ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

COVID-19 vaccination safety in patients with hymenoptera venom allergy referred by primary health care

Segurança da vacinação contra a COVID-19 em doentes referenciados dos cuidados de saúde primários por alergia ao veneno de himenópteros

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ABSTRACT

Introduction: Despite numerous reports of hypersensitivity reactions to COVID-19 vaccination, anaphylaxis is rare. Although hypersensitivity reactions to hymenoptera venom are the third most common cause of anaphylaxis in Portugal, they don't appear to enhance the risk of anaphylactic reaction to COVID-19 vaccination. **Objectives:** To assess the safety of COVID-19 vaccination in patients with a history of hymenoptera venom allergy. **Methods:** This retrospective observational study included patients with hymenoptera venom allergy referred by primary health care to the Immunoallergology Outpatient Clinic of a tertiary hospital between January and December 2021 to stratify the risk of hypersensitivity reactions to the SARS-CoV-2 vaccine. **Results:** A total of 18 patients were included: 72% women; mean age 61 (SD, 18 [range 21-89]) years. One-third of all reported reactions to hymenoptera venom were large and local. Topical systemic symptoms of anaphylaxis were mucocutaneous (33%), respiratory (28%), cardiovascular (33%) and gastrointestinal (11%). The honeybee was the most frequently involved hymenoptera species (61%). The basal tryptase levels of 3 patients were above the established cut-off (11.4 ng/mL) and they were formally indicated for vaccination in a hospital setting. Concerning the vaccination process, 46 doses were administered to the 18 patients and no reactions were recorded. Only 5 patients were vaccinated in a hospital environment; the rest were referred to primary health care centers. Patients with confirmed or suspected mastocytosis were premedicated with anti-H1 and anti-H2 antihistamines, as well as montelukast, the day before and on the day of vaccination. **Conclusions:** COVID-19 vaccination is safe for patients with hypersensitivity to hymenoptera venom. The risk assessment protocol effectively designated patients to primary or secondary/tertiary health care.

Keywords: Allergy, anaphylaxis, COVID-19 vaccination, hypersensitivity to hymenoptera venom, tryptase.

RESUMO

Introdução: As reações de hipersensibilidade após vacinação contra a COVID-19 têm vindo a ser descritas, embora a anafilaxia seja rara. A hipersensibilidade ao veneno de himenópteros constitui a terceira causa mais frequente de anafilaxia em Portugal, embora não pareça aumentar o risco de anafilaxia à vacinação contra a COVID-19. **Objetivos:** Avaliar a segurança da vacinação contra a COVID-19 em doentes com história de alergia ao veneno de himenópteros referenciados dos Cuidados de Saúde Primários (CSP). **Métodos:** Estudo observacional retrospectivo com inclusão dos doentes com alergia ao veneno de himenópteros referenciados pelos CSP ao serviço de Imunoalergologia, para estratificação do risco de reações de hipersensibilidade à vacina contra o SARS-CoV-2, entre janeiro e dezembro de 2021. **Resultados:** No total, incluíram-se 18 doentes, 72% do sexo feminino, média de idades de 61±18 [21-89] anos. Na caracterização do tipo da reação ao veneno de himenópteros, as reações locais exuberantes corresponderam a 33% de todas as reações referidas. Quanto a sintomas sistêmicos de anafilaxia, foram referidos sintomas mucocutâneos (33%), respiratórios (28%), cardiovasculares (33%) e gastrointestinais (11%). A abelha foi o inseto mais frequentemente implicado (61%). Relativamente aos valores de triptase basal, 3 doentes apresentaram níveis acima do *cut-off* estabelecido de 11,4 ng/mL, tendo indicação formal para iniciar esquema de vacinação em meio hospitalar. Durante o processo vacinal registrou-se um total de 46 administrações em 18 doentes, todas sem intercorrências. Apenas 5 doentes foram vacinados em meio hospitalar, tendo sido os restantes encaminhados para os CSP. Os doentes com mastocitose confirmada ou suspeita foram submetidos à pré-medicação com anti-histamínico anti-H1 e anti-H2, bem como montelucaste, na véspera e no dia da vacinação. **Conclusões:** A vacinação contra a COVID-19 é segura em doentes com reação de hipersensibilidade ao veneno de himenópteros. O protocolo utilizado mostrou ser eficaz na segregação de doentes entre CSP e cuidados secundários/terciários.

Descritores: Alergia, anafilaxia, hipersensibilidade ao veneno de himenópteros, triptase, vacinação COVID-19.

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Introduction

Vaccination is a key type of primary prevention in medicine, being considered one of the most successful public health strategies.[1] Since the beginning of the SARS-CoV-2 pandemic, the scientific community has joined efforts to effectively reduce the morbidity and mortality associated with this infection, creating new types of treatments in record time. However, the most promising results have been obtained with vaccine development.[2]

Given the speed with which vaccines were produced and approved, questions were raised not only about their efficacy but also about their safety.[3] However, there was a consensus among international organizations regarding the approval of several types of vaccines against COVID-19. Currently, 5 vaccines are approved by the European Medicines Agency (EMA) for use in Europe, as well as by the National Institute of Pharmacy and Medicines (INFARMED) in Portugal: viral vector vaccines Vaxzevria® (AstraZeneca) and Janssen® (Johnson&Johnson), mRNA vaccines Comirnaty® (Pfizer-BioNTech) and Spikevax® (Moderna), and the SARS-CoV-2 recombinant spike protein nanoparticle vaccine Nuvaxovid® (Novavax).[4,5]

In the phase 3 trials of these vaccines, there was no report of any case of anaphylaxis, but participants with a history of allergic reaction to any excipient of the vaccine in question were previously excluded, which raised some concerns about their safety in patients with known allergies.[6,7] Since then, multiple studies have been published pointing to the safety of COVID-19 vaccines, with an incidence of anaphylaxis of approximately 7.91-10.67 cases per million doses.[8,9] This incidence is higher than that reported for some commonly administered vaccines, such as influenza (0.8 per million doses) (1), but lower than that reported for some National Immunization Program vaccines, such as the human papilloma virus vaccine (13.65 per million doses) or the measles, mumps, and rubella vaccine (19.8 per million doses).[9] This fact does not exclude the need for health professionals to be aware of possible allergic reactions associated with vaccination, as well as their correct reporting, namely anaphylaxis.[1]

Referral criteria for hospital-based vaccination have changed with the increase in medical knowledge and publication of studies in the field. All protocols are flexible and require individual consideration. Regulations have been developed, according to which patients with mastocytosis should be referred to in-hospital vaccination.[10-13]

According to recent studies conducted by Gaspar et al, in the last decade, insect-sting anaphylaxis was the third most common cause of anaphylaxis in Portugal, accounting for 7.4% of all cases, after food-induced (48.2%) and drug-induced anaphylaxis (36.9%).[14,15] The diagnosis of mastocytosis in patients with Hymenoptera venom allergy is a risk factor for episodes of anaphylaxis.[16] In this context, baseline serum tryptase measurement in patients with Hymenoptera venom anaphylaxis plays a decisive role in choosing the referral site for SARS-CoV-2 vaccination, despite the fact that its ordering is not reimbursed by the National Health Service when it is prescribed in the primary care setting. However, several studies have already demonstrated that these patients can be safely vaccinated in a non-hospital setting, under a premedication protocol and 30-minute medical surveillance after vaccination.[6,17,18]

The current study aimed to evaluate the safety of COVID-19 vaccines in patients referred from primary care with Hymenoptera venom allergy, analyzing the importance of baseline serum tryptase measurement in the risk stratification of these patients.

Methods

Study Design , population, and data collection

We conducted a retrospective observational study of patients referred from primary care to the immunoallergology clinic for risk assessment of severe allergic reactions to SARS-CoV-2 vaccines due to a history of Hymenoptera sting reactions, between January and December 2021.

The patients were evaluated remotely by telephone calls and/or in a face-to-face consultation when it was not possible for the physician to have a correct perception of the patient's medical history without a physical examination.

The definition of anaphylaxis was based on the European Academy of Allergy and Clinical Immunology (EAACI) criteria,[19] which define anaphylaxis as a severe, potentially life-threatening systemic hypersensitivity reaction characterized by a rapid onset that may include mucocutaneous, respiratory, cardiovascular, or gastrointestinal manifestations.

Systemic hypersensitivity reactions were categorized according to the Mueller classification.[20] This classification divides reactions into 4 grades

according to their severity. Grade I systemic reaction is characterized by itching, urticaria, anxiety, and/or malaise. Grade II reaction includes any of the grade I symptoms plus 2 or more of the following: dizziness, nausea and vomiting, diarrhea, abdominal pain, angioedema, and/or a feeling of tightness in the chest. Grade III reaction includes grade I or II symptoms plus at least 2 of the following: dyspnea, dysarthria, wheezing, stridor, hoarseness, prostration, confusion, and/or a feeling of impending doom. Finally, grade IV reaction includes grade I, II, or III symptoms plus at least 2 of the following: loss of consciousness, urinary and fecal incontinence, and/or cyanosis.[19]

Data were collected from the patients' hospital medical records and the Health Data Platform in order to include relevant information about the primary care setting, as well as post-vaccination outcomes of patients referred to a non-hospital setting after risk vaccination.

Risk stratification protocol for hypersensitivity reactions

Risk stratification of severe hypersensitivity reaction to COVID-19 vaccines was performed in accordance with the protocol of the Immunoallergology Department, based on the regulations of the Directorate-General for Health and national and international guidelines.[16-18,20-24] This protocol is summarized in Table 1.

Baseline tryptase measurement was required at the first COVID-19 screening appointment for all patients referred for suspected Hymenoptera venom anaphylaxis and whose baseline tryptase level was unknown. Patients with levels lower than 11.4 ng/mL were considered at low risk and referred to out-of-hospital vaccination, whereas patients with tryptase levels greater than or equal to 11.4 ng/mL were referred to in-hospital vaccination, with further investigation to exclude mastocytosis or mast cell activation syndrome. These patients were premedicated with H1 and H2 antihistamines 1 hour before vaccination, as well as with montelukast 24 hours and 1 hour before vaccination.[6]

Results

In 2021, 19 patients with suspected Hymenoptera venom allergy were referred from primary care to the immunoallergology clinic for risk stratification of severe hypersensitivity reaction to COVID-19 vaccines, 1 of whom was excluded due to vaccine refusal. Table 2 shows the demographic and clinical characteristics of the study population. A total of 18 patients were included in the study, and the majority was female (72%). The mean age was 61 (SD, 18) years, with a minimum age of 21 years and a maximum age of 89 years.

Regarding concomitant immunoallergic pathologies, the most prevalent was allergic rhinitis, with 33% of patients reporting this diagnosis. Other reported pathologies were asthma (n = 2, 11%), mastocytosis (n = 1, 6%), and chronic urticaria (n = 2, 11%). Non-allergic pathologies, such as hypertension, heart failure, dyslipidemia, and chronic obstructive pulmonary disease, were reported by 22% of patients.

In the characterization of the reaction to Hymenoptera venom, 6 patients reported only exuberant local reaction. According to the Mueller classification, the most frequent systemic reaction was grade III, occurring in 5 patients (Table 2). Regarding the remaining systemic reactions, there was 1 grade I reaction, 2 grade II reactions, and 4 grade IV reactions. Honeybee was the species of Hymenoptera most commonly involved (61%), but there were also reports of several cases related to wasps (28%). The causative agent of the reaction could not be determined in the remaining cases (n=2, 11%).

Of the 18 patients with a history suggestive of hypersensitivity to Hymenoptera venom, 3 (17%) had baseline tryptase levels above 11.4 ng/mL and were referred to in-hospital vaccination. These 3 patients had a history of anaphylaxis, representing 25% of anaphylactic reactions to Hymenoptera venom. All patients were also asked about possible previous severe hypersensitivity reactions, with 33% reporting a history of drug-induced anaphylaxis, with nonsteroidal anti-inflammatory drugs corresponding to half of the cases and intravenous contrast to 6%. Food-induced (11%) and idiopathic anaphylaxis (11%) were also reported.

Of the patients with Hymenoptera venom anaphylaxis, 3 had already completed 5 years of bee venom immunotherapy, showing no further anaphylactic reactions to stings after completion of vaccination. The remaining patients were referred to specialist consultations for Hymenoptera venom allergy, but only 2 remained in follow-up and agreed to start immunotherapy.

After risk assessment and stratification of all patients in the immunoallergology clinic, 5 patients

(28%) were vaccinated in a hospital setting, 3 due to elevated baseline tryptase levels (one of them with a confirmed diagnosis of mastocytosis) and 2 due to other risk factors (idiopathic anaphylaxis in one patient, and a history of multiple drug allergies in the other), all of them under the premedication protocol. The remaining patients were referred to health centers or corresponding immunization centers for vaccination.

Overall, 11 vaccines were administered in a hospital setting and 35 in a non-hospital setting, as shown in Table 3. No complications were reported in any of the cases. Given the absence of hypersensitivity reactions, 3 of the patients who initially received the Comirnaty® vaccine in the hospital setting were able to proceed with their vaccine schedule at the immunization center on medical advice. This decision to proceed with out-of-hospital vaccination was based

Table 1
Risk stratification protocol for severe reaction to define the place for administration of the COVID-19 vaccine[16-19,21-23]

Risk of severe hypersensitivity reaction to the vaccine	Place for vaccination	Clinical diagnosis
Low risk	Vaccination at the Immunization Center	– Allergic rhinitis – Controlled asthma – Atopic dermatitis – Controlled chronic urticaria – Hereditary angioedema – Latex allergy/anaphylaxis – Hymenoptera venom allergy/anaphylaxis with normal tryptase levels – Food allergy/anaphylaxis
Intermediate-high risk	Hospital-based vaccination	– Anaphylaxis after vaccination – Anaphylaxis to multiple classes of drugs (> 2 drug classes), with tolerance of drugs containing polyethylene glycol – Anaphylaxis of unknown etiology – Hymenoptera venom allergy with elevated tryptase levels – Mastocytosis and/or mast cell activation syndromes
High risk	Investigation by immunoallergology	– History of severe hypersensitivity reaction to any of the components of COVID-19 vaccines – Prior hypersensitivity reaction to a COVID-19 vaccine

on the successful administration of the first dose in the hospital setting and on the growing evidence of the safety of COVID-19 vaccines in patients with mastocytosis.[6] All patients vaccinated in a hospital setting received premedication. No adverse allergic reactions were reported in patients vaccinated in the hospital setting, nor in those vaccinated in the primary care setting.

Discussion

The current retrospective observational study demonstrated the safety of SARS-CoV-2 vaccines in patients referred from primary care with a history of Hymenoptera venom allergy, including patients with elevated baseline serum tryptase levels.

One patient was excluded from our initial population due to vaccine refusal, for a total of 18 patients aged

Table 2
Population characteristics – demographic and clinical data related to Hymenoptera sting reaction

Total (nº)	**18**
Age years (mean±SD [min-max])	61±18 [21-89]
Sex (n (%))	
Female	13 (72)
Type of reaction (n (%))	
Exuberant local reaction	6 (33.3)
Systemic reaction (Mueller classification) (20)	
Grade I	1 (5.6)
Grade II	2 (11.1)
Grade III	5 (27.8)
Grade IV	4 (22.2)
Species of Hymenoptera involved (n (%))	
Bee	11 (61.1)
Wasp	5 (27.8)
Unknown	2 (11.1)
Tryptase level (ng/mL)	
Number of patients ≥ 11.4	3 (16.7)
Number of patients < 11.4	7 (38.9)
Number of patients undetermined	8 (44.4)
Mean (±SD)	10.8±8.7
Systemic mastocytosis (n (%))	
Confirmed	1 (5.6)
Under investigation	2 (11.1)
Excluded	15 (83.3)

SD = standard deviation.

21 to 89 years being vaccinated. A total of 35 vaccines were administered in a non-hospital setting, in 16 patients, and 11 vaccines in a hospital setting, in 5 patients, without complications. In addition, no complications were reported in the 3 patients who were initially vaccinated in a hospital setting and then proceeded with their vaccine schedule in a non-hospital setting. This fact demonstrates the effectiveness of the applied risk stratification protocol, as well as of the premedication regimen.

In patients with suspected or confirmed mastocytosis, the first dose was always administered in a hospital setting. However, the EAACI has recently released a position paper stating that there is no evidence for an increased risk of hypersensitivity reactions in the subgroup of patients with Hymenoptera venom allergy or in the subgroup of stable patients with mastocytosis.[25] In both cases, there is an indication for out-of-hospital vaccination under supervision for 30 minutes after vaccination,

Table 3
Characterization of the vaccination schedule of the study patients

Patient	In-hospital vaccination			Out-of-hospital vaccination		
	1st dose	2nd dose	3rd dose	1st dose	2nd dose	3rd dose
A	–	–	–	VAX	VAX	COM
B[a]	COM	COM	–	–	–	COM
C	COM	COM	–	–	–	COM
D[a]	COM	COM	COM	–	–	–
E	–	–	–	COM	COM	COM
F	–	–	–	SPI	SPI	–
G	–	–	–	COM	COM	–
H	–	–	–	COM	COM	COM
I	COM	–	–	–	COM	–
J	–	–	–	VAX	VAX	COM
K	–	–	–	COM	COM	–
L[a]	COM	COM	COM	–	–	–
M	–	–	–	COM	COM	–
N	–	–	–	COM	COM	COM
O	–	–	–	COM	COM	–
P	–	–	–	VAX	VAX	COM
Q	–	–	–	COM	COM	–
R	–	–	–	COM	COM	–
TOTAL	11	35				

[a] Patients with tryptase levels above the defined cut-off of 11.4 ng/mL.
COM = Comirnaty® (Pfizer vaccine), VAX = Vaxzevria® (AstraZeneca vaccine), SPI = Spikevax® (Moderna vaccine).

and patients with confirmed mastocytosis should receive a premedication regimen.

In this context, Rama et al recently published 2 articles that support the safety of COVID-19 vaccines in patients with mastocytosis, underscoring the need of a premedication regimen.[6,18] Numerous other studies have similarly demonstrated the safety of COVID-19 vaccines.[26-32]

Regarding the elevated baseline serum tryptase levels in some patients in our sample, it is important to note that these levels alone do not lead to the diagnosis of mastocytosis. Tryptase levels above 20 ng/mL, in the absence of concomitant pathologies that can explain levels of this magnitude, are only a minor criterion for the diagnosis of systemic mastocytosis.[33] Serum tryptase measurement is not a routinely ordered test in primary care and is not reimbursed by the National Health Service. Therefore, being unaware of that, many patients with a history of anaphylaxis were referred, in whom baseline serum tryptase levels had never been measured. Despite not meeting the referral criteria for hospital-based COVID-19 vaccination (Table 1),[21] the authors consider that the referral had the added value of raising awareness for this diagnosis and the importance of referring patients with Hymenoptera sting anaphylaxis to specialist immunoallergology consultation.

It is imperative to improve communication between primary care and secondary/tertiary care, as well as to work on the continuous improvement of referral criteria in this and all areas of immunoallergology, so that physicians can work in partnership with patients for the benefit of both, reducing the burden on secondary/tertiary care. We also highlight the importance of gaining knowledge of the diagnostic criteria for anaphylaxis, an often underdiagnosed and undertreated condition, which is potentially life-threatening and requires immediate treatment with intramuscular epinephrine to prevent progression to multiple organ failure.[34]

This study has some limitations, including the small sample size (n = 18), which limits the extrapolation of results, requiring further studies with larger sample sizes to obtain statistically relevant data. Another limitation is the retrospective design, given the possible absence of some information in the medical records. However, this limitation is considered of little relevance, since it was possible to obtain virtually all the data required for the study. In addition, the fact that the diagnosis of Hymenoptera venom allergy was considered only presumptive, based on a suggestive medical history, when deciding on the risk stratification. No skin tests or specific IgE assays for the suspected Hymenoptera venom were performed in the initial screening phase given the urgency of deciding on the place for vaccination. Nevertheless, the authors consider that the current study provides important information about the safety of COVID-19 vaccines in patients with Hymenoptera venom allergy.

Conclusions

COVID-19 vaccination is safe in patients with a history of severe hypersensitivity reaction to Hymenoptera venom and can be conducted in the primary care setting, with rare exceptions. The risk stratification protocol for severe hypersensitivity reactions applied in this study demonstrated to be effective in identifying patients to be vaccinated in a hospital setting. We highlight the importance of continuous improvement of referral criteria and protocols, as well as of communication between primary care and secondary/tertiary care.

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