ORIGINAL ARTICLE

Evaluation of Allergic Reactions following COVID - 19 Vaccination in Patients with Documented Allergies

Sunita Chhapola Shukla[1,2], Sukant Pandit[3], Dhruve Soni[3], Nithya J Gogtay[4]

Abstract

Background and Rationale: The government guidance regarding COVID-19 vaccination lists food allergy, drug allergy and history of anaphylaxis as contraindications for receiving vaccination. This study was planned to evaluate such patients listed in the database of an allergy center and who took any COVID-19 vaccine.

Methods: Data on n=255 patients was mined. Inclusions were those over 18 years, any allergic diathesis and receipt of at least one dose of any COVID-19 vaccine. Age, gender, nature of allergy and type of COVID vaccine taken along with outcome of interest [occurrence or otherwise of all allergic reaction post vaccination] was collated.

Results: Data of 227 patients were finally analysed. Eighty one took the first dose and 33 took both doses. None with food and/or drug allergy and/or a history of anaphylaxis developed any adverse event (AE) post vaccination. Three AEs were seen in those with other allergic diathesis. Two AEs [One to COVAXIN™ and one to COVISHIELD™] were only generalized itching that were self-limiting. A female patient had itching with palmar erythema [post COVISHIELD™] which subsided after a week's treatment with an antihistamine. She had a history of allergy to radiocontrast media containing polyethylene glycol/PEG] indicating possible allergy to polysorbate 80 [PEG related compound contained in COVISHIELD™].

Conclusion: No patient fitting contraindications for COVID-19 vaccination laid down by the Indian government developed any allergic reaction post vaccination. The guidelines for vaccination may be revisited to make them more inclusive with appropriate training of the vaccination centre staff.

Background and Rationale

Vaccines today form the mainstay for mitigation of the COVID-19 pandemic. Vaccination prevents severe disease, hospitalization and a fatal event. Several of these vaccines have Emergency Use Authorization [EUA] worldwide. In the United States, two mRNA vaccines [Pfizer and Moderna] were among the early ones to receive EUA. In India, currently COVISHIELD™ [Serum Institute of India, adenovirus vector vaccine] and COVAXIN™ [inactivated vaccine with a matrix adjuvant] are approved under EUA and more recently Sputnik V™ [adenovirus vector vaccine] has been added to this list.[1,2]

One of the key challenges with mass administration of vaccines is the guidelines pertaining to individuals with allergy. The initial guidance of the Ministry of Health and Family Welfare released in the form of a letter on 14th January 2021.[3] listed several contraindications to their use. These included - anaphylaxis to a previous dose of COVID vaccine, food allergy, drug allergy and allergies to vaccines, pharmaceutical products and injectables. This led to several people with above mentioned medical conditions being refrained to take the vaccine and hence putting them at risk of developing COVID-19 disease. Anecdotal evidence and information in the lay press suggests that many individuals with allergies who chose to get vaccinated, did not develop any severe allergic reactions after either dose. Yet others adhered strictly to these guidelines and either opted to remain unvaccinated or were turned away from vaccination centres due to the perceived risk of serious adverse events [AEs] including anaphylaxis.

The position statement of the World Allergy Organization [WAO] states that the risk of developing anaphylaxis with available COVID-19 vaccines worldwide is <1 per million.[4] Study suggests that the risk of development of hypersensitivity reaction post mRNA vaccination is 0.63 % and 1.5 % for Pfizer-BioNtech and Moderna vaccine respectively.[5] The vaccination policies of the United Kingdom and United States do not preclude patients with food and/or drug allergies to these vaccines[6,7] though persons with a history of anaphylaxis need to be assessed by an allergist and then decide further management for the patient.[8]

The lead author [SCS] of this paper runs an allergy centre where patients with documented allergic diathesis get diagnosed and treated for various allergies. Individuals with history of atopy get sensitized to allergens early in life due to atopic march and grow into adults with multiple allergy spectrum e.g.- allergic rhinitis, bronchial asthma, skin allergy, food and drug allergies etc.[9] Many of these patients consult regarding COVID-19 vaccination in view of their allergy history. An evaluation of this database would lend insights into the outcomes of these individuals post COVID-19 vaccination.

[1]Director, Mumbai Allergy Center and Honorary Visiting Allergist, [3]DM Resident, [4]Professor and Head, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra; *Corresponding Author
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Table 1: Demographic and vaccination profile of the patients

Criteria	Number
Patient forms screened	257
Sample eligible for the study	227
Median [range] age in years	36 [26-56]
Women	123
Men	104

Material and Methods

Ethics – The study protocol was approved by the Institutional Ethics Committee.

Selection criteria- All adult patients [over the age of 18 years] in the allergy centre's database were assessed. Inclusions were those with any allergic diatheses, including those with food and/or drug allergy and/or history of anaphylaxis who had undergone thorough clinical evaluation and allergy testing. Data was collected from their forms regarding their vaccine dosage and any allergic Adverse Event Following Immunization (AEFI). Exclusions were patient less than 18 years of age, incomplete demographics and incomplete allergy testing data. Privacy and confidentiality were maintained using unique identifiers.

Data extraction and outcome of interest – The extracted data included age, gender, nature of allergy [food, drug or other], whether COVID vaccination taken [or not] and if taken whether there was any allergic reaction post vaccination [the outcome of interest]. In the event of a documented allergic reaction following vaccination [to any COVID-19 vaccine], the following were noted – whether the reaction occurred after first, second or both doses and the severity of the reaction was recorded using the modified Hartwig -Siegel scale.[10]

Results

Demographics and final sample – The total number of patients registered in the database are n=255 of which n=227 fulfilled the selection criteria. The median [range] age is of these patients is 36 [26-56] years. There were a total of 123 [54.1%] women and 104 [45.8%] men. The details are summarized in Table 1. Details of various allergies is given in Table 2. Most of the patients had multiple clinical presentation of allergy spectrum e.g. allergic rhinitis, allergic asthma, skin allergy, food allergy, drug allergy or anaphylaxis etc.

Table 2: Details of Allergies

Details of allergy N = 227	n/N [%]
Food allergy [with or without drug allergy and history of anaphylaxis	90 [39.6]
Drug allergy [with or without food allergy and history of anaphylaxis]	22 [9.7]
History of anaphylaxis [with or without food or drug allergy]	22 [9.7]
Any allergic diathesis e.g. allergic rhinitis, asthma, skin allergy [without food allergy, drug allergy or history of anaphylaxis]	121 [53.3]
Food allergy alone	71 [31.3]
Drug allergy alone	9[4.0]
History of anaphylaxis	5[2.2]
Food and drug allergy	4 [1.8]
Food allergy with a history of anaphylaxis	8 [3.5]
Drug allergy with history of anaphylaxis	2 [0.9]
Food allergy, drug allergy and a history of anaphylaxis	7 [3.1]

Details of vaccination- Of the 227 patients, at least 81 patients received one dose of a COVID-19 vaccine. Of these, a majority received COVISHIELD™ [69, 85.2%], 10 [12.3%] received COVAXIN™ and one each had taken Moderna™ and the Sputnik™ vaccine. Of the 81, 33 [40.7%] patients took the second dose. Of these 33, 25 [75.7%] received COVISHIELD™, 7 [12.3%] COVAXIN™, and one [1.2%] Moderna™. Details are described in Table 3.

Details of Adverse Events [AEs] post vaccination

No serious AEs were seen in patients with any allergies including either food or drug allergy or a history of anaphylaxis or a combination of these allergies (Table 4). Three patients from the general group of allergic diathesis [n=121, non food, non drug, non anaphylaxis group] were the ones who developed mild allergic AEs. One patient each developed itching after the first dose of COVISHIELD™ and COVAXIN™ that was self-limiting. One female patient post second dose COVISHIELD™ developed palmar rash with warm extremities. The onset of the rash was 15 minutes post vaccination and resolved with an anti-histamine for a week. The patient gave a past history of reaction to radiocontrast media few years back where she developed rash on trunk, face, lip and angioedema that also subsided after treatment with an anti- histaminic. Only one Level 3 severity ADR as per Hartwig Scale (defined as an AE which requires intervention) developed in a total of the total 114 vaccine doses (81 + 33) administered. None developed

Table 3: Details of vaccination

Total number of patients from the database who received any COVID-19 vaccine	First Dose (N = 81) n (%)	Second Dose (N = 33) n (%)
COVISHIELD™	69 (85.2)	25 (75.7)
COVAXIN™	10 (12.3)	7 (21.2)
Moderna™	1 (1.2)	1 (3)
Sputnik V™	1 (1.2)	0 (0)

severe Adverse Events following immunization [AEFI] or anaphylaxis or required hospitalization or ICU care. The details of AEs are summarized in Table 4.

Discussion

The present study analyzed mined data of 227 patients with multiple allergies. Of these 81 patients took at least one dose of the vaccine and 33 received both doses. These patients had multiple allergic diathesis in which almost half of them (39) had either food and/or drug allergy and/or a past history of anaphylaxis. No patient with either of these allergies developed any AEs. Three mild AEs which included two AE of itching and one of rash post vaccination were seen in the general allergic diathesis category indicating reasonable safety of the COVID-19 vaccination in this group of patients.

The risk of an allergic reaction following vaccination remains an important concern for patients and policy makers alike. During the early phase of vaccine development, patients with allergies are excluded from the human clinical trials and these reactions come to light only when a large number of people are vaccinated.[11] The EUA of the mRNA vaccines Pfizer and Moderna brought to fore cases of anaphylaxis associated with these vaccines with the current prevalence figures at 4.7 per million and 2.5 per million respectively.[12] Usually it is the excipients, preservatives and adjuvants rather than the vaccine itself that are the likely culprits for causing reactions.[13] The challenge with regards to the mRNA vaccines lies in the use of high molecular weight Polyethylene Glycol [PEG2000] which envelopes the naked mRNA and prevents its degradation. PEG is widely used in food additives, tablet binders, bone cements and bowel preparations. IgE-mediated reactions to polyethylene glycol (PEG) and its derivatives are the most suspected reasons for allergic reactions to the mRNA vaccines which

Table 4: Adverse Events [AEs] post vaccination

Allergic Diathesis	COVID vaccine first dose	COVID vaccine second dose	Serious AEs after either dose
Food allergy (with or without drug allergy or history of anaphylaxis) (n=90)	32/90 COVISHIELD™= 28 COVAXIN™=3 MODERNA™ =1	13/32 COVISHIELD™= 11 COVAXIN™=1 MODERNA™ =1	None
Drug allergy (with or without food allergy or history of anaphylaxis) (n=22)	9 /22 COVISHIELD™=8 COVAXIN™=1	2/9 COVISHIELD™=1 COVAXIN™=1	None
History of anaphylaxis (with or without food or drug allergy) (n = 22)	12/22 COVISHIELD™= 11 COVAXIN™=1	5/12 COVISHIELD™= 5	None
Food allergy (n = 71)	22/71 COVISHIELD™= 19 COVAXIN™=2 MODERNA™ =1	9/22 COVISHIELD™= 7 COVAXIN™=1 MODERNA™ =1	None
Drug allergy (n = 9)	3/9 COVISHIELD™= 3	1/3 COVISHIELD™= 1	None
Past history of anaphylaxis (n = 5)	3/5 COVISHIELD™= 3	2/3 COVISHIELD™= 2	None
Food and drug allergy (n = 4)	2/4 COVISHIELD™= 2	1/2 COVISHIELD™= 1	None
Food allergy and having a history of anaphylaxis (n = 8)	5/8 COVISHIELD™= 5	3/5 COVISHIELD™= 3	None
Drug allergy and history of anaphylaxis (n = 2)	1/2 COVISHIELD™= 1	0	None
Drug allergy and history of anaphylaxis (n = 7)	3/7 COVISHIELD™= 2 COVAXIN™= 1	0	None
Allergic diathesis without food allergy or drug allergy or history of anaphylaxis (n = 121)	42/121 COVISHIELD™= 34 COVAXIN™= 07 Sputnik = 01	17/42 COVISHIELD™= 11 COVAXIN™= 06	*

*Three mild AEs. One patient each developed itching (Level 1 severity a per Hartwig scale) after first dose of COVISHIELD and COVAXIN. One patient developed palmar rash and warm extremities (Level 3 severity as per Hartwig scale) after second dose of COVISHIELD and required anti-histaminic for a week to resolve.

is a novel technology in itself. In India, Moderna the mRNA vaccine was accorded approval in June 2021[14] but at present, it uptake is less compared to COVISHIELD™ and COVAXIN™. COVISHIELD™ contains Polysorbate 80 (P-80) which has a lower molecular weight and has cross-reactivity with PEG.

The vaccine and consequently the compound of interest in terms of vaccine allergy in India is P-80 that has a similar structure to PEG but a lower molecular weight. Thus patients with a history of reactions to PEG should be tested for P-80 hypersensitivity if they are opting to take COVISHIELD™. The female patient with the rash following COVISHIELD™ is the most relevant to risk of AEs post COVID -19 vaccination. Radiocontrast media are known to contain Polyethylene Glycol [PEG] and COVISHIELD™ contains the related polysorbate 80. She most likely was sensitized to polysorbate 80 after the first dose of COVISHIELD™ and post second dose developed an allergic reaction. It is though important to note here that the same Polysorbate 80 is also part of some influenza, meningitis and pneumococcal vaccines[15] which do not have food or drug allergy as a contraindication.

What does this audit tell us? Though limited by its small sample size, none of the patients with history of food allergy or drug allergy or history of anaphylaxis actually developed any allergic reaction. The three patients who did develop allergic reactions did not in fact fit into the government's exclusion criteria. The answer therefore lies in learning from the UK or the US model where food and drug allergies are not a contraindication for COVID-19 vaccination. Hence at vaccination centers, staff should be encouraged to vaccinate these patients under the care of a specialist capable of managing AEs. Most of the allergic AEFI occur in the first 15 minutes of vaccination.[16] In India the observation period is 30 mins, which is good enough to identify and treat any serious AEFI. Often times, a vasovagal attack after vaccination is interpreted as anaphylaxis. Hence , the healthcare worker should be aware of the difference between anaphylaxis, syncope and vasovagal attack (Table 6) and similarly the grading of the anaphylaxis (Table 7) as the management depends on it.

Table 6: Summary of the main difference in clinical signs and symptoms between vasovagal and anaphylaxis[17]

Observations	Vasovagal attack	Anaphylaxis
Pulse	Bradycardia	Tachycardia
Blood pressure	Normal	Hypotensive
Hoarseness of voice	Absent	Present (progressive)
Cough, Wheeze and stridor	Absent	Present
Skin color	Pale	Reddish pink
Angioedema, urticaria	Absent	Present
Onset of time	Almost immediate	Within minutes to hours

In our study, the low number of second doses taken is likely due to the waiting period of 84 days between both doses. We can only surmise that the remainder of the patients in the database who are yet unvaccinated are largely vaccine hesitant and unwilling to bypass the guidelines. Their belief is reinforced at vaccine centers where many are turned away after history taking as center staff are also hesitant. Such patients should be referred to and evaluated by an allergist for further management. The answer to this hitherto neglected group of patients lies in revising the guidelines, offering allergy testing and more specifically allergy testing for PEG and polysorbate 80 wherever expertise exists or refer patients to an allergist for confirmation. Patients with allergies should be encouraged to visit vaccination centers and get vaccinated with any available COVID-19 vaccine. Education of vaccine center staff and facilitating specialist medical care at these centers to manage the very rare immediate reactions should be promoted. Only then will the Indian COVID-19 vaccination program be truly inclusive.

Conclusion

No patient fitting contraindications for COVID-19 vaccination laid down by the Indian government developed any allergic reaction post vaccination. The guidelines for vaccination may be revisited to make them more inclusive with appropriate training of the vaccination centre staff.

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Table 7: Grading of Anaphylaxis[18]

Grade	Skin	Gastrointestinal	Respiratory	Cardiovascular	Neurological
1	Localized rash and pruritus Urticaria Angioedema	Oral discomfort Lip swelling	Pharyngeal itchiness and discomfort	-	-
2	Generalized pruritus and rash, urticaria, angioedema	Nausea, Vomiting, Diarrhea,	Mild nasal congestion/ rhinorrhea	-	Loss of activity
3	As Above	Repeated vomiting/ diarrhea, persistent colic	Severe nasal congestion/ rhinorrhea, continuous coughing, laryngeal itchiness	Tachycardia	Anxiety
4	As above	As above	Choking sensation, husky voice, barking cough, wheeze, dyspnea, cyanosis	Arrhythmia, Hypotension	Irritability, Impending doom
5	As above	As above	Respiratory arrest	Severe bradycardia, severe hypotension, cardiac arrest	Loss of consciousness

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