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Daniela Brandão Abreu, Mariana Bragança, José Luís Plácido, Alice Coimbra

The impact of the COVID-19 pandemic in Hymenoptera venom immunotherapy: a single center experience

Department of Allergy and Clinical Immunology, Centro Hospitalar Universitário de São João, Porto, Portugal

Key words

Hymenoptera venom allergy; immunotherapy; COVID-19; pandemic; allergy.

Corresponding author
Daniela Brandão Abreu
Department of Allergy and Clinical Immunology
Centro Hospitalar Universitário de São João
Alameda Prof. Hernâni Monteiro
4200-319 Porto, Portugal
ORCID: 0000-0001-7369-3723
E-mail: danielabrandaoabreu@gmail.com

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To the Editor,

Hymenoptera stings can induce allergic systemic and potentially fatal reactions. Hymenoptera Venom Immunotherapy (VIT) is safer and effective and the only treatment that can prevent systemic sting reactions in patients with hymenoptera venom allergy (1). The Coronavirus disease 2019 (COVID-19) pandemic led to the suspension of all scheduled activities at Centro Hospitalar Universitário São João on March 12th, 2020. The contingency plan continued VIT in the maintenance phase as it is a life-saving treatment and the decision to maintain administration was made on an individual basis and each patient was informed about the risks and benefits. Although there are recommendations on how to manage immunotherapy during COVID-19 (2), it does not include a detailed approach on how to resume VIT after a long delay from the last injection, with one clinical experience of an allergology center in Italy in the literature (3).

The aim of the present study was to describe the experience of a single specialized allergy and clinical immunology department in Portugal performing VIT during the COVID-19 pandemic. We retrospectively collected data of patients treated with VIT in the maintenance phase from January 2019 to May 2021, and analyzed demographic and clinical characteristics: age, gender, type of VIT performed; presence of concomitant asthma, allergic rhinitis, and/or systemic mastocytosis, and treatment with beta-blocker or angiotensin converting enzyme inhibitor (ACEI). The first pandemic wave in Portugal was defined as the time from March to May 2020, second pandemic wave between October and December 2020, and third pandemic wave between January and April 2021. No modification to the type of venom was made during this time and all the venom extracts used were aqueous. VIT was administered by trained personnel under medical supervision in our department and all patients were in treatment with a single dose of 100 µg (1 mL) unless otherwise stated. We have considered a VIT interruption when patients had more than 20 weeks of interval between administrations. Patients remained for at least 30 minutes following each administration. Adverse reactions were treated according to EAACI guidelines (4). The

Table I – *Demographic and clinical characteristics of patients.*

	Pooled patients n = 86	**Interval increase n = 15**	**VIT interruption* n = 4**
Male, n (%)	65 (75.6)	12 (80)	2 (50)
Age, median (min-max), years	46 (11-77)	45 (21-77)	37 (22-61)
Beehives < 3 km home/work	36 (41.9)	8 (53.3)	0
Beekeepers, n (%)	31 (36)	5 (33.3)	1 (25)
Asthma, n (%)	8 (9.3)	1 (6.7)	1 (25.0)
Allergic rhinitis, n (%)	11 (12.8)	1 (6.7)	1 (25.0)
Beta-blocker and/or ACEI, n (%)	13 (12.1)	2 (13.3)	1 (25.0)
Mastocytosis, n (%)	1 (1.2)	0	0
Types of VIT, n (%)			
Bee	50	8 (53.3)	2 (50)
Wasp	36	7 (46.7)	2 (50)

ACEI: angiotensin converting enzyme inhibitor; VIT: Venom Immunotherapy. *VIT interruption was considered when patients had more than 20 weeks of interval between administrations.

records of 86 patients were evaluated (75.6% males; median age (minimum-maximum) 46 years (11-77)) and baseline characteristics are depicted in **table I**.

Fifteen patients (17%) increased the interval between administrations. The median administration interval was nine weeks (6.7-15.1). All fifteen patients resumed treatment in an outpatient setting without a new build-up phase. In three patients the dose was reduced by half, with administration of the remainder in the following week, as at the beginning the authors have been more cautious. Given the lack of reported reactions, the remaining patients resumed treatment with a single injection. Ten cases (67%) underwent premedication with a single dose antihistamine one hour prior to VIT administration, given previous occurrence of extensive local reactions.

Four patients (5%) interrupted administration of VIT during the first pandemic wave for a median of 26.5 weeks (25.1-36.0), two under wasp VIT and two with bee VIT. None of the four patients had previous systemic reactions neither systemic mastocytosis. Although two patients restarted VIT without dose adjustment neither build-up-phase, one female patient resumed bee VIT with a three-step protocol (*i.e.*, 100 µg divided into three injections of 20 µg, 30 µg and 50 µg, with a 30-minute interval between them), in a day hospital regimen, since she had an interval of 36 weeks since the last administration; one male patient on wasp VIT had dose reduction by half, with administration of the remainder after 15 days, to prevent a possible systemic reaction. No systemic reactions neither extensive local reactions were reported in all cases. The reasons for interrupting or spacing administrations were fear of going to the hospital or prophylactic isolation at the time of the scheduled administration.

Overall, our data suggests that VIT can be safely resumed after prolonged intervals up to 36 weeks, without the need to restart. This included patients with cardiovascular comorbidities, treatment with beta-blockers and/or ACEI, with a wide range of age.

International recommendations advise an individual assessment concerning immunotherapy during COVID-19 pandemic (2, 5). A previous study reported that prolonged intervals can be safe and well tolerated, which was also verified in our population (6). However, the authors defend more caution in resuming VIT in case of long pre-pandemic maintenance intervals, previous severe reactions, recent VIT initiation, older age, multidrug treatments, and bee venom allergy. Also, there is the question of immunotherapy efficacy with prolonged delays. In our study, however, we did not assess risk factors for systemic reactions since those were not reported during the evaluation period neither in the pre-COVID time. In the previous study, even with delays up to 22 weeks, 68 of 87 patients (78%) had the usual maintenance dose administered in a single day by dividing the dose (1 to 4 injections) and only three moderate systemic reactions were observed (Müller grade I-II) (6). In our cohort, patients had delays up to 36 weeks and the usual maintenance dose was administered in a single injection in most cases, without any systemic reactions. The Stinging Insects Task Force suggests that the next booster of VIT should be postponed until cure in the event of infection or the possibility of infection with COVID-19, dividing the dose according to the delay (5). This decision should be made on an individual basis, taking into consideration comorbidities, duration of VIT and its tolerance. In our cohort, we did not have any patients with COVID-19 infection at the time of the administration. In the

case of prophylactic isolation, patients were advised to reschedule VIT administration at the end of the isolation period.

This study has some limitations. Since all the venom extracts used were aqueous, we cannot infer the outcome for other types of extracts. Moreover, our sample included only one patient with mastocytosis and whose VIT did not alter during this period, so our results must be interpreted with caution regarding this population since systemic mastocytosis is associated with an increased risk of adverse events during VIT. Finally, the retrospective analysis and our small sample are also limitations.

Currently, the decision on how to proceed in the event of prolonged intervals between VIT administrations is subjective. The data from our center suggests that VIT can be safely resumed in patients in maintenance phase with intervals up to 36 weeks, without the need for a new build-up phase. Guidelines regarding this topic are needed.

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Contributions

DBA, MB: data collection. DBA: writing - original draft, statistical analysis. All authors: writing - review & editing. JLP, AC: final review.

Conflict of interests

The authors declare that they have no conflict of interests.

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