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Original Article

Exacerbation of Chronic Spontaneous Urticaria Following Coronavirus Disease 2019 (COVID-19) Vaccination in Omalizumab-Treated Patients

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What is already known about this topic? Urticarial rash is a common cutaneous adverse reaction after COVID-19 vaccination. However, the impact of vaccination on preexisting chronic spontaneous urticaria (CSU) is largely unknown.

What does this article add to our knowledge? Approximately 15% of patients with well-controlled CSU experienced a flare after COVID-19 vaccination. The presence of urticaria (vs none) before vaccination and the development of systemic reactogenicity were associated with a higher risk for exacerbation.

How does this study impact current management guidelines? Additional attention is required in the management of patients with CSU during COVID-19 vaccination.

BACKGROUND: The rapid development and rollout of vaccines against coronavirus disease 2019 (COVID-19) has led to more than half of the world's population being vaccinated to date. Real-world data have reported various adverse cutaneous reactions, including delayed-onset urticaria, which was highly ranked as a common manifestation across studies. However, the impact of these novel mRNA or viral vector COVID-19 vaccines on preexisting chronic spontaneous urticaria (CSU) remains largely unknown.

OBJECTIVE: To investigate the impact of COVID-19 vaccination on the clinical status of patients with relatively stable CSU who are undergoing omalizumab treatment and to identify risk factors for exacerbation.

METHODS: We conducted a questionnaire-based cross-sectional study in a tertiary hospital. Adult patients with relatively stable CSU under regular omalizumab treatments who had received at least one COVID-19 vaccination were included.

RESULTS: There were 105 study subjects who received 230 COVID-19 vaccinations between March and December 2021. Fifteen patients (14.3%) experienced aggravation of urticaria at least once after COVID-19 vaccination. The demographics and clinical characteristics of the patients were comparable regardless of the exacerbation of CSU. However, case-level analysis revealed that the presence of urticaria (vs none) before vaccination (odds ratio [OR] = 4.99; 95% CI, 1.57-15.82) and the development of systemic reactogenicity (OR = 4.57; 95% CI, 1.62-12.90) were associated with a higher risk for exacerbation.

CONCLUSIONS: The novel COVID-19 vaccination induced exacerbation in more than one-tenth of patients with well-controlled CSU. The establishment of a proper management strategy during COVID-19 vaccination is necessary for patients with CSU. © **2023 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;■:■-■)**

key words: COVID-19 vaccines; Chronic spontaneous urticaria; Exacerbation; Risk factors

INTRODUCTION

The rapid development and rollout of vaccines against coronavirus disease 2019 (COVID-19) have led to more than half of the world's population being vaccinated.[1] As of March 2022, approximately 85% of the Korean population had completed the vaccination. Despite the clinical benefits of vaccines, such as the prevention of infection and mitigation of infection severity, unexpected adverse reactions have been reported during mass vaccination.[2,3] Although the benefits of the vaccine outweigh the risks, continuous reports of adverse reactions caused by vaccine may cause hesitancy in the general population and individuals with chronic diseases to receive vaccination.[4,5]

Real-world data have elucidated various cutaneous adverse reactions, including delayed-onset urticaria, which was highly

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Abbreviations used
COVID-19- Coronavirus disease 2019
CSU- Chronic spontaneous urticaria
H1RA- Histamine 1 receptor antagonist
NSAIDs- Nonsteroidal anti-inflammatory drugs

ranked as a common manifestation across studies.[6-8] A recent meta-analysis reported that the overall incidence of urticaria after COVID-19 vaccination was approximately 1.1%.[9] Although most urticaria cases resolve within a week of medical treatment, some patients progressed to chronic urticaria that required continuous treatment with histamine 1 receptor antagonist (H1RA) or even omalizumab.[10-13] The incidence of chronic spontaneous urticaria (CSU) after COVID-19 booster vaccination was approximately 20/100,000 in Switzerland.[14] However, the impact of these novel COVID-19 mRNA or viral vector vaccines on preexisting CSU remains largely unknown. Currently, only one study has characterized the impact of COVID-19 mRNA vaccines on patients with CSU, showing that 13.8% experienced exacerbation after vaccination.[15] Bermingham and colleagues[16] estimated that approximately four million patients with CSU in middle-income countries would experience postvaccination flares if the incidence of exacerbation were 10%. This can lead to a substantial burden of disease for patients and physicians alike.

CSU is a heterogeneous disease in terms of pathophysiology and clinical characteristics, with variable activity levels depending on internal and external factors.[17] The heterogeneity of the underlying pathologic mechanisms also contributes to different reactions within the same medical conditions, such as pregnancy and even COVID-19 infection.[18] The goal of CSU management is to achieve complete control of symptoms with regular medication. At present, omalizumab is the only biological agent available for H1RA-refractory CSU, and its continuation is recommended during COVID-19 vaccination.[19] Although omalizumab is not considered to decrease the efficacy of vaccination, data on the impact of COVID-19 vaccines on omalizumab treatment are scarce.[15,20]

Estimation of the vaccine-related exacerbation of CSU and identification of risk factors are important to eliminate unnecessary vaccination hesitancy and prevent exacerbation with proper management of the risks. The waxing and waning nature of CSU makes it challenging to determine whether the exacerbation is coincidental or induced by vaccination. In this report, our objectives were to investigate the impact of COVID-19 vaccination on patients with stable CSU controlled by regular omalizumab treatment and to identify the risk factors for exacerbations.

MATERIALS AND METHODS

Study design

We conducted a questionnaire-based cross-sectional study in a tertiary hospital from December 2021 to February 2022. Patients visiting the outpatient allergy clinic regularly for omalizumab treatment were consecutively enrolled in the study when they were eligible and agreed to participate. Enrolled participants completed a questionnaire that gathered information on CSU status before vaccination, details of the vaccination received, and any manifestation experienced after vaccination. The study was approved by the Institutional Review Board of Asan Medical Center (Institutional Review Board No. 2021-1687); we obtained written informed consent from all participants.

Study population

The study population included patients with a diagnosis of CSU who (1) were aged 18 to 80 years, (2) were regularly treated with omalizumab, (3) had received at least one dose of COVID-19 vaccination between March and December of 2021 during the omalizumab treatment, and (4) had no or mild (present but not annoying or troublesome) CSU at the time of COVID-19 vaccination. Chronic spontaneous urticaria was diagnosed when spontaneous wheals or angioedema lasted for more than 6 weeks.[17]

Add-on medications to omalizumab were allowed when they were administered regularly with no changes in dosage. Patients with a history of COVID-19 infection were excluded. To minimize confusion between uncontrolled urticaria and vaccine-induced aggravation, patients with uncontrolled urticaria (classified by patients as moderate [troublesome but does not interfere with normal daily activity or sleep] or severe [troublesome to interfere with normal daily activity or sleep]) despite omalizumab treatment were excluded.

Collected data

We collected demographic data, including age, sex, body mass index, smoking history, and comorbidities. We also recorded a history of influenza vaccination and related adverse reactions to assess the difference between traditional and novel vaccines. Urticaria characteristics, such as disease duration, the presence of combined angioedema or dermographism, aggravating factors, and medication use, were documented. Information pertaining to omalizumab treatment, including the duration of treatment, injection interval, and total accumulated doses before the first COVID-19 vaccine, were collected. Because most of the Korean population had received the second dose of COVID-19 vaccination by December 2021, information regarding each vaccine dose was requested separately. The control state of urticaria before and after vaccination was evaluated by patients' response to the question "How would you rate the severity of urticaria before and after the COVID-19 vaccination?" The questionnaire used a four-point Likert scale with the following options: (1) none (asymptomatic), (2) mild (present but not troublesome), (3) moderate (troublesome but does not interfere with normal daily activity or sleep), and (4) severe (troublesome to interfere with normal daily activity or sleep).[18] Patients were also asked to indicate the type of vaccine administered, any adverse reactions, cutaneous manifestations other than urticaria, and systemic reactogenicity after vaccination. Systemic reactogenicity included fever, chills, fatigue, myalgia, arthralgia, diarrhea, and headache, which could be considered physiologic immune reactions. The severity of these symptoms was classified from grades 1 to 4, in which grade 1 was mild (does not interfere with activity), grade 2 was moderate (interferes with activity), grade 3 was severe (prevents daily activity), and grade 4 was potentially life-threatening (requiring an emergency department visit or hospitalization).[21] In addition, we obtained information on the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) after vaccination to check whether NSAIDs aggravated urticaria in individuals with NSAID hypersensitivity. For patients who experienced exacerbation of urticaria, information regarding the time of onset, details of aggravated manifestations, and additional medications for symptomatic relief were collected. Acute- or delayed-onset urticaria was defined based

TABLE I. Baseline characteristics of participants according to exacerbation of urticaria

Clinical variables	All participants (n = 105)	No exacerbation (n = 90)	Exacerbation (n = 15)	*P*
Age, y	43.14 ± 13.31	43.11 ± 13.69	43.33 ± 12.20	.953
Women (%)	62 (59.0)	54 (60.0)	8 (53.3)	.662
Body mass index, kg/m^2	23.57 ± 3.24	23.33 ± 3.22	24.96 ± 3.10	.072
Smoking history				.297
Ever smoker (%)	24 (22.9)	19 (21.1)	5 (33.3)	
Never smoker (%)	81 (77.1)	71 (78.9)	10 (66.7)	
Comorbidities				
Allergic rhinitis (%)	17 (16.2)	15 (16.7)	2 (13.3)	.746
Hypertension (%)	6 (5.7)	4 (4.4)	2 (13.3)	.170
Diabetes mellitus (%)	5 (4.8)	3 (3.3)	2 (13.3)	.092
None (%)	65 (61.9)	55 (61.1)	10 (66.7)	.682
History of influenza vaccination (%)	85 (81.0)	73 (81.1)	12 (80.0)	.919
History of drug adverse reaction (%)	22 (21.0)	21 (23.3)	1 (6.7)	.142
History of chronic spontaneous urticaria				
Duration of symptom, mo	65.58 ± 68.87	68.54 ± 69.80	47.80 ± 62.22	.282
Presence of angioedema (%)	36 (34.3)	30 (33.3)	6 (40.0)	.614
Presence of dermographism (%)	34 (32.4)	27 (30.0)	7 (46.7)	.202
Presence of aggravating factors (%)	47 (44.8)	43 (47.8)	4 (26.7)	.128
Treatment with omalizumab				
Duration of treatment, mo	14.99 ± 15.16	15.02 ± 15.83	14.80 ± 10.76	.958
Total doses of administration, vials	11.00 ± 10.00	10.62 ± 9.49	13.33 ± 12.77	.333
Interval of omalizumab, wk	5.15 ± 1.85	5.26 ± 1.91	4.53 ± 1.41	.164
Omalizumab only (%)	72 (68.6)	61 (67.8)	11 (73.3)	.768
Omalizumab plus standard H1RA (%)	13 (12.4)	12 (13.3)	1 (6.7)	
Omalizumab plus up-dosed H1RA (%)	20 (19.0)	17 (18.9)	3 (20)	
Total IgE, kU/L	302.40 ± 391.55	306.54 ± 415.83	276.89 ± 190.67	.809
Absolute eosinophil count, cells/μL	167.53 ± 231.46	159.48 ± 233.12	219.55 ± 222.07	.387
Absolute basophil count, cells/μL	31.74 ± 20.27	32.22 ± 20.35	28.62 ± 20.26	.554
Presence of antinuclear antibody (%) (n = 41)	3 (7.3)	2 (5.6)	1 (20.0)	.245

H1RA, histamine 1 receptor antagonist.

on whether symptoms began within or after 1 hour from the vaccination, respectively. Any changes in maintenance medication after vaccination were collected from medical records. Data from laboratory tests were included when available before omalizumab therapy began.

Statistical analysis

Data are summarized as mean ± SD for continuous variables and frequencies (percentage) for categorical variables. Student *t* or χ^2 test was used for comparisons between groups. We also performed univariate and multivariate logistic regression analyses to examine risk factors for CSU exacerbation. All statistical analyses were performed using SPSS software (version 22.0, IBM Corporation, Armonk, NY). *P* less than .05 was considered statistically significant.

RESULTS

Characteristics of participants

Among 255 patients who were treated with omalizumab at least once from December 2021 to February 2022, 107 participated in the study. We excluded two patients (the first had a reduced scheduled dose of omalizumab from two vials to one before vaccination, and the other visited the clinic beyond schedule) because the reason for aggravation could not be determined. As a result, 105 patients and 230 vaccination cases (2.19 ± 0.52 vaccinations per individual) were finally included.

Table I lists participants' baseline characteristics. Mean age was 43.14 years and 59.0% of participants were women. Among the 105 patients with CSU, 85 had received influenza vaccination (81.0%) and only one patient experienced delayed rash after vaccination. Approximately one-fifth of participants (22 of 105; 21.0%) had a history of drug-related adverse reactions. Mean duration of CSU was 65.58 ± 68.87 months. Approximately one-third of patients reported coexisting angioedema (36 of 105; 34.3%) and dermographism (34 of 105; 32.4%). Mean duration of omalizumab treatment was 14.99 months; 11 vials were administered before the first COVID-19 vaccination. Mean interval between omalizumab treatments was 5.15 ± 1.85 weeks. We noted that 31.4% of participants (33 of 105) were receiving regular H1RA treatment in addition to omalizumab. At the time of the first vaccination, 45 patients had mild CSU(42.9%), whereas 60 did not have symptomatic CSU (57.1%).

Comparison of characteristics according to exacerbation

Among the 105 participants, 15 experienced a CSU exacerbation at least once after COVID-19 vaccination (14.3%). A comparison of baseline characteristics of participants according to the history of exacerbation showed that demographic factors, comorbidities, history of CSU, and omalizumab treatment (total dose and interval) were comparable irrespective of exacerbation

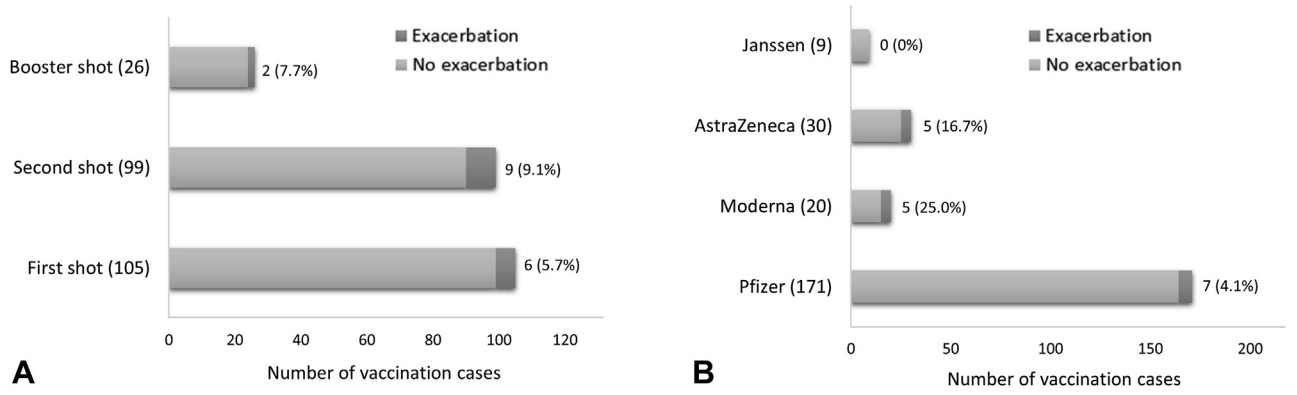

FIGURE 1. Proportion of cases of exacerbation according to (A) order and (B) type of vaccination.

of urticaria (Table I). The proportion of patients with mild CSU was also comparable between groups. Laboratory data, including total IgE level, eosinophil and basophil counts, and positive antinuclear antibody frequency, showed no significant differences between groups. No factor was related to CSU exacerbation in the univariate analysis (data not shown).

Clinical characteristics of cases of exacerbation

Of the 230 vaccinated patients, the proportions of CSU exacerbations were 5.7% (six of 105), 9.1% (nine of 99), and 7.7% (two of 26) after the first, second, and booster vaccines, respectively. Based on the type of vaccine, 4.1% (seven of 171), 16.7% (five of 30), 25.0% (five of 20), and 0% (none of 9) of the Pfizer (New York, NY), AstraZeneca (Cambridge, UK), Moderna (Cambridge, MA), and Janssen (Beerse, Belgium) vaccines, respectively, were associated with CSU exacerbations (Figure 1). No participants reported a nonurticarial rash. Of the 15 patients who experienced an exacerbation of urticaria after vaccination, two experienced repeated exacerbations. Table II lists the clinical characteristics of 17 exacerbated cases. For the 17 patients, the severity of CSU at vaccination was mild in 13 (76.5%), whereas four were asymptomatic before vaccination (23.5%). After vaccination, the severity became mild, moderate, and severe in one (5.9%), 10 (58.8%), and six (35.3%) patients, respectively. In approximately 70% of patients, CSU was exacerbated after the first vaccination. Symptoms included larger and increased numbers of wheals with increasing frequency along with exacerbated pruritus. Angioedema occurred only in two patients. To relieve flared urticaria, additional H1RA was used in seven patients (41.2%), whereas both H1RA and systemic corticosteroids were used in six (35.3%). Six patients (35.3) did not experience systemic reactogenicity, whereas two (11.8%), seven (41.2%), and two (11.8%) patients showed mild, moderate, and severe systemic reactogenicity, respectively. Table III lists details, including patient information, management of exacerbated symptoms, recurrence with consecutive vaccination, and systemic symptoms of exacerbated cases. Two patients (nos. 14 and 15) experienced repeated exacerbation of CSU, whose onset time was less than 1 hour after the first and second shot in common. One patient (no. 14) had dyspnea in addition to urticaria, suggesting anaphylaxis. The remaining patients experienced a CSU exacerbation only once, and the onset time was greater than 1 hour after vaccination. Regarding the treatment of exacerbated symptoms, only two patients managed the symptoms themselves without intervention.

TABLE II. Characteristics of 17 exacerbated cases

Clinical variables	n (%)
Severity of chronic spontaneous urticaria before vaccination	
None	4 (23.5)
Medium	13 (76.5)
Severity of chronic spontaneous urticaria after vaccination	
Mild	1 (5.9)
Moderate	10 (58.8)
Severe	6 (35.3)
Order of vaccination	
First	6 (35.3)
Second	9 (52.9)
Booster shot	2 (11.8)
History of exposure to vaccination	
First exposure	12 (70.6)
Second exposure	5 (29.4)
Type of vaccination	
AstraZeneca	5 (29.4)
Pfizer	7 (41.2)
Moderna	5 (29.4)
Change in urticaria	
Larger-sized and more wheals	14 (82.4)
Increased frequency of urticaria	12 (70.6)
Exacerbated pruritus	13 (76.5)
Exacerbated angioedema	2 (11.8)
Systemic reactogenicity	
None	6 (35.3)
Grade 1 (mild)	2 (11.8)
Grade 2 (moderate)	7 (41.2)
Grade 3 (severe)	2 (11.8)
Grade 4 (potentially life-threatening)	0

To treat exacerbated urticaria, additional H1RA was prescribed in 11 patients, and systemic corticosteroids in five. Four patients visited the clinic before the scheduled time because of uncontrolled symptoms. Among the 15 patients with CSU exacerbation, 11 received controller medication changes by increasing the H1RA dose or reducing the time interval between omalizumab injections. Among the 13 patients with delayed-onset urticaria, five received the next vaccination shot and none experienced

TABLE III. Detailed characteristics of 15 patients with exacerbated urticaria

Patient no.	Age/sex	Change in severity	Shots	Administered vaccine	Onset time of urticaria	Treatment	Change in controller medication	Recurrence
1	56/M	Mild → severe	First	Pfizer	1 d	Early visit H1RA	Reduce interval of omalizumab	No (Pfizer)
2	40/F	Mild → moderate	First	AstraZeneca	5 h	H1RA	Add H1RA	No (Pfizer)
3	24/M	None → mild	First	Moderna	3 h	Observation	No	No (Moderna)
4	43/F	None → moderate	First	AstraZeneca	1 wk	H1RA	Add H1RA	No (Pfizer)
5	42/M	None → moderate	Second	Moderna (second use)	1 wk	Early visit	Reduce interval of omalizumab	Unknown
6	43/M	None → severe	Second	Moderna (second use)	6 h	Early visit	Reduce interval of omalizumab and add H1RA	Unknown
7	49/F	Mild → severe	Second	Pfizer (second use)	1 d	Observation	Add H1RA	Unknown
8	40/M	Mild → severe	Second	Moderna (first use)	3 wk	H1RA, SCS	Add H1RA	Unknown
9	35/F	Mild → moderate	Second	Pfizer (second use)	1 d	H1RA	Add H1RA	Unknown
10	39/M	Mild → moderate	Second	Pfizer (first use)	2 d	H1RA	No	Unknown
11	51/M	Mild → moderate	Second	Moderna (second use)	1 wk	H1RA, SCS	No	No (Moderna)
12	72/F	Mild → severe	Third	Pfizer (first use)	1 d	H1RA, SCS	No	—
13	46/F	Mild → moderate	Third	Pfizer (first use)	10 h	H1RA	Add H1RA	—
14	30/F	Mild → moderate	First	AstraZeneca	15 min	H1RA, SCS	No	No (Pfizer)
		Mild → moderate	Second	AstraZeneca	15 min	Early visit H1RA, SCS	Reduce interval of omalizumab	
15	40/F	Mild → moderate	First	AstraZeneca	30 min	H1RA, SCS	Add H1RA	Unknown
		Mild → severe	Second	Pfizer	20 min	H1RA	No	

H1RA, histamine 1 receptor antagonist; SCS, systemic corticosteroids.

TABLE IV. Comparison of cases according to exacerbation of urticaria

Clinical variables	No exacerbation (n = 213)	Exacerbation (n = 17)	*P*
Severity of chronic spontaneous urticaria before vaccination			.010
None (n = 133)	129 (55.9)	4 (23.5)	
Mild (n = 97)	84 (44.6)	13 (76.5)	
Order of vaccination			.652
First shot (n = 105)	99 (46.5)	6 (35.3)	
Second shot (n = 99)	90 (42.3)	9 (52.9)	
Booster shot (n = 26)	24 (11.3)	2 (11.8)	
Use of vaccines			.162
First exposure (n = 125)	113 (53.1)	12 (70.6)	
Reexposure (n = 105)	100 (47.0)	5 (29.4)	
Type of vaccine			.155
mRNA vaccine (n = 191)	179 (84.0)	12 (70.6)	
Viral vector vaccine (n = 39)	34 (16.0)	5 (29.4)	
Systemic reactogenicity			.002
Absence (n = 158)	152 (71.4)	6 (35.3)	
Presence (n = 72)	61 (28.6)	11 (64.7)	
Severity of systemic reactogenicity			.045
Grade 1 (mild) (n = 32)	30 (49.2)	2 (18.2)	
Grade 2 (moderate) (n = 40)	29 (50.8)	7 (81.8)	
Grade 3 (severe) (n = 4)	2 (3.3)	2 (18.2)	

aggravation of urticaria even after readministration of the identical vaccine. In two patients who experienced repeated acute exacerbation of urticaria, only one received the booster shot with a different vaccine, and no adverse reactions were observed.

Risk factors associated with exacerbation

We sought to identify risk factors for exacerbation of CSU by analyzing 230 vaccinated patients. First, we compared characteristics between 213 patients without CSU exacerbation and 17 with it (Table IV). A higher proportion of mild cases (vs none) before vaccination was observed (76.5% vs 44.6%; $P = .01$) among cases of CSU exacerbation. The order of vaccines administered and the history of exposure were similar between groups. The proportion of mRNA and viral vector vaccines was also comparable between groups. The presence of systemic reactogenicity (64.7% vs 28.6%; $P = .002$) was more common

TABLE V. Factors associated with exacerbation of urticaria

Clinical variables	Univariate		Multivariate	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Severity of chronic spontaneous urticaria before vaccination*				
None	Reference		Reference	
Mild	4.99 (1.57-15.82)	.006	4.14 (1.24-13.80)	.021
Order of vaccination				
First shot	Reference			
Second shot	1.65 (0.57-4.82)	.360		
Booster shot	1.38 (0.26-7.24)	.707		
Use of vaccines				
First exposure	Reference			
Reexposure	0.63 (0.22-1.76)	.376		
Type of vaccine				
mRNA vaccine	Reference			
Viral vector vaccine	2.19 (0.73-6.63)	.164		
Presence of systemic reactogenicity	4.57 (1.62-12.90)	.004		
Grade of systemic reactogenicity*				
Absence	Reference		Reference	
Grade 1 (mild)	1.69 (0.33-8.77)	.533	1.45 (0.27-7.69)	.663
Grade 2 (moderate)	6.12 (1.92-19.52)	.002	5.77 (1.76-18.92)	.004
Grade 3 (severe)	25.33 (3.03-211.68)	.003	13.17 (1.52-113.92)	.019

*Variables included in multivariable logistic regression.

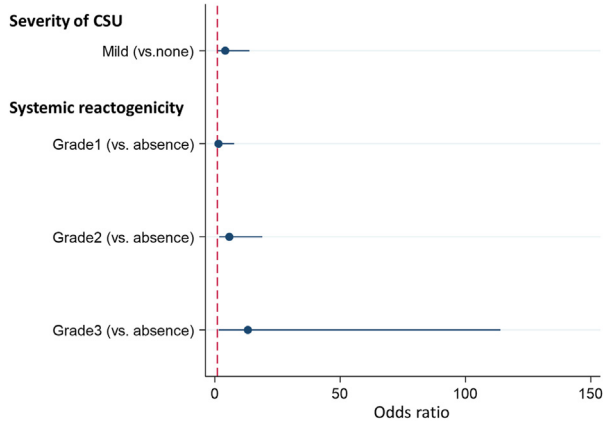

FIGURE 2. Risk factors related to exacerbation of chronic spontaneous urticaria (CSU).

in exacerbated cases. The severity of systemic reactogenicity was also significantly different. Severe cases were frequent among exacerbation cases ($P = .045$).

In univariate analysis, mild urticaria (vs none) (odds ratio [OR] = 4.99; 95% CI, 1.57-15.82) was significantly associated with the aggravation of CSU. The presence of systemic reactogenicity was associated with a higher risk for exacerbation (OR = 4.57; 95% CI, 1.62-12.90) with an increased OR according to severity, especially in moderate and severe cases (grade 1 OR = 1.69; 95% CI, 0.33-8.77; grade 2 OR = 6.12; 95% CI, 1.92-19.52); and grade 3 OR = 25.33; 95% CI, 3.03-211.68). In multivariate analyses considering possible interactions among variables, the presence of mild urticaria (vs none) before vaccination (OR = 4.14; 95% CI, 1.24-13.80) and the coexistence of moderate (OR = 5.77; 95% CI, 1.76-18.92) or severe (OR = 13.17; 95% CI, 1.52-113.92) systemic reactogenicity remained significantly associated with CSU exacerbation (Table V and Figure 2).

DISCUSSION

In this study, we uncovered the impact of COVID-19 vaccination on CSU activity. Among patients with stable CSU controlled by omalizumab, approximately 14% experienced exacerbation of CSU after vaccination. Notably, the presence of urticaria before vaccination, although not bothersome, and the development of vaccine-induced systemic reactogenicity were associated with an increased risk for CSU exacerbation. Moreover, patients with delayed-onset urticaria (1 hour or more) did not experience a recurrence of exacerbation, whereas patients with immediate-onset urticaria (less than 1 hour) experienced repeated exacerbation at the following vaccination dose. To our knowledge, this is the first study to evaluate the impact of COVID-19 vaccines based on mRNA and viral vector on stable CSU with omalizumab treatment and to determine clinical factors related to the exacerbation of CSU.

After the introduction of COVID-19 vaccines, real-world data were used for information about various cutaneous adverse reactions after vaccination.[22-24] McMahon et al[8] described 414 cases of cutaneous reactions after vaccination, in which urticaria was classified as the first and third manifestations in patients administered Pfizer and Moderna vaccines, respectively. A similar study conducted in Spain reported that urticaria was the second most common reaction after only local site reactions in participants vaccinated with Pfizer, Moderna, or AstraZeneca vaccines.[7] In an Italian cohort study, urticarial rash and angioedema were the most common cutaneous adverse reactions.[24] Most urticarial reactions reported from large databases were resolved with antihistamines within days to weeks.[7,8,24] However, clinicians have

begun to recognize the development of CSU triggered by vaccination requiring continuous medical treatment.[10-13]

Unexpected cutaneous reactions to the novel COVID-19 vaccines raised concerns regarding the impact of vaccination on preexisting dermatologic diseases.[23,25] In the context of CSU, Grieco et al[15] conducted a Web-based survey to assess the impact of COVID-19 mRNA vaccines on the disease course of CSU. Of the 160 participants (104 of whom were treated with omalizumab and 56 who were treated with antihistamines), 13 experienced urticaria aggravation after vaccination (8.13%; nine with Pfizer and four with Moderna vaccines). However, factors associated with the altered course of the disease were not further investigated. The weekly urticaria activity score (UAS7) was collected before and 3 days after vaccination to determine exacerbation, which hindered assessing the change afterward. Our face-to-face survey and medical record review enabled us to acquire information about various aspects of CSU and identify risk factors for exacerbation.

We have revealed two factors related to the exacerbation of the CSU. Compared with patients with fully controlled CSU with omalizumab treatment, those with symptomatic, albeit mild CSU were more likely to experience flares. This suggests that mast cells are not fully suppressed by omalizumab and are readily degranulated by immune reactions induced by vaccination.[26] In the study by Grieco et al,[15] a higher proportion of patients with CSU exacerbation was observed among those treated with H1RA compared with those treated with omalizumab (10 of 56 vs three of 104; $P < .001$). We inferred that this may be related to the less controlled status of urticaria in the H1RA-treated group, which was reflected by the higher UAS7 score before vaccination (13.7 in the H1RA group vs 2.52 in the omalizumab group). Therefore, proactive adjustment of medication, such as increasing H1RA to suppress urticaria fully, or vaccination during the asymptomatic period might be helpful in preventing CSU exacerbation.[14]

The presence of systemic reactogenicity was another factor related to the exacerbation of CSU. This finding provides indirect evidence about the mechanistic link between the vaccine-induced immune reaction and the CSU exacerbation. This is further supported by the gradually increased risk for exacerbation as well as the increased severity of systemic reactogenicity. Mechanistically, mRNA and viral vector vaccines induced immune reactions with a mechanism similar to that of a real viral infection.[27] When reviewing the literature assessing the impact of COVID-19 infection on patients with CSU, a study in Romania reported increased severity of urticaria during and after COVID-19 in 44% of patients with CSU and a positive correlation between the severity of COVID-19 and symptoms of CSU.[28] Consistent with this, a multicenter study reported that COVID-19 infection resulted in CSU exacerbation in one-third of patients, with a higher proportion in those with severe COVID-19.[29] Recruitment and degranulation of mast cells during COVID-19 infection were demonstrated in postmortem lung biopsies of patients with COVID-19 and animal models.[30,31] Intriguingly, all patients with CSU exacerbation in the current study experienced neither adverse reactions to conventional influenza vaccines nor exacerbated urticaria during viral infections such as upper respiratory infection. This suggests distinct characteristics of novel vaccines or SARS-CoV-2 itself.

No patients with CSU exacerbation with delayed urticaria experienced recurrence of the exacerbation. Therefore, exacerbated urticaria may not always be a risk factor for allergic reactions in the next shot, especially when the onset is longer than 1 hour and/or the duration is longer than 1 day.[32] This finding is important to guide patients with vaccine hesitancy properly after exacerbation of urticaria during the previous dose. However, caution is still required for patients with immediate urticaria irrespective of progression to chronic urticaria. Considering that a single omalizumab vial contains 0.5 mg of polysorbate 20, patients regularly receiving omalizumab are less likely to be allergic to polysorbate 80 or polyethylene glycol, which are ingredients in the mRNA and viral vector COVID-19 vaccines.[32] For omalizumab users, other components may have a role as allergens.[33]

There are several limitations to this study. First, we did not use a validated tool, such as UAS7 or the urticaria control test, to assess the activity or response to CSU treatment. Instead, we used simple questionnaires for participants to recall the status of CSU easily before and after each vaccination was administered. We also evaluated the changes in medication to assess the effect of CSU exacerbation objectively. Second, we did not assess the possible involvement of autoimmunity in all participants by performing an autologous serum skin test or measuring functional autoantibodies. Among the 105 patients, antinuclear antibody was evaluated in only 41 patients. Thus, the involvement of autoimmunity in the exacerbation of urticaria was difficult to determine, which may occur considering the molecular mimicry between the spike protein of SARS-CoV-2 and the human proteome.[34] Third, the duration of exacerbated urticaria was not evaluated, which could implicate the underlying mechanism, particularly with respect to IgE participation. Fourth, only limited patients were reexposed to the following vaccination dose after an exacerbation. Finally, the causal relationship between vaccination and exacerbated urticaria remains unclear. To minimize the possibility of naturally exacerbated CSU, we included only patients with stable urticaria who were under regular omalizumab treatment. Furthermore, the incidence of exacerbated urticaria in patients with CSU is much higher than that of any cutaneous adverse reactions in the general population.[24] Despite several limitations, our study provided real-world data that comprehensively evaluated the effect of COVID-19 vaccination on CSU.

Of the 105 participants, 15 (14.3%) experienced exacerbation of urticaria, and physicians changed the regular medical treatment in 11 patients afterward (10.5%). We have demonstrated the nonnegligible impact of COVID-19 vaccines in well-controlled patients with CSU treated with omalizumab. Notably, we observed no recurrence of exacerbation in patients with delayed urticaria. By actively managing symptomatic urticaria before vaccination and informing patients about the low recurrence rate, we may be able to facilitate the safe completion of the vaccination program for patients with CSU. As more nonviral vaccines are expected to be developed against various medical conditions, the establishment of an effective management strategy using these agents for patients with CSU may be required.

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