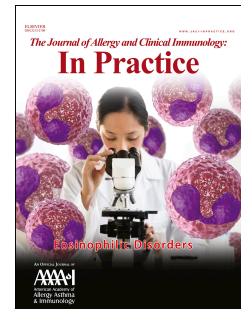


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Safety of COVID-19 vaccination in patients with clonal mast cell disorders

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39 **Conflict of interest statement**

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42 have no conflicts of interest to disclose.

43
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46 **Key words:** Adverse effects; Clonal Mast Cell Disorders; COVID-19; Mast Cell
47 Release Symptoms; Mastocytosis; Vaccination.

48

49 **Clinical Implications:** In our series, COVID-19 vaccination in patients with clonal mast
50 cell diseases receiving antihistamine prior to vaccination turned out to be safe and the rate
51 of adverse reactions was comparable with the general population.

52

Mast cell activation syndromes (MCAS) encompass a heterogeneous group of pathologies characterized by the presence of symptoms secondary to release of mast cell (MC) mediators. The presenting symptomatology may vary from mild to severe symptoms, including anaphylaxis.¹ MCAS are classified as secondary (to allergy or due to other underlying diseases), idiopathic and primary. This latter may be also divided in: (i) clonal or monoclonal MCAS (c-MCAS or MMAS) which is a condition that courses with systemic symptoms due to release of MC-mediators and the presence of clonal MCs (expression of CD25 and/or KIT mutation) while the complete diagnostic criteria for systemic mastocytosis (SM) are not met, and (ii) SM, a disease characterized by proliferation and accumulation of neoplastic MCs in an extracutaneous organ(s), with well-defined diagnostic criteria.¹ It is widely known that patients with clonal MC diseases (MCD) 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 the 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 them have been already answered by experts in the field.² It has been reported that in SM patients infected with SARS-CoV-2, symptoms, severity and mortality rates were comparable with the general population.² At the beginning of the world-wide COVID-19 vaccination campaign, several reports indicated an increased anaphylaxis incidence (0.2 to 1.2 /100 000 doses, for Moderna and Pfizer-BioNTech, respectively) that was up to 10 times higher compared to other vaccines³. The European Competence Network on Mastocytosis (ECNM) and the Spanish Network on Mastocytosis (REMA), imparted several recommendations which included the maintenance of the MC-mediator blocking drugs during the COVID-19 infection and

prior to the administration of any COVID-19 vaccines, as an effective and preventive measure previously known to 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 have been reported, all of them well tolerated.⁵⁻⁷

The goal of this multicenter study carried out in two Spanish tertiary hospitals was to evaluate the safety of the administration of COVID-19 vaccines in a large series of patients diagnosed with clonal MCD. For that purpose, we included a total of 119 patients diagnosed with MMAS or SM after a complete BM study according to the WHO 2016 proposed criteria,¹ including BMMC 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 followed up at the Ramon y Cajal Hospital (Madrid) and Hospital Clinic (Barcelona). We contacted all of them by phone call within one week after the end of the vaccination campaign, to confirm whether they took an antihistamine before vaccination and to evaluate any MC release symptom or adverse reaction (AR) 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 that had received the full vaccination schedule (two doses or a single dose in case of Janssen vaccine). Thus, 5 patients were excluded from the main patient cohort (n = 124) for having received a single vaccine dose (except those who received Janssen vaccine), due to considering them immunologically protected because they had passed COVID-19 infection in the previous six months. Following the recommendation of ECNM/REMA, patients took an antihistamine 1 hour before the 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 1 and Table E1 (Online Repository).

One hundred nineteen patients were included. Forty-nine (41.2%) had atopy background and twenty-seven (22.7%) had history of anaphylaxis (see Table 1 and E1, Online Repository). Four patients (3.5%) had suffered COVID-19 infection more than 6 months prior to receiving the corresponding COVID-19 vaccine, so they received full vaccination schedule. One hundred one patients (84.9%) took an antihistamine as premedication between 30 minutes and 1 hour before the administration of each dose of vaccine. One hundred one (84.9%) were vaccinated in a hospital setting and the remaining 18 (15.1%), in their health care center (n = 9) or in one of the national facilities centers authorized for the safe administration of COVID-19 vaccine (n = 9).

None of the recruited patients had any significant MC-release symptom nor any exacerbation of their clonal MCD after the administration of the vaccine. AR, as defined by the WHO,⁸ was observed in 26 patients (21%). Only one (0.8%) reacted to both doses, presenting fever in both of them. The remaining 25 presented a reaction only after one dose (9 after the first one and 16 after the second one). Among the 16 patients with local reaction (LR), 11 (69%) had received Spikevax® (Moderna) and all but one were premedicated (see Table 1 and Table E1). All the ARs occurred within the first 48 hours, but none in the first hour after the administration of the vaccine. We observed a comparable rate of AR to COVID-19 vaccine in our patients compared to the data provided by the Spanish Agency for Drugs and Health Products (AEMPS) for general population, where local reactions were observed in 5-18% of patients and fever in 35-51%, with a variable frequency depending on the type of vaccine.⁹

126 All the patients who presented an AR but four had been medicated prior to the
127 administration of the vaccine. Twenty-one out of 26 patients (81%) were vaccinated in a
128 hospital center, four (15%) in one of the national facilities centers authorized for the safe
129 administration of COVID-19 vaccine and one (4%) in his health care center.

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

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Table 1. Demographic characteristics of the patients, type of clonal MC disease, vaccines administered and the reactions presented after its administration.

Variables	Total number of patients (n=119)	Patients with AR after vaccine (n=26)
Gender		
Female	66 (55.5)	15 (57.7)
Male	53 (44.5)	6 (23.1)
Age		
Mean (range)	54.7 (20-86)	50.8 (30-73)
Allergy background[†]		
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		
MMAS	2 (1.7)	0 (0)
BMM	35 (29.4)	0 (0)
ISM	79 (66.4)	25 (96.2)
SSM	1 (0.8)	0 (0)
SM-AHNMD [*]	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 + Fever	NA	1 (0.8)
Local Reaction + Fever + Lymphadenopathy	NA	1 (0.8)

Results expressed as number of patients/total patients studied (percentage).

AR, adverse reaction; BMM, Bone marrow mastocytosis; ISM, Indolent systemic mastocytosis; MMAS, Monoclonal mast cell activation syndrome; NA; not applicable, SM-AHNMD, Systemic mastocytosis with Associated Clonal Hematological Non-Mast Cell Lineage Disease; SSM, Smoldering systemic mastocytosis.

† Patients may have more than one allergic pathology and they may be placed in more than one of the following disease groups.

†† Causes of anaphylaxis: drug allergy (10), food allergy (7), hymenoptera venom allergy (9), idiopathic (1). More details in Table E1.

††† Causes of anaphylaxis in the population with adverse reaction to vaccine: Food allergy (2), hymenoptera venom allergy (2). More details in Table E1.

*One of them presented an acute myeloid leukaemia and the other one a MALT-type lymphoma.

**We considered an adverse reaction, as defined by the WHO “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”.¹⁰ All ARs reported in our series appeared within 48 hours after the 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 the injection.