISM	Comirnaty	2	First	FV	Yes
13	Male	48	HA‡	BMM	Comirnaty	2	NA	None	Yes
14	Female	64	FA‡	BMM	Vaxzevria	2	NA	None	Yes
15	Male	40	FA‡	BMM	Vaxzevria	2	NA	None	Yes
16	Male	57	None	BMM	Comirnaty	2	NA	None	Yes
17	Female	35	None	ISM	Comirnaty	2	NA	None	Yes
18	Male	40	None	ISM	Comirnaty	2	First	FV	Yes
19	Female	35	None	ISM	Vaxzevria	2	NA	None	Yes
20	Male	27	RA, FA‡	BMM	Comirnaty	2	NA	None	Yes
21	Male	49	None	BMM	Comirnaty	2	NA	None	Yes
22	Female	45	None	ISM	Comirnaty	2	NA	None	Yes
23	Male	63	None	SM AHNMD*	Comirnaty	2	First	FV	Yes
24	Female	53	SA	ISM	Comirnaty	2	NA	None	Yes
25	Female	66	None	ISM	Vaxzevria	2	Second	FV	Yes
26	Female	42	None	ISM	Comirnaty	2	NA	None	Yes
27	Male	85	DA	BMM	Comirnaty	2	NA	None	Yes
28	Female	47	None	ISM	Spikevax	2	NA	None	Yes
29	Male	53	None	SSM	Comirnaty	2	NA	None	Yes
30	Female	38	None	ISM	Spikevax	2	NA	None	Yes
31	Male	79	HA, FA	BMM	Comirnaty	2	NA	None	Yes
32	Female	84	None	BMM	Comirnaty	2	NA	None	Yes
33	Male	61	DA, FA, RA, HA‡	BMM	Vaxzevria	2	Second	FV	Yes
34	Female	66	FA‡	BMM	Spikevax	2	NA	None	Yes
35	Female	76	FA	ISM	Comirnaty	2	NA	None	Yes
36	Female	66	FA	ISM	Spikevax	2	NA	None	Yes
37	Female	47	None	ISM	Spikevax	2	NA	None	Yes
38	Male	66	DA‡	BMM	Vaxzevria	2	NA	None	Yes
39	Female	52	None	ISM	Comirnaty	2	NA	None	Yes
40	Male	49	FA, RA	BMM	Comirnaty	2	NA	None	Yes
41	Female	30	RA	ISM	Spikevax	2	Second	LR	Yes
42	Female	41	None	BMM	Comirnaty	2	NA	None	Yes
43	Female	84	None	ISM	Comirnaty	2	NA	None	Yes
44	Female	37	None	ISM	Spikevax	2	First and second	FV	Yes
45	Female	48	FA, RA	BMM	Comirnaty	2	NA	None	Yes
46	Female	80	None	ISM	Comirnaty	2	NA	None	Yes

(continued)

TABLE E1. *(Continued)*

Patient ID	Sex	Age, y	Allergy background	Clonal mast cell disorder type	COVID-19 vaccine	Vaccine doses received, n	Adverse reaction to vaccine		H1 blocker premedication
							Reactive dose	Symptoms	
47	Female	51	None	ISM	Vaxzevria	2	First	FV	Yes
48	Male	48	IA‡	BMM	Comirnaty	2	NA	None	Yes
49	Female	64	None	ISM	Comirnaty	2	NA	None	No
50	Female	43	DA	MMAS	Comirnaty	2	NA	None	Yes
51	Male	62	None	ISM	Spikevax	2	First	LR	Yes
52	Female	31	None	ISM	Spikevax	2	NA	None	Yes
53	Female	36	FA	BMM	Spikevax	2	Second	LR	Yes
54	Female	49	None	ISM	Comirnaty	2	NA	None	Yes
55	Female	56	DA	BMM	Spikevax	2	Second	LR	Yes
56	Male	65	DA, FA	BMM	Vaxzevria	2	NA	None	Yes
57	Male	60	None	ISM	Spikevax	2	NA	None	Yes
58	Female	64	DA‡	BMM	Comirnaty	2	NA	None	Yes
59	Male	69	None	BMM	Vaxzevria	2	NA	None	Yes
60	Male	74	None	ISM	Comirnaty	2	NA	None	Yes
61	Female	63	None	ISM	Vaxzevria	2	NA	None	Yes
62	Female	54	None	ISM	Comirnaty	2	NA	None	Yes
63	Male	57	None	ISM	Johnson & Johnson	1	NA	None	Yes
64	Male	68	HA‡	BMM	Comirnaty	2	NA	None	Yes
65	Male	55	HA‡	BMM	Spikevax	2	Second	LR	Yes
66	Female	55	DA	ISM	Vaxzevria	2	NA	None	Yes
67	Male	45	None	ISM	Comirnaty	2	NA	None	No
68	Male	76	None	ISM	Comirnaty	2	NA	None	Yes
69	Male	62	None	BMM	Vaxzevria	2	NA	None	Yes
70	Male	73	None	MMAS	Comirnaty	2	NA	None	Yes
71	Male	59	DA‡	ISM	Comirnaty	2	NA	None	Yes
72	Female	43	None	ISM	Comirnaty	2	NA	None	Yes
73	Male	48	None	ISM	Comirnaty	2	NA	None	Yes
74	Female	35	None	ISM	Comirnaty	2	Second	FV	Yes
75	Female	54	HA‡	ISM	Comirnaty	2	NA	None	Yes
76	Female	50	None	ISM	Comirnaty	2	First	FV	Yes
77	Male	86	RA	ISM	Comirnaty	2	NA	None	Yes
78	Female	49	RA	ISM	Comirnaty	2	NA	None	Yes
79	Male	58	None	ISM	Spikevax	2	Second	LR	Yes
80	Female	42	None	ISM	Spikevax	2	NA	None	Yes
81	Female	41	None	ISM	Spikevax	2	Second	LR. FV	Yes
82	Female	53	None	BMM	Comirnaty	2	Second	LR	Yes
83	Female	79	None	ISM	Comirnaty	2	NA	None	No
84	Female	65	None	ISM	Spikevax	2	NA	None	Yes
85	Male	54	RA, DA‡	ISM	Comirnaty	2	NA	None	No
86	Female	78	None	ISM	Spikevax	2	NA	None	Yes
87	Male	56	FA‡	ISM	Comirnaty	2	Second	FV	Yes
88	Male	43	None	ISM	Spikevax	2	NA	None	Yes
89	Female	58	None	ISM	Comirnaty	2	Second	LR	Yes
90	Male	75	DA‡	ISM	Spikevax	2	NA	None	Yes
91	Male	68	DA‡	SM-AHNMD*	Spikevax	2	NA	None	Yes
92	Male	73	None	ISM	Comirnaty	2	Second	LR	No
93	Female	23	None	ISM	Spikevax	2	NA	None	No
94	Female	67	None	ISM	Spikevax	2	First	LR	No
95	Male	72	HA‡	BMM	Comirnaty	2	NA	None	No
96	Male	58	FA‡	BMM	Spikevax	2	Second	LR. FE. LY	Yes
97	Female	56	RA	ISM	Comirnaty	2	Second	LR	No
98	Female	63	None	ISM	Vaxzevria	2	First	LR	No

(continued)

TABLE E1. *(Continued)*

Patient ID	Sex	Age, y	Allergy background	Clonal mast cell disorder type	COVID-19 vaccine	Vaccine doses received, n	Adverse reaction to vaccine		H1 blocker premedication
							Reactive dose	Symptoms	
99	Female	58	None	ISM	Spikevax	2	NA	None	Yes
100	Female	32	None	ISM	Spikevax	2	NA	None	Yes
101	Female	23	RA	ISM	Spikevax	2	NA	None	Yes
102	Female	39	None	ISM	Spikevax	2	NA	None	Yes
103	Female	36	None	ISM	Vaxzevria	2	NA	None	No
104	Male	40	None	ISM	Spikevax	2	First	LR	Yes
105	Male	43	DA‡	BMM	Spikevax	2	NA	None	Yes
106	Female	53	None	ISM	Spikevax	2	NA	None	Yes
107	Female	57	DA‡	ISM	Spikevax	2	NA	None	Yes
108	Female	44	None	ISM	Spikevax	2	NA	None	Yes
109	Female	69	None	BMM	Spikevax	2	First	LR	Yes
110	Male	49	None	ISM	Spikevax	2	NA	None	Yes
111	Female	41	None	ISM	Spikevax	2	NA	None	Yes
112	Male	45	None	BMM	Comirnaty	2	NA	None	No
113	Female	58	DA‡	BMM	Comirnaty	2	NA	None	Yes
114	Male	46	None	ISM	Spikevax	2	NA	None	No
115	Male	70	None	ISM	Comirnaty	2	NA	None	No
116	Male	20	DA‡	ISM	Comirnaty	2	NA	None	No
117	Male	49	RA	ISM	Comirnaty	2	NA	None	No
118	Male	77	None	ISM	Comirnaty	2	NA	None	No
119	Female	38	SA, RA	ISM	Comirnaty	2	NA	None	No

BMM, bone marrow mastocytosis; *DA*, frug allergy; *FA*, food allergy; *FV*, fever; *HA*, Hymenoptera allergy; *IA*, idiopathic anaphylaxis; *ISM*, indolent systemic mastocytosis; *LR*, local reaction; *LY*, lymphadenopathy; *NA*, not applicable; *MMAS*, monoclonal mast cell activation syndrome; *RA*, respiratory allergy; *SA*, skin allergy; *SM-AHNMD*, systemic mastocytosis with associated hematologic non-mast cell lineage disease; *SSM*, smoldering systemic mastocytosis.

*One presented with acute myeloid leukemia and the other had mucosa-associated lymphoid tissue−type lymphoma.

‡Anaphylaxis.