Brief Report

Covid-19 Vaccination and Chronic Urticaria: A Paradigm Study

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Abstract

Background: Multiple vaccines were introduced during 2020–2021 to combat Covid-19 pandemic, being one of the successful vaccine programmes in the present era. Very few studies are available on status of chronic urticaria (CU) post Covid-19 vaccination. **Aim:** The aim of this study was to study effect of Covid-19 vaccination on our urticaria cohort. **Materials and Methods:** In this retrospective study, case records of CU patients registered in urticaria clinic, who had received any type of Covid-19 vaccine during the interval of March 2021–2022 were retrieved. Patients were classified as 'vaccine induced urticaria' (VIU) when CU developed for first time post-vaccination and 'vaccine exacerbated urticaria' (VEU) when administration of vaccine exacerbated disease activity in previously diagnosed CU. **Results:** Overall, 353 CU patients registered with us during this period, 265 had received atleast one dose of a Covid-19 vaccine, of which 12 reported VEU (ten of whom had received adenovirus vector vaccine), and three patients were diagnosed with VIU (all had received inactivated virus vaccine). Mean vitamin D3 levels were significantly higher in patients who had VEU as compared to those CU patients without exacerbation (p = 0.003). Significant correlation was observed between level of concern regarding adverse effects of vaccination, pre-vaccination, and post-vaccination urticaria activity score (UAS-7), (Pearson correlation coefficient = 0.66, P = 0.007) in both VEU and VIU. Urticaria symptoms were controlled in 75% and 66.6% patients, respectively, of VEU and VIU, after one month of initiating standard antihistamine treatment. **Conclusion:** Hence, we conclude that though Covid-19 vaccines can trigger CU, standard treatment protocols control disease activity in most patients.

Keywords: *Chronic urticaria, Covid-19 vaccine, reaction, vaccine exacerbated, vaccine-induced*

Introduction

The world has recently experienced one of the most significant pandemics known to mankind, during which various Covid-19 virus directed vaccines were introduced as an important public health measure in curbing infection rates, reducing morbidity and mortality in infected individuals. This policy-move by the whole fraternity proved to be a boon for the common mass. Vaccine-related adverse events are commonly encountered, including non-allergic symptoms like fever, local site pain, myalgia, joint pains, etc., and allergic symptoms like urticaria, angioedema, and anaphylaxis. Herein, we aimed to study the effect of Covid-19 vaccination on chronic urticaria (CU).

Materials and Methods

This was a cross-sectional retrospective study wherein all patients diagnosed as CU, enrolled in our 'urticaria clinic' between March 2021 and March 2022, were assessed. The data were collected both by direct patient enquiry and from patient records that were later tabulated in a structured proforma. Patients with CU adversely affected by vaccination were further divided into 'vaccine induced urticaria' (VIU) referring to those patients who developed urticaria for the first time within eight weeks after Covid-19 vaccination, and 'vaccine exacerbated urticaria' (VEU) referring to those with already diagnosed CU but developed disease flare within eight weeks after Covid-19 vaccination. The disease characteristics of both these groups were noted with respect to urticaria activity score (UAS-7), treatment administered and response to treatment after one month of initiation. The treatment was in accordance with European academy of allergy and clinical immunology guidelines.[1] Control of urticaria

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disease activity was classified according to UAS-7 as urticaria symptom free (UAS-7 = 0), well-controlled (UAS-7 = 1–6), mild activity (UAS-7 = 7–15), moderate activity (UAS-7 = 16–27), and severe activity (UAS-7 = 28–42). Statistical analysis was carried out using statistical package for social sciences (SPSS for Windows, version 28, IBM, New York, USA). Qualitative data were compared using Chi-square test and Fisher test. Quantitative data were compared using unpaired t-test. *P* value < 0.05 was considered as significant in all the tests.

Results

Totally 353 CU cases were enrolled in the study, of which 265 had received atleast one dose of Covid-19 vaccine. The demographic details and disease characteristics of the cohort is summarized in Table 1. Mean vitamin D3 levels (75.0 ng/ml) of VEU group were significantly higher than the levels (19.7 ng/ml) of those who did not have an exacerbation (p = 0.003), however no significant differences were observed in the other parameters between the two groups.

Four (1.5%) patients had developed fever and myalgia and one patient (0.4%) had developed erythema at vaccination site after vaccine. Three patients (1.1%) developed CU for first time after the first vaccine dose (VIU) and 12 patients (4.5%) of previously diagnosed CU (already under our follow-up) had an exacerbation of their previous urticaria (VEU) [Tables 2 and 3]. Amongst the patients of VEU, nine patients developed exacerbation after first dose, whereas three patients had exacerbation only after second vaccine dose. Patients in VIU group had received inactivated virus vaccine (BBV152) and majority (10/12) who developed VEU received adenovirus vector vaccine (ChAdO × 1 nCoV-19) [p = 0.04]. None of the patients reported any reactions to the previous vaccinations as far as they could recall nor did they develop Covid-19 infection before they presented to us.

Mean age of VIU group was 44.7 ± 27.8 years and that of VEU group was 36.6 ± 13.8 years [Table 4]. Mean thyroid-stimulating hormone (TSH) levels of VIU and VEU group were 2.1 ± 0.6 mIU/l and 2.9 ± 1.9 mIU/l, respectively, and the difference between the two was significant (p = 0.02). However, no difference was seen between the anti-TPO antibody levels, which was raised only in a single patient with VEU. There were also no statistically significant differences in the serum IgE, D-Dimer, and vitamin D3 levels between the groups [Figure 1].

In VIU group, mean UAS-7 was 22.7 ± 10.8 before treatment initiation. The mean duration from vaccination to onset of urticaria was 7.7 days. Two patients were treated with standard doses of second generation antihistamines while the other one patient received four times standard doses of antihistamines along with the intermittent courses of oral corticosteroids. After one month of treatment, the mean UAS-7 decreased significantly to 4.7 ± 5.0 (p = 0.036). One patient was urticaria-free, and remaining two patients had well-controlled urticaria and mild improvement, respectively.

In VEU group, mean UAS-7 before exacerbation was 8.8 ± 9.8 and post-exacerbation it increased significantly to 28.4 ± 10.6 (p = 0.0001). The mean duration from vaccination to onset of exacerbation of CU was 9.1 days [Figure 2]. Three patients received up-dosing of anti-histamines after exacerbation, after which two patients became symptom-free and one patient had well-controlled disease. Intermittent oral corticosteroids were added to antihistamines in six patients, of whom five had well-controlled urticaria and one patient had mild-disease at the end of one month. Oral cyclosporine at a dose of 3 mg/kg/day was administered to two patients after which one patient demonstrated an immediate cessation of symptoms while the other had only partial improvement. A single patient received omalizumab injection (300 mg subcutaneously once a month) but was lost to follow-up after single dose. The overall mean UAS-7 decreased significantly to 4.5 ± 3.8 after one month of treatment in VEU group (p = 0.0001).

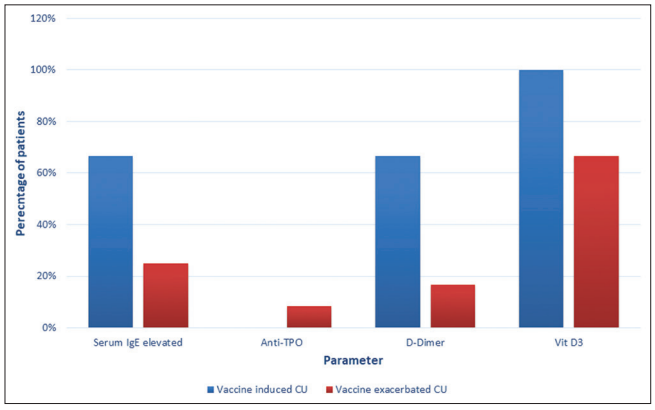

Figure 1: Graphical representation of the number of patients with elevated serum IgE, vitamin D3, D-Dimer, and anti-TPO antibodies

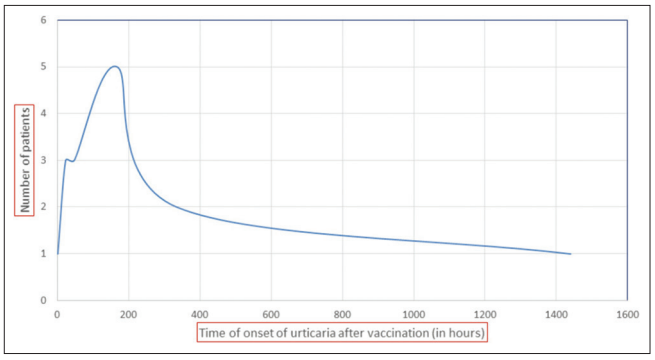

Figure 2: Graphical representation of the distribution of time of onset of urticaria reactions after vaccination

Table 1: Demographic details and disease characteristics of Covid-19 vaccinated patients of chronic urticaria registered from March 2021 to March 2022 (*n*=265)

Parameter		Values
Age in years (Mean±SD)		34.7±14.8
		Range: 18 years–87 years
Sex	Male [*n* (%)]	102 (38.5%)
	Female [*n* (%)]	163 (61.5%)
Type of urticaria	Chronic spontaneous urticaria	188 (70.9%)
	Chronic inducible urticaria	73 (27.5%)
	Both	4 (1.5%)
UAS-7 (Mean±SD)		9.1±15.5
Duration in months (Mean±SD)		39.5±62.1
		Range: 1.5–456 months
Symptoms	Wheals	157 (59.2%)
	Wheals + angioedema	108 (30.8%)
Co-morbidities		78 (29.4%)
		Most common-hypertension (7.5%)
		Second most common-hypothyroidism (7.2%)
Allergies		20 (7.5%)
		[Most common-food items]
NSAID intolerance		17 (6.4%)
Alcohol intake history		7 (2.6%)
Smoking history		0 (0.0%)
Total IgE in IU/ml (*n*=145) [Mean±SD]		390±480.6
TSH in mIU/l (*n*=87) [Mean±SD]		2.6±1.4
		Elevated TSH-8 (3.0%)
		Low TSH-4 (1.5%)
Anti-TPO IgG in IU/ml (*n*=76) [Mean±SD]		85.6±237.1
		Elevated anti-TPO IgG- 18 (6.8%)
D-dimer in mg/L (*n*=76) [Mean±SD]		348.8±708.3
		Elevated D-Dimer-10 (3.8%)
Vitamin D3 mmol/L (*n*=75) [Mean±SD]		29.1±87.8
		Deficient-16 (21.3%)
Previous vaccine reactions		2 (0.8%)
		(One patient had a local site reaction, other patient had a flu like reaction)
Covid infection before Covid vaccination		10 (3.8%)
Doses of Covid vaccine received	One	72 (27.2%)
	Two	193 (72.8%)
Reasons for not taking second dose	Second dose due according to schedule	70 (26.4%)
	Fear of second dose due to reaction after first dose	1 (0.4%)
Vaccines administered	Adenovirus vector vaccine (ChAdO×1 nCoV-19)	212 (80.0%)
	Inactivated virus vaccine (BBV152)	53 (17.4%)
Concerns regarding vaccination	None	86 (33.6%)
	Somewhat concerned	54 (21.1%)
	Slightly concerned	110 (42.9%)
	Moderately concerned	13 (5.1%)
	Extremely concerned	2 (0.8%)
Premedication before vaccination		None
Treatment before vaccination (*n*=259)*	Standard dose of AH	163 (62.9%)
	Standard dose of AH + leukotriene receptor antagonists	21 (8.1%)

Contd...

Table 1: Contd...

Parameter		Values
	Higher than standard dose of AH	55 (21.2%)
	Systemic steroids	15 (5.8%)
	Cyclosporine	3 (1.2%)
	Omalizumab	2 (0.8%)
Covid infection after vaccination		3 (1.2%)

SD-Standard deviation. UAS-Urticaria activity score. NSAID-Non-steroidal anti-inflammatory drugs. TPO-Thyroid peroxidase. TSH-Thyroid stimulating hormone. AH-antihistamines (second generation)

No correlation was observed between the type of vaccine given and time of onset of urticaria or severity of urticaria in both groups. Overall, 14 patients (in both groups) had reported concerns regarding the adverse events due to vaccine and significant correlation was observed between the level of concern and post-vaccination UAS-7 (Pearson correlation coefficient = 0.66, $P = 0.007$).

Discussion

Pathogenesis of chronic urticaria has always intrigued us.[2] Drugs and vaccine have been known to play a major role in triggering mast cell degranulation by both immune-mediated type 1 hypersensitivity and non-immune inflammatory mediators like prostaglandins and kinins.[3] Vaccine-induced urticaria has been reported with a myriad of vaccines.[3] In post-pandemic era, Covid-19 vaccine has achieved utmost importance for policy-makers and care-givers in curbing transmission and severity of Covid-19 infection. However, vaccine related adverse events and anxiety surrounding their safety have served as a source of concern amongst general population. Polysorbate-80, a common vaccine excipient has been implicated in triggering vaccine induced hypersensitivity.[4]

Being a tertiary care centre, our urticaria clinic caters to a large and diverse population corresponding to 5–6 states and a large number of patient records were reviewed. Only 4.5% of all vaccinated patients of CU developed exacerbation of urticaria after vaccine, while even a lesser number of patients (1.1%) developed CU for the first time after vaccination. Magen *et al*.[5] have reported an almost equal incidence of new-onset and exacerbated urticaria, however exacerbation of previously diagnosed CU was seen more-commonly in our cohort. It was noteworthy that majority of patients of VEU had been vaccinated using the adenovirus vector, whereas all patients of VIU had received the inactivated virus vaccine. Both immediate and delayed urticarial reactions have been observed after vaccination against Covid.[6] However, in our cohort, most experienced a delayed type of CU, with a latency period ranging from 24 to 48 hours for 1–2 weeks. Only one patient of VEU developed an immediate urticarial exacerbation (within 2 hours of receiving the vaccine). It is also noteworthy that none in our cohort experienced anaphylaxis or severe angioedema requiring hospital admission. Most patients had already received over-the-counter antihistamines with partial relief, before visiting our clinic. In both the groups, patients were either free of urticaria, had well-controlled disease or had mild disease activity after one month of treatment, which re-emphasises the vaccine safety.

Previous studies have reported female sex, history of atopy, third decade of life, and concomitant allergic diseases as risk factors for VIU, however, no such correlations were noted among our patients.[5] Interestingly, patients with sufficient levels of vitamin D3 were more at risk for developing an urticarial reaction as compared to those with vitamin D3 deficiency. We hypothesize that this could be the result of vitamin D3 enhancing both innate and adaptive immunity,[7] thereby increasing the immunogenicity to vaccine and its products. This property could also translate into its immunogenic role in triggering VIU. Apart from the inherent immunogenicity of vaccine components, the apprehensions surrounding the pandemic as well as concerns regarding vaccine safety could have played a role in induction or exacerbation of CU via the neuro-humoral-endocrine axis. This is corroborated by the fact that majority who experienced a flare had concerns regarding vaccine adverse events and significant correlation was observed between the level of concern and urticaria severity.

Conclusion

Although vaccine-related adverse effects like urticaria can occur after Covid-19 vaccination, they are relatively rare and easily manageable with the standard therapies. Our study intends to stress upon the safety of Covid-19 vaccine in CU. Although Covid infection is still lingering on, the vaccination drive in the country has been a huge success, and to protect ourselves against the pandemic, further vaccinations may be encouraged across all populations, including patients of urticaria.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Table 2: Characteristics of Covid-19 vaccine-exacerbated urticaria in individual patients

Serial No.	Age/ sex	Angioedema present	Time of onset of reaction after vaccine	UAS score before exacerbation	UAS score after exacerbation	Treatment before exacerbation	Treatment after exacerbation	Reaction after which dose of vaccine	UAS one month post treatment	UCT after treatment	Vaccine details	Concerns regarding vaccine
Patient 1	60/F	No	24 hours	14	21	Higher than standard dose of AH	Higher than standard dose of AH, steroids	First	6	14	Adenovirus vector	Moderately concerned
Patient 2	34/F	Yes	48 hours	0	24	Standard doses of AH	Higher than standard doses of AH, steroids	First	2	16	Inactivated virus	Somewhat concerned
Patient 3	52/M	Yes	1 week	15	42	Higher than standard doses of AH	Steroids, cyclosporine	First	12	12	Adenovirus vector	Moderately concerned
Patient 4	23/M	No	24 hours	4	21	Standard doses of AH	Higher than standard doses of AH	First	3	15	Adenovirus vector	Slightly concerned
Patient 5	31/M	No	48 hours	0	12	Standard doses of AH	Higher than standard doses of AH	Second	0	16	Inactivated virus	Slightly concerned
Patient 6	51/F	Yes	1 week	2	16	Standard doses of AH	Higher than standard doses of AH	First	0	16	Adenovirus vector	Slightly concerned
Patient 7	51/F	No	24 hours	0	25	Standard doses of AH	Higher than standard doses of AH, steroids	Second	4	14	Adenovirus vector	Somewhat concerned
Patient 8	39/M	Yes	2 hours	6	36	Higher than standard doses of AH	Higher than standard doses of AH, steroids	First	8	13	Adenovirus vector	Moderately concerned
Patient 9	23/F	No	2 weeks	12	42	Steroids, higher than standard doses of AH	Cyclosporine	Second	2	15	Adenovirus vector	Moderately concerned
Patient 10	25/M	No	1 week	24	35	Higher than standard doses of AH	Higher than standard doses of AH, steroids	First	6	12	Adenovirus vector	Extremely concerned
Patient 11	31/M	Yes	1 week	28	42	Steroids, higher than standard doses of AH	Omalizumab	First	9	11	Adenovirus vector	Somewhat concerned
Patient 12	19/F	Yes	2 months	0	25	Standard doses of AH	Higher than standard doses of AH, steroids	First	2	15	Adenovirus vector	Slightly concerned

AH-antihistamines (second generation). M: Male; F: Female. UAS-7-Urticaria activity score. UCT-Urticaria control test

Table 3: Characteristics of Covid-19 vaccine-induced urticaria in individual patients

Patient	Age/ sex	Angioedema present	Time of onset of urticaria after vaccine	UAS before treatment	Treatment given	UAS after treatment	UCT after treatment	Vaccine details	Concerns regarding adverse effects of vaccination
Patient 1	76/F	No	48 hours	18	Standard dose of AH	4	14	Inactivated virus	Somewhat concerned
Patient 2	35/F	Yes	2 weeks	35	Higher than standard dose of AH, short course oral steroids	10	11	Inactivated virus	Extremely concerned
Patient 3	23/F	Yes	1 week	15	Standard dose of AH	0	16	Inactivated virus	Not concerned

AH: Antihistamine (second generation); M: Male; F: Female. UAS-7-Urticaria activity score. UCT-Urticaria control test

Table 4: Characteristics of patients based on type of urticarial reaction (vaccine-induced urticaria and vaccine-exacerbated urticaria)

Parameter		Vaccine induced urticaria (*n*=3)	Vaccine-exacerbated urticaria (*n*=12)	*P*
Age in years [Mean±SD]		44.7±27.8	36.6±13.8	0.07
Serum IgE (IU/ml) [Mean±SD]		195.9±99.5	87.4±92.9	0.09
Serum TSH (mIU/ml) [Mean±SD]		2.1±0.6	2.9±1.9	0.02
Serum anti-TPO IgG antibodies (IU/ml) [Mean±SD]		3.0±5.2	106.4±349.1	0.31
D-Dimer levels (ng/L) [Mean±SD]		486±399.1	172.9±325.8	0.54
Vitamin D_3 (mmol/L) [Mean±SD]		9.9±4.0	75.0±217.4	0.32
Type of vaccine	Adenovirus vector	0	10	0.04
	Inactivated virus	3	2	
Time of onset after vaccine (hours) [Mean±SD]		184±144.7	218.2±397.1	0.54
UAS-7 before treatment		22.7±10.8	28.4±10.6	0.75
UAS-7 after treatment		4.7±5.0	4.5±3.8	0.73
Decrease in UAS-7 after treatment		18±0 6.0	23.9±8.3	0.45
Control of urticaria disease activity (based on UAS)	Urticaria free	1	2	0.75
	Well controlled	1	7	
	Mild disease activity	1	3	
UCT		14.1±1.7	13.7±2.5	0.57

SD-Standard deviation. TPO-Thyroid peroxidase. TSH-Thyroid stimulating hormone. UAS-7-Urticaria activity score. UCT-Urticaria control test

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