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Disease activity of patients with chronic urticaria receiving COVID-19 vaccines

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Abstract

Background: Cutaneous adverse events after receiving a COVID-19 vaccine were identified. The disease activity of urticaria after a COVID-19 vaccine has never been explored in chronic urticaria patients.

Objectives: To evaluate disease activity of chronic urticaria after receiving a COVID-19 vaccine.

Methods: A prospective cross-sectional study was conducted in chronic urticaria patients aged 18 or above who visited Siriraj Hospital between July and September 2021, and received the first and second dose of COVID-19 vaccine. The status prior to vaccination, including disease activity, disease control and disease severity was assessed by a urticaria activity score over seven days, urticaria control test, and modified medication score. The disease activity after vaccination was recorded.

Results: A total of 130 patients with a mean age of 45.9 ± 14.7 were enrolled in this study. Adenoviral and inactivated vaccines were administered to 85 (65.4%) and 45 patients (34.6%), respectively. Exacerbation was reported in 20 cases (15.4%) after the first dose and 17 cases (13.1%) after the second dose. Nine patients (45%) reported exacerbation after both the first and second dose. The majority of patients only had wheal, while three patients reported wheal with angioedema. No anaphylaxis was reported. Factor predicting exacerbation was concurrent thyroid disease (aRR 2.78, $p < 0.01$).

Conclusion: Approximately 15% of chronic urticaria patients reported exacerbation after receiving a COVID-19 vaccination. No serious events were observed. Chronic urticaria patients should be vaccinated against COVID-19 after a discussion of the risk of disease flare-up.

Key words: chronic urticaria, COVID-19 vaccination, adenovirus-based vaccine, inactivated vaccine, disease activity

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Introduction

Chronic urticaria (CU) is defined as the development of wheals, angioedema, or both for more than six weeks. CU is classified as chronic spontaneous urticaria (CSU) when there is no apparent cause and chronic inducible urticaria (CIndU) when specific triggers, such as cold, heat, and pressure, induce urticaria symptoms.[1,2] Severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (COVID-19) is an RNA virus belonging to the *Coronavirinae* subfamily. It is responsible for the third pandemic caused by a coronavirus after the emergence of SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus).[3,4] Patients with COVID-19 present a variety of symptoms ranging in severity from mild to severe. The common symptoms include fever, cough, shortness of breath, muscle pain and fatigue.[5] Extra-respiratory manifestations,

such as gastrointestinal, cardiac, and cutaneous symptoms, have also been reported.[6] Morbiliform (22%), pernio-like lesions (18%), urticaria (16%) are also common dermatological presentations of COVID-19.[7] Some potential treatments, such as favipiravir, remdesivir, monulpiravia, and nirmatrelvir/ritonavir are currently being studied and are selectively used. However, there are increasing reports of post-COVID complications such as long COVID, and post-COVID cholangiopathy.[8,9] Hence, effective vaccination plays an important role in outbreak control and prevention of post-COVID complications.

Various types of COVID-19 vaccines have been developed, including inactivated vaccines, adenoviral vector vaccines, mRNA vaccines, and subunit vaccines. Local and systemic reactions from vaccines have been observed regardless of platforms. The most common reported local reactions include pain, redness and swelling. Meanwhile, fatigue, fever and headache are commonly reported systemic reactions.[10-12] There have also been cases of cutaneous adverse events after receiving COVID-19 vaccines. The most common dermatological side effect is delayed large local reactions, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions.[13]

Due to the novelty of SAR-CoV2, it is yet to be known whether COVID-19 vaccines can also trigger disease by introducing antigens to stimulate the body's immune response. There was a report of well-controlled CSU in two patients whose condition clinically declined after being vaccinated with mRNA vaccines.[14] However, studies with more subjects and different types of vaccines are still lacking. This study aimed to study disease activity of CU after receiving COVID-19 vaccines.

Material and methods

The study design was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 510/2021). A prospective cross-sectional study was carried out in CU patients aged 18 or above visiting Siriraj Hospital between July to September 2021, who had already received their first and second COVID-19 vaccine. All participants were asked for the permission and written their informed consent. CU was defined as having wheal, angioedema, or both for over six weeks. The participants' condition was evaluated before vaccination and post-vaccination (i.e., co-morbidity, severity, control of CU, and medication use). The urticaria activity score measured over seven days (UAS7) was used to determine disease activity. The score was calculated by the sum of scores according to urticaria signs and symptoms (wheal 0-3 points, itch 0-3 points) over seven days.[1] UAS7 was categorized into five score bands; complete control of symptoms (0 points); minimal disease activity (1-6 points); mild disease activity (7-15 points); moderate disease activity (16-27 points); and severe disease activity (28-42 points).[15] The disease severity was reported on using the modified medication score. The original medication score of urticaria treatment was generated by Sussman et al.[16] The score of each medication was defined as follows; antihistamine (regular dose, 2 points; 4 times the regular dose, 8 points); oral glucocorticoids (< 11 mg, 5 points; 11-25 mg, 10 points; > 25 mg, 15 points); cyclosporine 3.0 mg/kg (8 points); hydroxychloroquine (6 points); and montelukast (2 points). This score was modified to add the score of omalizumab (8 points) to be equivalent to cyclosporin. The disease severity was categorized into three groups by the modified medication score as follows; mild degree (score < 2 points), moderate degree (score 3-17 points), severe degree (score > 18 points). The urticaria control test (UCT) is a simple 4-item questionnaire used to access disease control status in patients with CU using a retrospective approach for four weeks. The minimum and maximum UCT scores were 0 (uncontrolled disease) and 16 (disease under complete control). The cutoff point for well-controlled disease in UCT was 12. Poorly controlled disease was defined by a score of < 11.[1] Patients reported severity of exacerbation using the Likert-type scale, including none, mild, moderate, and severe based on the amount of wheals and symptoms. The details of COVID-19 vaccinations, including date of vaccination, type of vaccine, local and systemic side effects after vaccination were also assessed. The data of both the first and second doses were collected. Data was presented as mean ± standard deviation (SD), median (P25, P75), number and percentage as appropriate. Continuous data with normal and non-normal distribution was compared using the 2-sample t-test and Mann-Whitney U test respectively. Categorical data was compared using the chi-square test or Fisher's exact test. To determine factors associated with exacerbation after vaccination, variables with univariable *p*-value less than 0.15 were entered into the log-linked binomial model to get the adjusted relative risk (aRR). Statistical analysis was performed using PASW for Windows, version 18 (SPSS, Inc., Chicago, IL, USA). *P*-values < 0.05 were considered statistical significance.

Results

A total of 130 patients were enrolled in this study. The mean age of patients was 45.9 ± 14.7 years, and females accounted for 73.8% of all cases. Most patients (89.2%) were diagnosed with CSU, followed by CSU with concomitant CIndU (6.9%) and CIndU (3.8%). Cold urticaria (five patients, 35.7%) and symptomatic dermographism (five patients, 35.7%) were the most reported CIndUs followed by cholinergic urticaria (three patients, 21.4%), and delayed pressure urticaria (one patient, 7.1%). Half of all patients (52%) had no comorbidities. The most reported comorbidity was dyslipidemia (16.2%), followed by hypertension (13.1%), diabetes mellitus (6.9%), atopic disease (6.2%) and thyroid disease (5.4%). The status of almost all patients (94.6%) prior to the first dose was a UAS7 score that ranged from 0-15, which represented complete symptom control and mild disease activity. Eighty percent of patients' disease was well under control, with a UCT score > 12. However, the modified medication score had a range of disease severity as follows: mild (32.2%), moderate (36.9%) and severe (30.8%) (**Table 1**).

Table 1. Baseline characteristics of patients injected with the COVID-19 vaccine.

Characteristics	Number (%)
Age, year	
- mean ± SD	45.9 ± 14.75
- min, max	18, 81
Sex	
- female	96/130 (73.8)
Type of chronic urticaria	
- CSU	116/130 (89.2)
- CIndU	9/130 (6.9)
- both of CSU and CIndU	5/130 (3.8)
Type of chronic inducible urticaria	
- cold urticaria	5/14 (35.7)
- symptomatic dermographism	5/14 (35.7)
- cholinergic urticaria	3/14 (21.4)
- pressure urticaria	1/14 (7.1)
Underlying disease	
- dyslipidemia	21/130 (16.2)
- hypertension	17/130 (13.1)
- diabetes mellitus	9/130 (6.9)
- atopy	8/130 (6.2)
- thyroid disease	7/130 (5.4)
- others*	35/130 (26.9)

Characteristics	Number (%)
Pre-vaccination status prior to 1st dose	
UAS7 before vaccination	
- complete symptom control (score 0)	57/130 (43.8)
- minimal disease activity (score 1-6)	41/130 (31.5)
- mild disease activity (score 7-15)	25/130 (19.2)
- moderate disease activity (score 16-27)	3/130 (2.3)
- severe disease activity (score 28-42)	4/130 (3.1)
UCT before vaccination	
- Effective disease control (score ≥ 12)	104/130 (80.0)
- poor disease control (score ≤ 11)	26/130 (20.0)
Medication score before vaccination	
- mild	42/130 (32.3)
- moderate	48/130 (36.9)
- severe	40/130 (30.8)
Pre-vaccination status prior to 2nd dose	
UAS7 before vaccination	
- complete symptom control (score 0)	55/130 (42.3)
- minimal disease activity (score 1-6)	46/130 (35.4)
- mild disease activity (score 7-15)	13/103 (12.6)
- moderate disease activity (score 16-27)	7/130 (6.8)
- severe disease activity (score 28-42)	5/130 (4.9)
UCT before vaccination	
- effective disease control (score ≥ 12)	104/130 (80.0)
- poor disease control (score ≤ 11)	26/130 (20.0)
Disease severity by medication score	
- mild	41/130 (31.5)
- moderate	48/130 (36.2)
- severe	42/130 (32.3)

Abbreviation: SD, standard deviation; IQR, interquartile range; CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; UAS7, Urticaria Activity Score Over 7 Days; UCT, Urticaria Control Test; VAS, visual analog scale

*Other underlying diseases included non-alcoholic fatty liver disease (3 patients, 2.3%), migraine (2 patients, 1.5%), chronic hepatitis (2 patients, 1.5%), osteoporosis (2 patients, 1.5%), gastroesophageal reflux disease (1 patient, 0.7%), varicose vein (1 patient, 0.7%), benign prostatic hyperplasia (1 patient, 0.7%), essential tremor (1 patient, 0.7%), cerebellar ataxia (1 patient, 0.7%), endometriosis (1 patient, 0.7%), palindromic arthritis (1 patient, 0.7%), valvular heart disease (1 patient, 0.7%), human immunodeficiency virus infection (1 patient, 0.7%), systemic lupus erythematosus (1 patient, 0.7%), polycystic ovary syndrome (1 patient, 0.7%), breast cancer (1 patient, 0.7%), colon cancer (1 patient, 0.7%), nasopharynx cancer (1 patient, 0.7%), obstructive sleep apnea (1 patient, 0.7%), scoliosis (1 patient, 0.7%), psoriasis (1 patient, 0.7%).

After getting the first dose of the vaccine, 110 patients (84.6%) did not experience any changes in symptoms while 20 (15.4%) reported exacerbation. The median time until onset of exacerbation was 24 hours. All patients presented only wheals and none had angioedema or anaphylaxis. Regarding the Likert scale, which evaluates exacerbation, eight patients who previously had complete control over the symptoms reported mild (six cases) and severe (two cases) exacerbation. Six patients with minimal disease activity also had moderate and severe exacerbation (two and four patients, respectively). Five patients with mild disease activity had moderate and severe exacerbation (three and two patients, respectively). One patient with severe disease activity also reported mild exacerbation. Overall, the mean change in UAS7 in exacerbated cases was 10.3 points. Focusing on each group who experienced exacerbation, the mean UAS7 increased 4.67 points (11.12%), 9.0 points (21.42%) and 16.29 points (38.78%) in the mild, moderate and severe exacerbation groups, respectively. Only one patient decided to increase dosage of second-generation antihistamines. The average duration of exacerbation was three days (**Table 2**).

A total of 17 patients (13.1%) reported flaring of symptoms after the second dose of vaccine. Meanwhile, eight patients reported exacerbation after the second dose only. Nine patients reported exacerbation after both the first and second doses of the vaccine. To compare the severity of exacerbation between the first and second doses of the vaccine among the nine patients, three patients reported increasing exacerbation severity after the second dose. Another three patients experienced the same degree of exacerbation, while the last three experienced exacerbation to a lesser degree of disease severity after the second dose. Regarding clinical presentations after the second dose, the majority of patients presented only wheals, while three patients developed wheals with angioedema. There were no reports of anaphylaxis after vaccination in this study. The median time of onset of exacerbation, and the mean UAS7 score change regarding exacerbation and severity of symptoms was similar to data after the first dose. Five participants increased dosage of second-generation antihistamines. The average duration of exacerbation was four days. **Table 2** compares the sequelae between the first and second doses of the vaccine and shows that the local side effects of pain at injection site was significantly higher after the first dose than the second dose ($p = 0.02$).

Table 2. Types of COVID-19 vaccines and patient status after vaccination.

Clinical characteristics	1st dose	2nd dose	*P*-value	1st dose			2nd dose		
				adenoviral (n = 85)	inactivated (n = 45)	*P*-value	adenoviral (n = 85)	inactivated (n = 45)	*P*-value
Clinical status after vaccination									
Unchanged	110/130 (84.6)	113/130 (86.9)	0.59	70/85 (82.4)	40/45 (88.9)	0.32	72/85 (84.7)	41/45 (91.1)	0.30
Worsening	20/130 (15.4)	17/130 (13.1)	0.08	15/85 (17.6)	5/45 (11.1)	-	13/85 (15.3)	4/45 (8.9)	0.65
- urticaria only	20/20 (100.0)	14/17 (87.5)		15/15 (100.0)	5/5 (100.0)		11/13 (84.6)	3/4 (75.0)	
- urticaria with angioedema	0/20 (0)	3/17 (17.6)		0/15 (0)	0/5 (0)		2/13 (15.4)	1/4 (25.0)	
- angioedema	0/20 (0)	0/17 (0)		0/15 (0)	0/5 (0)		0/13 (0)	0/4 (0)	
- anaphylaxis	0/20 (0)	0/17 (0)		0/15 (0)	0/5 (0)		0/13 (0)	0/4 (0)	
Severity of exacerbation of urticaria by patients' self-report									
- mild	7/20 (35.0)	6/17 (35.3)		4/15 (26.7)	3/5 (60.0)		5/13 (38.5)	1/4 (25.0)	
- moderate	5/20 (25.0)	6/17 (35.3)	0.73	3/15 (20.0)	2/5 (40.0)	0.11	4/13 (30.8)	2/4 (50.0)	1.00
- severe	8/20 (40.0)	5/17 (29.4)		8/15 (53.3)	0/5 (0)		4/13 (30.8)	1/4 (25.0)	
Worsening onset, hour	n = 18	n = 17		n = 15	n = 5		n = 13	n = 4	
- median (IQR)	24.0 (7.5, 45.0)	24.0 (18.0, 60.0)	0.64	24.0 (12.0, 36.0)	24.0 (3.5, 108.0)	0.87	24.0 (18.0, 60.0)	27.0 (6.8, 133.5)	1.00
- min, max	1.0, 240.0	1.0, 168.0		1.0, 240.0	1.0, 168.0		1.0, 168.0	1.0, 168.0	

Table 2. (Continued)

Clinical characteristics	1st dose	2nd dose	*P*-value	1st dose			2nd dose		
				adenoviral (n = 85)	inactivated (n = 45)	*P*-value	adenoviral (n = 85)	inactivated (n = 45)	*P*-value
Duration of worsening, day	n = 20	n = 16		n = 15	n = 5		n = 12	n = 4	
- median (IQR)	3.0 (1.0, 12.5)	4.0 (2.0, 12.0)	0.60	4.0 (1.0, 14.0)	2.0 (1.0, 6.5)	0.31	4.5 (3.3, 10.8)	2.5 (1.3, 11.3)	0.26
- min, max	1.0, 28.0	1.0, 14.0		1.0, 28.0	1.0, 10.0		1.0, 14.0	1.0, 14.0	
UAS change after vaccination	n = 20	n = 17		n = 15	n = 5		n = 13	n = 4	
- mean ± SD	10.3 ± 9.0	9.6 ± 7.0	0.79	11.9 ± 9.8	5.4 ± 3.1	0.03**	9.08 ± 7.2	11.3 ± 6.9	0.60
- min, max	3.8, 20.3	0, 23.0		2.0, 28.0	2.0, 10.0		0.0, 23.0	4.0, 20.0	
Urticaria treatment after vaccination									
- Increasing dose of 2nd generation antihistamine	1/20 (5.0)	5/17 (29.4)	0.07	0/15 (0)	1/5 (20.0)	0.25	3/13 (23.1)	2/4 (50.0)	0.53
Other adverse reactions									
Local cutaneous reactions	23/130 (17.7)	11/130 (8.5)	0.02*	17/85 (20.0)	6/45 (13.3)	0.34	10/85 (11.8)	1/45 (2.2)	0.06
- Pain	23/130 (17.7)	11/130 (8.5)	0.02*	17/85 (20.0)	6/45 (13.3)	0.34	10/85 (11.8)	1/45 (2.2)	0.06
- Swelling	2/130 (1.5)	0/103 (0)	0.49	2/85 (2.4)	0/45 (0)	0.54	0/85 (0)	0/45 (0)	-
- Erythema	1/130 (0.8)	0/130 (0)	1.00	1/85 (1.2)	0/45 (0)	1.00	0/85 (0)	0/45 (0)	-
- Vesicle	0/130 (0)	0/130 (0)	-	0/85 (0)	0/45 (0)	-	0/85 (0)	0/45 (0)	-
Systemic	35/130 (26.9)	29/130 (22.3)	0.38	28/85 (32.9)	7/45 (15.6)	0.03*	24/85 (28.2)	5/45 (11.1)	0.02*
- Myalgia	18/130 (13.8)	11/130 (8.5)	0.16	15/85 (17.6)	3/45 (6.7)	0.08	9/85 (10.6)	2/45 (4.4)	0.23
- Fever	16/130 (12.3)	12/130 (9.2)	0.42	15/85 (17.6)	1/45 (2.2)	0.01**	10/85 (11.8)	2/45 (4.4)	0.17
- Headache	16/130 (12.3)	12/130 (9.2)	0.42	13/85 (15.3)	3/45 (6.7)	0.15	9/85 (10.6)	3/45 (6.7)	0.46
- Fatigue	11/130 (8.5)	4/130 (3.1)	0.06	8/85 (9.4)	3/45 (6.7)	0.59	1/85 (1.2)	3/45 (6.7)	0.11
- Diarrhea	5/130 (3.8)	2/130 (1.5)	0.44	5/85 (5.9)	0/45 (0)	0.16	2/85 (2.4)	0/45 (0)	0.54
- Nausea	3/130 (2.3)	1/130 (0.8)	0.62	2/85 (2.4)	1/45 (2.2)	1.00	0/85 (0)	1/45 (2.2)	0.34
- Vomiting	0/130 (0)	0/130 (0)	-	0/85 (0)	0/45 (0)	-	0/85 (0)	0/45 (0)	-
- Others	2/130 (1.6)	2/130 (1.6)		1/85 (1.2)	1/45 (2.2)	-	1/85 (1.2)	1/45 (2.2)	-

Abbreviation: SD, standard deviation; IQR, interquartile range; min, minimum; max, maximum; UAS7, urticaria activity score over 7 days
*Significant *p* value was < 0.05

In this study, there were two types of vaccines; inactivated (82.2% CoronaVac, and 17.8% BBIBP-CorV) and adenoviral (ChAdOx1 nCoV-19). To compare them, an incidence of exacerbation after vaccination was slightly higher in adenoviral vaccine without statistical differences. Mean UAS7 score change in those who received the first dose of an adenoviral vaccine was significantly higher than those who received inactivated vaccine ($p = 0.03$). Additionally, the systemic side effects were significantly higher after receiving the adenoviral vaccine than inactivated vaccine for both doses ($p = 0.03$ and $p = 0.02$, respectively) (**Table 2**).

Table 3 demonstrates the difference between the group who experienced flare-up and those who did not. For the first dose of vaccine, four factors, including being female, concurrent thyroid diseases, disease severity by medication score, and systemic side effects were significantly higher in the group that experienced flare-up than in the group that did not ($p = 0.01$, $p < 0.01$, $p = 0.03$ and $p < 0.01$, respectively). In contrast, no different factors, except systemic side effects, were noticed after the second dose.

Table 3. Comparison between flare-up and non-reaction group of urticarial disease activity.

Clinical characteristics	1st dose			2nd dose		
	Flaring N = 20 (%)	Non-flaring N = 110 (%)	*P*-value	Flaring N = 17 (%)	Non-flaring N = 113 (%)	*P*-value
Age						
- mean ± SD	47.1 ± 16.1	45.8 ± 14.6	0.71	50.3 ± 13.3	45.4 ± 14.9	0.19
Sex						
- female	19/20 (95.0)	33/110 (30.0)	0.01*	2/17 (11.8)	32/113 (28.3)	0.14
Underlying diseases						
- dyslipidemia	3/20 (15.0)	18/110 (16.4)	0.87	4/17 (23.5)	17/113 (15.0)	0.37
- hypertension	2/20 (10.0)	15/110 (13.6)	0.65	2/17 (11.8)	15/113 (13.3)	0.86
- diabetes mellitus	0/20 (0)	9/110 (8.2)	0.18	1/17 (5.9)	8/113 (7.1)	0.85
- thyroid diseases	4/20 (20.0)	3/110 (2.7)	< 0.01*	2/17 (11.8)	5/113 (4.4)	0.21
- atopy	0/20 (0)	8/110 (7.3)	0.21	0/17 (0)	8/113 (7.1)	0.25
- others	2/20 (10.0)	33/110 (30.0)		3/17 (17.6)	32/113 (28.3)	
Type of vaccines						
- Inactivated vaccines[a]	5/20 (25.0)	40/110 (36.4)	0.32	4/17 (23.5)	41/113 (36.3)	0.30
- Adenoviral vector vaccines[b]	15/20 (75.0)	70/110 (63.3)		13/17 (76.5)	72/113 (63.7)	
Pre-vaccination status						
UAS7 before vaccination						
- Complete symptoms control (score = 0)	8/20 (40.0)	49/110 (44.5)		9/17 (52.9)	46/113 (40.7)	
- Minimal disease activity (score 1-6)	6/20 (30.0)	35/110 (31.8)		3/17 (17.6)	43/113 (38.1)	
- Mild disease activity (score 7-15)	5/20 (25.0)	20/110 (18.2)	0.82	4/17 (23.5)	12/113 (10.6)	0.17
- Moderate disease activity (score 16-27)	0/20 (0)	3/110 (2.7)		0/17 (0)	8/113 (7.1)	
- Severe disease activity (score 28-42)	1/20 (5.0)	3/110 (2.7)		1/17 (5.9)	4/113 (3.5)	
UCT before vaccination						
- Well disease control (score ≥ 12)	14/20 (70.0)	90/110 (81.8)	0.22	11/17 (64.7)	93/113 (82.3)	0.09
- Poor disease control (score ≤ 11)	6/20 (30.0)	20/110 (18.2)		6/17 (35.3)	20/113 (17.7)	
Disease severity by medication score						
- Mild-Moderate	9/20 (45.0)	81/110 (73.6)	0.01*	11/17 (64.7)	77/113 (68.1)	0.77
- Severe	11/20 (55.0)	29/110 (26.4)		6/17 (35.3)	36/113 (31.9)	

Table 3. (Continued)

Clinical characteristics	1st dose			2nd dose		
	Flaring N = 20 (%)	Non-flaring N = 110 (%)	*P*-value	Flaring N = 17 (%)	Non-flaring N = 113 (%)	*P*-value
Pre-vaccination status (Continued)						
Patient Global Assessment						
- Well-controlled	12/20 (60.0)	69/110 (62.7)		8/17 (47.1)	75/113 (66.4)	
- Partial-controlled	5/20 (25.0)	31/110 (28.2)	0.71	7/17 (41.2)	30/113 (26.5)	0.30
- Poor-controlled	3/20 (15.0)	10/110 (9.1)		2/17 (11.8)	8/113 (7.1)	
Adverse effects						
- local adverse effects	5/20 (25.0)	18/110 (16.4)	0.35	1/17 (5.9)	10/113 (8.8)	0.68
- systemic adverse effects	15/20 (75.0)	20/110 (18.2)	< 0.01*	8/17 (47.1)	21/113 (18.6)	< 0.01*

Abbreviation: IQR, interquartile range; UAS7, Urticaria Activity Score over 7 Days; UCT, Urticaria Control Test
*Significant *p* value was < 0.05
[a]Sinovac, Sinopharm
[b]Astrazeneca

Table 4. Independent risk factors predicting disease flare-up after vaccination.

Factors	aRR	95% CI	*P*-value
Concurrent thyroid diseases	2.78	1.44-5.37	< 0.01*
Adenoviral vector vaccine	1.55	0.66-3.66	0.31
Severe disease severity by modified medication score	1.55	0.81-2.99	0.18

Abbreviation: aRR, adjusted relative risk
*Significant *p* value was < 0.05

To uncover predicting factors for disease flare-up regardless of the dose, factors including age, sex, underlying disease, type of vaccines, and pre-vaccination status were analyzed with the patients who had the exacerbation episode either on the first or the second dose of the vaccine. Four factors with $p < 0.15$ included being female (26.0% vs 8.8%, $p = 0.06$), concurrent thyroid diseases (71.4% vs 18.7%, $p < 0.01$), adenoviral vector vaccine (25.9% vs 13.3%, $p = 0.11$), and severe disease severity (32.5% vs 16.7%, $p = 0.04$). Concurrent thyroid disease, adenoviral vaccine, and severe disease severity were chosen to analyzed with the multivariable analysis. Concurrent thyroid disease (aRR = 2.78 $p < 0.01$) was an independent risk factor in this study (**Table 4**).

Discussion

There is an increase in evidence of adverse reactions after receiving a COVID-19 vaccine, including urticaria.[13,17] However, a lack of information on the adverse effects of COVID-19 vaccines in CU patients, may attribute to the hesitancy of getting vaccinated despite its importance. Previously, there was a report of two cases of well-controlled CSU that was aggravated after a Moderna vaccine.[14] The new onset of CU in those vaccinated for COVID-19 has also been reported.[18] However, our study found that approximately 15% of CU patients' condition exacerbated after a COVID-19 vaccine. Half of CU patients whose condition exacerbated after the first dose did not experience the same after the second dose. In fact, a slightly lower percentage of exacerbation happened after the second dose. This was similar to other cutaneous adverse events that occurred more frequently after the first dose.[17] Regarding patient-reported outcomes of disease activity using the UAS7 score, Susan D Mathias, et. al. previously reported minimal clinical important difference (MCID) of the UAS7 in a range of 9.5-10.5 points.[25] However, the MCID of the UAS7 was originally calculated from patients with clinical improvements, and did not include patients whose conditions worsened. The MCID of UAS7 in cases in which there was a clinical decline in the condition has not been previously explored. In our study, the mean change in UAS7 in cases where the condition worsened was 10.3 points. The mean change in UAS7 in patients who reported a 1-step change from the baseline to mild exacerbation was 4.67 points. Thus, the MCID of the UAS7 in patients who experienced a clinical decline in condition is important and requires a further study for clarification.

Very few patients in our study developed angioedema during worsening episodes and did not require immediate care. There were also no life-threatening episodes or anaphylaxis observed in this study. According to Chiang et al. and Alhumaid et al., both studies also reported a low incidence of anaphylaxis-related events after COVID-19 vaccines.[19,20]

The main pathophysiology for CU was mast cell activation.[1] Muntean et al. reported cases in which CU was exacerbated after COVID-19 infection, which was likely caused by the release of pro-inflammatory cytokines and mast cell involvement in COVID-19 pathogenesis.[21,22] Referring to the Centers for Disease Control and Prevention (CDC), the immediate allergic reactions were defined as symptoms, including wheal, wheezing and hypotension within four hours after exposure to the vaccine.[23] In our study, patients reported onset of exacerbation from one to 240 hours after vaccination. Thus, both immunoglobulin (Ig)E and non-IgE mediated mechanisms might play role in disease exacerbation in CU patients. However, the pathophysiology of disease exacerbation after a COVID-19 vaccine is still unclear. These gaps in knowledge require further studies.

For predicting factors associated with the exacerbation, we chose three variables with p-value < 0.15 (concurrent thyroid disease, adenoviral vector vaccine, and severe disease severity) for multivariable analysis. Only concurrent thyroid diseases were associated with disease triggers. In a previous report, the mean thyroid-stimulating hormone level was significantly higher in patients who had relapsed CSU compared to the CSU control group after BNT162b2 mRNA vaccination (p = 0.01). Other reported factors associated with CSU relapse were a positive autologous serum skin test result, basopenia, and allergic comorbidities.[24] On the contrary, allergic comorbidities were not associated with disease exacerbation in our study. How these factors can contribute to the exacerbation of chronic urticaria remains unknown.

Our data was limited to viral-vector-based and inactivated vaccines, which were the main source of COVID-19 vaccines in Thailand in 2021. All participants received the same type of the first and second dose of vaccination because there was no recommendation of cross-vaccination regimen during performing this study. Lastly, the third dose of the vaccination was recorded in 50 patients. The type of third dose was mostly reported in mRNA-based vaccines (68%) following by adenoviral vaccine (18%), inactivated vaccine (14%) and was different from the type of first and second dose. The results revealed that 6 patients (12%) reported exacerbation of wheals without angioedema after the third dose. Among 6 patients, 4 patients (66.7%) had the previous history of the exacerbation of urticaria in the first and/or second dose of vaccinations. In the third dose, the mRNA-based vaccines were mostly reported in 66.7% of patients with exacerbation, following by adenoviral vaccine (16.7%), inactivated vaccine (16.7%). Moreover, the majority of patients who received COVID-19 vaccines had low disease activity of urticaria (complete control of symptoms, minimal and mild disease activity). Some patients with active disease who were on many immunosuppressive drugs had delayed vaccination during the early periods of the research. Therefore, the information of severe cases was limited.

We recommend that patients with CU get vaccinated for COVID-19 because there is only a slight chance of disease flare-up, and most cases are manageable. However, a discussion about the risks and benefits with patients before vaccination is still needed.[26]

Conclusion

Approximately 15% of patients with CU reported an exacerbation of disease activity after the COVID-19 vaccine. No case of anaphylaxis was observed. Almost all patients' conditions resolved spontaneously without further intervention. Therefore, patients with CU should be recommended to get vaccinated for COVID-19 after a discussion of the risk of disease flare-up.

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Conflict of interest declaration

All authors declare no conflicts of interest.

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Author contributions

- PT, KK, LC, CR, and BP designed the study.
- PT, KK, LC, CR, BP, and OP collected data.
- BP performed the analysis and interpretation the data.
- PT, KK, CR, and BP involved in drafting the manuscript.
- PT and KK intellectually revised the manuscript.
- All the authors reviewed and approved for the final manuscript.

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