Original paper

Vaccination against the SARS-CoV-2 virus in patients undergoing Hymenoptera venom immunotherapy

Wojciech Żurek, Magdalena Baron, Łukasz Moos, Katarzyna Kapeluszna, Liwia Starczewska-Dymek, Zenon Brzoza

Department of Internal Diseases, Allergology, Endocrinology and Gastroenterology, Institute of Medical Sciences, University of Opole, Opole, Poland

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Abstract

Introduction: The SARS-CoV-2 epidemic has unquestionably left a significant mark on the global healthcare system. Implementation of the commonly available vaccinations against COVID-19 is intended to reduce the risk of a severe course of the disease. Due to a very brief development period of the new vaccines, concerns have appeared among the public with regard to the possible adverse effects of the newly-developed preparations, as well as to the risks of causing allergic reactions. Regular medical observation during the Hymenoptera venom immunotherapy provides significant possibilities to note any potential adverse effects of vaccines against COVID-19, as well as of complications of an experienced SARS CoV-2 infection.

Aim: To assess the issues connected with vaccination against COVID-19, complications following vaccination, as well as incidence and course of the disease among patients undergoing venom immunotherapy (VIT) due to an allergy to Hymenoptera venom.

Material and methods: We investigated 37 persons aged 19 to 70 (20 women; 17 men) undergoing Hymenoptera venom immunotherapy in our department.

Results: 21.6% have experienced an infection with the SARS-CoV-2 virus, confirmed by a diagnostic test. No person participating in the study had experienced a severe infection which would require hospitalization. Elderly people have been vaccinated statistically significantly more often than young people.

Conclusions: The risk related to vaccination in this group of patients does not seem to be higher than in the general population.

Key words: COVID-19, Hymenoptera immunotherapy, vaccination.

Introduction

The SARS-CoV-2 epidemic has unquestionably left a significant mark on the global healthcare system. The discovery of the structure of the virus, as well as of the mechanism of its penetration into different cells of human body, has enabled introduction of new vaccines against COVID-19.

Implementation of the commonly available vaccinations against COVID-19 is intended to contain the viral transmission, to reduce the of risk a severe course of the disease, including death prevention. The 3-year struggle against the epidemic, in spite of a 2-year free vaccination scheme, have proven that humankind will most probably continue to face the SARS-CoV-2 virus for many years to come.

Currently, two mRNA-based vaccines (Comirnaty by Pfizer-BioNTech; Spikevax by Moderna), two vector vaccines (Vaxzevria by Astra Zeneca; Jcovden by Janssen), and a recombinant adjuvanted vaccine (Nuvaxovid by Novavax) have been authorized for use in Poland.

Due to a very brief development period of the new vaccines, concerns have appeared among the public with regard to the possible adverse effects of the newly-developed preparations, as well as to the risks of causing allergic reactions (including the most severe allergic reaction, i.e. anaphylaxis). Potential factors giving rise to concerns among mRNA-based preparations included polyethylene glycol (PEG 2000), its derivatives (e.g., thromethamine in the Moderna preparation), as well as Polysorbate 80 contained in vaccines based on the viral vector mechanism.

To mitigate the concerns of the society, and thus to encourage vaccination, an official position on vaccination has been published, developed by the European Academy of Allergy and Clinical Immunology, concerning the general recommendations intended to increase the safety of vaccination, contraindications to vaccina-

Address for correspondence: Dr Wojciech Żurek, Department of Internal Diseases, Allergology, Endocrinology and Gastroenterology, Institute of Medical Sciences, University of Opole, 15/6 Ligonia St, 45-362 Opole, Poland, phone: +48 696463456, e-mail: 00wojtekzurek00@gmail.com
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tion against COVID-19, as well as the procedure in case of occurrence of anaphylaxis upon administration of the preparation [1].

The Polish Society of Allergology has also issued guidelines concerning the general recommendations during vaccination [2]. It should be stressed that asthma, atopic dermatitis, food allergy, allergic rhinitis, allergy to insect venom, allergic contact dermatitis, urticaria, cutaneous adverse drug reactions are not contraindications to vaccination against COVID-19. Neither is occurrence of prior episodes of IgE-dependent anaphylaxis to foods and insect venoms.

On the other hand, the documents mentioned above point out that patients with a history of idiopathic anaphylaxis, anaphylaxis upon medicines which could contain macrogols (oral antibiotics, laxatives, painkillers, certain oncology drugs, glucocorticosteroids for parenteral use), as well as with allergy to cosmetics and chemicals containing PEG, are characterized by an increased risk of anaphylaxis upon COVID-19 vaccination. Such patients should not be vaccinated with these vaccines. The role of the proper procedure at vaccination points in case of occurrence of anaphylaxis (adrenaline administration, application of fluid therapy, as well as collection of a blood sample up to 30 min since the onset of symptoms in order to determine the tryptase level) has been emphasized as well.

The Ministry of Health of Poland has issued national guidelines and prepared a survey facilitating qualification of patients for vaccination against COVID-19. Factors requiring medical assessment included a history of severe allergic reaction to food, insect sting or medicine [3].

Patients with an IgE-dependent allergy to Hymenoptera venom, who have experienced a life-threatening anaphylactic reaction, are a peculiar group. The necessity to conduct long-term subcutaneous immunotherapy and the related effect on the immunologic system require more cautious observation of this group of patients. Regular medical observation during the immunotherapy provides significant possibilities to note any potential adverse effects of vaccines against COVID-19, as well as of complications of an experienced SARS-CoV-2 infection.

Another interesting issue is the possibility to compare the occurrence of anaphylaxis upon administration of a vaccine against COVID-19 in patients who have already experienced a generalized allergic reaction. This group of patients provides an intriguing possibility of observation whether immunotherapy conducted during the epidemic could have affected the incidence and severity of COVID-19 in this group.

Additionally, an analysis of the socio-economic diversity, level of education, or place of residence may turn out interesting data regarding the effect of such factors on the immunization rate of patients.

Aim

The goal of our study was to assess the issues connected with vaccination against COVID-19, complications following vaccination, as well as incidence and course of the disease among patients undergoing venom immunotherapy (VIT) due to an allergy to Hymenoptera venom.

Material and methods

The study was conducted at the Department of Internal Medicine, Allergology, Endocrinology, and Gastroenterology of the University Hospital in Opole in 2021–2022. The research included patients undergoing VIT due to their allergy to Hymenoptera venom, upon experiencing an anaphylaxis of grade 3 or 4 according to the Mueller's scale [4]. The questionnaire method was used; a survey was prepared, including questions concerning the issues discussed in the introduction. The analysis took into account the insect type causing the anaphylaxis (wasp/bee); education (vocational and primary/secondary and higher); place of residence (rural/urban); age, sex, body mass (in kg) of patients; the length of insect venom immunotherapy in years.

Statistical analysis

The statistical analyses were conducted using the Statistica 13.3 software (STATSOFT INC., USA). The *U* Mann-Whitney and Spearman tests were utilized. The values of $p < 0.05$ were considered statistically significant.

Results

The study included 37 persons aged 19 to 70 (20 women; 17 men); among them, 81.1% were allergic to wasp venom and 13.5% were allergic to bee venom, whereas the remaining persons were allergic to venoms of both insects.

Among the surveyed, 21.6% have experienced an infection with the SARS-CoV2 virus, confirmed by a diagnostic test. The most frequent symptoms occurring during the infection, as reported by the surveyed, included muscle and joint pain, headache, as well as loss of smell and taste (Table 1). One of the surveyed persons had experienced an asymptomatic infection. It is worth stressing that no person participating in the study had experienced a severe infection which would require hospitalization.

In the surveyed group, 64.9% were vaccinated against the SARS-CoV-2 virus (Pfizer vaccine – 75%, other vaccines – 8.33% each). Elderly people with a history of anaphylaxis following a Hymenoptera sting have been vaccinated statistically significantly more often than young people with the same disease ($p < 0.001$). Statistically significant differences in the immunization rate between

persons allergic to wasp venom and those allergic to bee venom have not been observed in the group of respondents (p = 0.34). The severity of the experienced anaphylactic reaction did not affect the immunization rate either (p = 0.49). Similarly, such criteria as sex (p = 0.81), place of residence (p = 0.45), education level (p = 0.92), or the length of the VIT (p = 0.49) had no effect on making a decision on vaccination.

The reasons for non-vaccination may be divided into two groups. The first group of answers is related to a concomitant allergy, of which the most frequent are fear of a possible allergic reaction following vaccination, a concomitant allergy to Hymenoptera venom, and a history of a severe anaphylactic reaction. The second group of reasons for non-vaccination against COVID-19 is not directly related to any concomitant allergy – in this case, the most frequently selected answers include fear of possible late vaccination complications, lack of confidence in the available vaccines, and lack of sufficient information on the safety of vaccines (Table 2).

However, it should be stressed that, in spite of the mentioned concerns, every third unvaccinated person expresses a wish to be vaccinated in the future.

The most frequent adverse effect in the surveyed group, both after the first dose and after the second dose, was pain at the injection site (Table 3). It is worth stressing that 41.7% of the surveyed had no adverse effects following the second vaccination dose.

Discussion

The main objective of our study was to assess the effect of individual factors on the rate of vaccination against SARS-CoV-2 virus in the group of persons allergic to Hymenoptera venom. Regardless of great concerns raised by vaccinations, in our group as much as 64.9% of patients with a history of severe sting anaphylaxis have been vaccinated against the SARS-CoV-2 virus, whereas the Polish population as at 10 August 2022 had an immunization rate of 59.3% [3].

In the general population, elderly people who are at a greater risk of a more severe course of the COVID-19 in-

Table 1. Symptoms during a COVID-19 infection in patients allergic to Hymenoptera venom, undergoing insect venom immunotherapy

Symptom	Occurrence rate
Muscle and joint pain	75%
Headache	50%
Loss of smell and taste	50%
Fever	25%
Cough	25%
Sore throat	12.5%
Runny nose	12.5%
Dyspnoea	12.5%

Table 2. Causes of non-vaccination against COVID-19 in patients allergic to Hymenoptera venom, undergoing insect venom immunotherapy

Causes of non-vaccination	Occurrence rate
Fear of a potential anaphylactic reaction	50%
Allergy to Hymenoptera venom	50%
Experienced severe anaphylactic reaction	33.3%
Fear of potential late vaccination complications	66.6%
Lack of confidence in the available vaccines	33.3%
Insufficient information concerning the safety of the vaccines	33.3%
Planned pregnancy	16.6%

Table 3. Adverse effects following administration of the first and second dose of a vaccine against COVID-19 in patients allergic to Hymenoptera venom, undergoing insect venom immunotherapy

Adverse effects	After the 1st dose	After the 2nd dose
Headache	0%	12.5%
Pain at the injection site	58.33%	41.7%
Swelling at the injection site	12.50%	0%
Fever	12.50%	0%
Tremor	8.33%	0%
Malaise	12.50%	8.33%
Fatigue	25%	16.7%
Muscle and joint pain	20.83%	12.5%
No symptoms	20%	41.7%

fection, become vaccinated more frequently than young people [3]. A similar relation has been observed in the group of our patients.

In the following part of our survey, we have assessed the occurrence rate of adverse effects following immunization and the intensity thereof, both following the first and the possible second dose. The data concerning the high level of safety of vaccines are confirmed by other studies. Shimabukuro *et al*. presented a preliminary analysis of the VAERS data concerning anaphylaxis related to a mRNA COVID-19 vaccine [5]. The study was based on nationwide VAERS data of 18 January 2021 and demonstrated anaphylaxis rates of 4.7 and 2.5 cases per million administered doses of the Pfizer-BioNTech and Moderna vaccine, respectively [5]. An equally low anaphylaxis risk was connected with intake of viral vector vaccine preparations. In France, the anaphylaxis rate was 0.0005% per administered doses (upon analysis of 13,610,000 administrations), whereas in the UK, it was 789 reported cases per 101.1 million administered doses (amounting to 0.77 per 100,000 doses) [6, 7]. Furthermore, a low risk of occurrence of severe allergic reactions is confirmed by the research conducted by Anis *et al.,* summarizing the reported allergic reactions during vaccination with the Pfizer-BioNTech vaccine. The study shows that, out of 14,475,979 administered injections, reactions which would require administration of adrenaline occurred only 37 times, with confirmation of an immediate allergic reaction being obtained in 34 cases, which gives 2.5–3.3 cases of severe anaphylaxis per million inhabitants [8].

Nittner-Marszalska *et al.* [9] also evaluated the tolerance of a vaccine against COVID-19 (Pfizer-BioNTech) in persons with broadly understood allergies, as well as in persons with no history of allergy. Based on the obtained results, they concluded that the vaccine is well-tolerated by both allergic and non-allergic persons. In our group of patients with a history of a severe generalized allergic reaction (Grade 3 and 4 according to the Mueller's scale), we have noticed no severe adverse effects following immunization either. The main symptoms following vaccination included local reactions, such as pain at the injection site.

An interesting analysis of the 14,611 reported allergic reactions following vaccination against COVID-19 has been presented by Bian *et al.* [10]. Most cases of allergic reactions occurred in women (84.6%) following the administration of the first vaccine dose (63.6%). Similarly, in our study, more than 40% of the surveyed have observed no adverse effects following the second dose.

Furthermore, we wished to know reasons why some persons allergic to Hymenoptera venom have not been vaccinated against COVID-19, in spite of the clear position of scientific authorities concerning vaccination in this group of patients. It turns out that the fear of potential late vaccination complications is the most frequently stated reason; however, a concomitant allergy and fear of an anaphylactic reaction in view of having experienced one it in the past are significant as well.

Despite high exposure to contact with the SARS-CoV-2 virus, connected with regular visits to the hospital due to the immunotherapy, we have found the incidence rate of COVID-19 among the patients (infection confirmed by a test) amounting to 21.6% of the surveyed. It is difficult to relate this percentage unambiguously to the official statistics concerning SARS-CoV-2 infections in Poland. Lorent *et al.* [11], by monitoring the presence of the coronavirus in the Poznań sewer system, have proven that the incidence numbers announced by the Ministry of Health could have been underestimated more than four times. Incidences confirmed by a test detecting SARS-CoV-2 infection may be underestimated in the general population due to the fact that a part of the infected population do not report to healthcare units, and thus are not included in the register of incidences. In the population undergoing Hymenoptera venom immunotherapy, remaining under constant medical supervision, unreported infections are likely to occur less frequently; however, this surely requires further close scrutiny. Considering the aspects above and referencing the official statistics of incidence for the Polish population, amounting to 16.3% of the population of Poland as at 23 October 2022, we cannot exclude that the infection rate among the patients surveyed by us could have even been lower than the actual rate for the population of Poland.

Conclusions

Persons who have experienced an anaphylactic reaction following Hymenoptera sting should not be afraid of vaccination against COVID-19. The risk related to vaccination in this group of patients does not seem to be higher than in the general population.

Inclusion of a question concerning reactions after insect stings into vaccination qualification questionnaires is unnecessary, causing a delay in the vaccination or non-vaccination decision in some patients.

In this group of patients, a significant cause of non-vaccination is the fear against repeated anaphylaxis, hence it is necessary to conduct an awareness campaign concerning the safety of vaccinations, especially among such patients. In the face of concerns to vaccination against COVID-19 of patients with anaphylaxis to Hymenoptera venom (yes or no hyposensitized) it is advisable to consult an allergist.

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None.

Conflict of interest

The authors declare no conflict of interest.

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