Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Second-dose COVID-19 vaccines are well tolerated in patients with allergic reactions to the first dose – a single center experience

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ABSTRACT

COVID-19 vaccines contain additives such as Polyethylenglycol-2000 (PEG2000; mRNA vaccines) or Polysorbat 80 (vector vaccines), which have been described previously as culprits for anaphylactic events.

This retrospective study included 46 individuals, who were referred to Comprehensive Allergy Center at the Department Dermatology and Venereology, Kepler University Hospital, Linz, Austria, with suspected allergic reactions to the first COVID-19 vaccine dose with either mRNA or vector-based vaccines.

Patients underwent detailed anamnesis, clinical examination, and in most cases, skin prick testing using pure additive substances (PEG – different molecular weights, Polysorbate 80).

Out of 46, 7 patients' reactions were classified as possibly anaphylactic and graded according to Ring & Messmer. Forty patients out of 46 were assessed with skin prick tests for potential allergens in COVID-19 vaccines. Only 1 patient showed an immediate positive prick test to PEG2000. Second-dose vaccination with mRNA or vector-based vaccines were tolerated well in all patients, including the individual with a positive skin prick test against PEG2000.

The currently available COVID-19 vaccines have an overall low allergic potential and may be administered safely in patients with suspected allergic reactions to the first dose.

Keywords: COVID-19, Allergy, Anaphylaxis, Vaccination

In general vaccines rarely trigger severe anaphylactic reactions, with an estimation of 1 in 1.3 million people. Initial reports of severe anaphylactic reactions to COVID-19 vaccines in the public press led to insecurities and perceived elevated anaphylactic risk of these new vaccines. Polyethyleneglycol (PEG)-2000 contained in mRNA vaccines (BioNTech/Pfizer, Moderna) is suspected to be culprit for such possible allergic reactions.[1] PEGs are polymers with varying molecular sizes (up to 5000g/mol) contained in various drugs or external formulations to stabilize lipid nanoparticles. A sparse number of type-I IgE mediated allergies against PEG have been reported, mostly after administration of large quantities of PEG (contained in e.g., laxatives or certain intravenous administered drugs).[2] Vector-based vaccines (AstraZeneca, Janssen) are lacking PEG2000 but contain Polysorbat-80 which has been also described previously as a potential allergen in rare cases.[3] To date, no commercial

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skin prick-test (SPT) solution for the testing of these additives is available. In prior publications used SPT substances were laxatives or drugs (e.g. MiraLAX; methylprednisolone acetate; both containing PEG-3350) resulting sometimes in positive SPT with little relevance.[4]

This retrospective single-centered study included 46 patients that were referred to Comprehensive Allergy Center at the Department Dermatology and Venereology, Kepler University Hospital, Linz, Austria, with a history of potential allergic reaction to the first COVID-19 vaccination (Supplemental Table 1).

Of these patients, 39 had histories of unspecific immediate reactions (most likely non-allergic reactions eg, hypertension, head-ache or unspecific reactions such as vertigo, tingling or pricking sensations, etc) or delayed reactions (eg, intense local reactions, flush, nausea or urticaria more than 1 day after vaccination). Only 7 (15%) patients displayed a history consistent with a possible anaphylactic reaction according to Ring and Messmer's[5] (Grade I: 2x, Grade II: 3x; Grade III: 1x, see Table 1). These patients reported immediate treatment including antihistamines, corticosteroids and in one case adrenaline (Grade III reaction). None of them needed intensive care treatment. Serum tryptase level determination of these events was not performed.

We performed SPT in 40/46 patients with the culprit allergens as listed in Supplemental Table 2. All patients were tested with all substances. In 37/40 cases, immediate type sensitization to PEG and/or Polysorbate-80 was ruled out by SPT (2 invalid tests, 1 positive reaction). None of the performed tests resulted in delayed skin reactions. Six patients were directly assigned to the second vaccination without prior SPT (medical history ruled out risk of anaphylaxis or inability to test because of systemic anti-allergic medication or dermographism).

Selection of the second COVID vaccine was based on severity of the previous allergic reaction and the consenting of the patients (see Fig. 1). Importantly, we did not observe any anaphylactic reaction after administration of the second COVID-19 vaccine dose in all 22 revaccinated patients. This included the individual with a positive SPT to PEG2000, who was vaccinated with an alternative vector vaccine (see Table 1). Premedication with single or double dose of second-generation antihistamines 30–60 min prior to the vaccination was given in 17 cases.

Of the remaining 24 patients, around two-thirds received the second vaccine in a peripheral setting (vaccination center, general practitioners, etc), without reported immediate reactions. The remaining patients refused further vaccination with the second dose despite allergological clearing or were lost to follow up.

Recent reports have shown that the second (and even third) dose of COVID-19 vaccines are important in protecting individuals against severe COVID-19 disease. It is thus highly recommended, even for patients with suspected allergic reactions to the first dose, to continue with vaccination protocols. We report a cohort of 46 patients with a history of suspected allergic reactions to the first dose of COVID-19 vaccines. In all cases, except one, allergy to PEG-2000 and Polysorbate-80 was ruled out and second dose vaccination was well tolerated in all patients. Other authors reported positive results more frequently, but they used complex medications with different ingredients.[4] Accordingly, we think that SPT with pure PEG and Polysorbate solutions could be of value in selected cases of patients (see also 6). Since the vaccines are now abundantly available they could also be used for skin prick testing, as alternative. If the use of these is superior to testing of the additives alone is currently not known and there is the possibility of a delayed skin reaction as immune response to virus particles or adjuvances[7] that do not reflect allergic reactions. Our observations are also in line with previous reports showing that both mRNA-based vaccines (BioNTech/Pfizer and Moderna) were re-administered in patients with anaphylactic reactions to the first dose without any problems.[8]

Although the mode of action of reactions associated with SARS-CoV-2 mRNA and vector-based vaccines are currently unknown, our results and observations by others suggests that non–IgE-mediated immune responses to PEG may be responsible in most individuals.[8,9] In a recent case series with 22 patients with suspected allergic reactions to mRNA COVID-19 vaccines SPT to PEG and Polysorbate-80 was negative in most cases.[9] In contrast, 11/11 patients had positive

Nr	Sex	Age (y)	Known prior anaphylaxis (Grad)[a]	1st dose	Time of onset	Symptoms after 1st dose	Anaphylaxis classification[a]	Medication received due to reaction	Prick test	2nd dose	Premed. - before 2nd dose	Symptoms after 2nd dose
1	F	29	–	Vector, AstraZeneca	<30 min	Dyspnea, Lightheadedness	II	–	Negative	mRNA, Pfizer	AH	None
2	F	60	Contrast agent (Grade II)	Vector, AstraZeneca	<30 min	Flush, Pruritus	I	GC, AH	Negative	mRNA, Pfizer	AH	None
3	F	33	–	Vector, AstraZeneca	<30 min	Flush, Lightheadedness	I	GC, AH	Negative	mRNA, Pfizer	AH	None
4	F	54	–	mRNA, Pfizer	<30 min	Dyspnea, Lightheadedness	II	GC, AH	Invalid[b]	Vector, Janssen	AH	None
5	F	20	–	mRNA, Moderna	<30 min	Dizziness, unconscious	III	GC, AH	Positive -PEG 2000	Vector, Janssen	AH	None
6	F	40	–	mRNA, Pfizer	<30 min	Lightheadedness, globus sensation, Nausea	II	GC, AH	Negative	–	–	–
7	F	40	Peanuts (Grade IV)	Vector, Janssen	<30 min	Dyspnea, Lightheadedness, Nausea	II	GC, AH	Negative	–	–	–

Table 1. Details of patients with anaphylaxis to the first dose of the SARS-CoV-2 mRNA and vector-based vaccines. *Nr, number; premed, Premedication; y, years; F, female; PEG, polyethylene glycol; SPT, skin-prick test; AH, antihistaminic drug; GC, glucocorticoids.* [a]*After the Ring and Messmer (11) scale.* [b]Positive control: no wheal

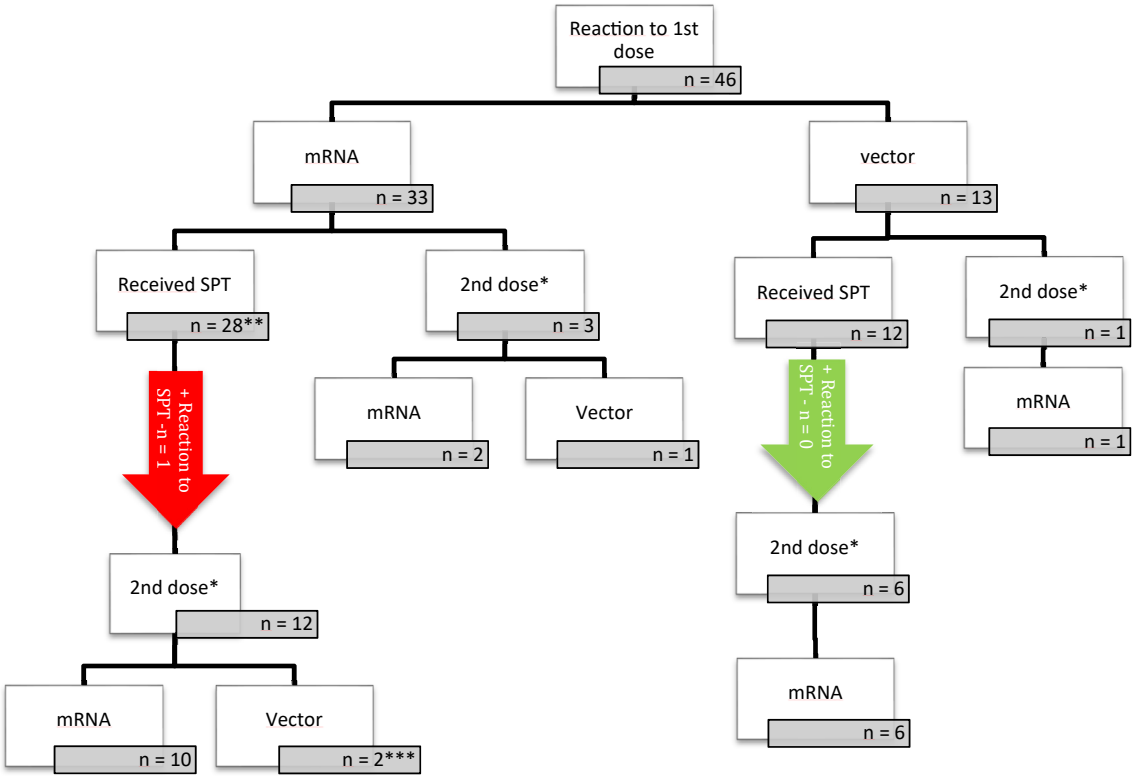

Fig. 1 Representation of the study cohort: After comprehensive anamnesis patients with suspected allergic reactions after first COVID vaccination were stratified per expert group into a monitored vaccination group without prior testing and into a group with prior SPT. * anamnestical no evidence for allergic reaction in context with the vaccination, ** 2 invalid SPT included, *** including the Patient with reaction to SPT, # until timepoint of assessment or lost to follow up (incl. possible external vaccination). SPT, skin-prick test.

basophil activation test results to their administered mRNA vaccine and anti-PEG IgG was found in tested individuals.[9] These results suggest that allergic reactions to mRNA vaccines are likely due to non–IgE-mediated mechanisms, eg, complement activation-related pseudoallergy (CARPA). However, further research is needed to address the pathophysiology of anaphylactic reactions to COVID-19 vaccines.

As a limitation, our study reflects a modest cohort that was retrospectively analyzed and documented in a single center. Furthermore, despite the fact, that patients were advised to report events after discharge from the clinic, minor reactions might have been missed. Yet, immediate reactions within at least 30 min after vaccination can be ruled out according to our data.

Overall, we think that this report is important to gain confidence on the safety of the vaccines. Positive SPT results were rare and tolerability of the vaccinations was good, similar as reported in the literature.[3,6,10] The relevance of SPT to stratify adjustments of the individual vaccination plan in selected patients of suspected high risk remains to be verified. The currently available COVID-19 vaccines have overall a low allergic potential and can be safely administered, even to the majority of people with a high allergic potential and in patients with suspected anaphylactic reactions to the first dose. Further research is needed to address the problem of correctly diagnosing suspected anaphylactic reactions to COVID-19 vaccines and to have more sensitive and specific tests available.

Abbreviations

COVID-19, Corona Virus Disease (2019); PEG, polyethylene glycol; SPT, skin prick test.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

VP was in charge for data collection, data management and drafting of the manuscript.
TB was involved in patient care and data entry.
KH was involved in patient care and data entry.
EG was involved in critical proof reading of the manuscript.
WH supervised the project and was in charge for critical proof reading of the manuscript.
SA was head of the patient care and patient vaccinations and was involved in manuscript preparation.
All authors read and approved the final manuscript.

Ethics approval and consent to participate

Retrospective data analysis. Ethical approval was seeked at the ethical committee of the Kepler University Hospital (EK Nr. 1304/2021).

Consent for publication

All authors consent the publication of the manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.
Outside this topic and work, Sabine Altrichter has conducted studies for/was advisor for/was speaker for AstraZeneca, Allakos, ALK, CSLBehring, LeoPharma, Moxie, Novartis, Sanofi, Takeda, Thermofisher.
Wolfram Hoetzenecker has conducted studies for/was advisor for/was speaker for Novartis, Eli Lilly, Bencard, ALK, Leo Pharma, Kyowa Kirin, Takeda, Sanofi-Aventis and AbbVie, outside this topic and work.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100654.

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