Urticaria exacerbations and adverse reactions in patients with chronic urticaria receiving COVID-19 vaccination: Results of the UCARE COVAC-CU study

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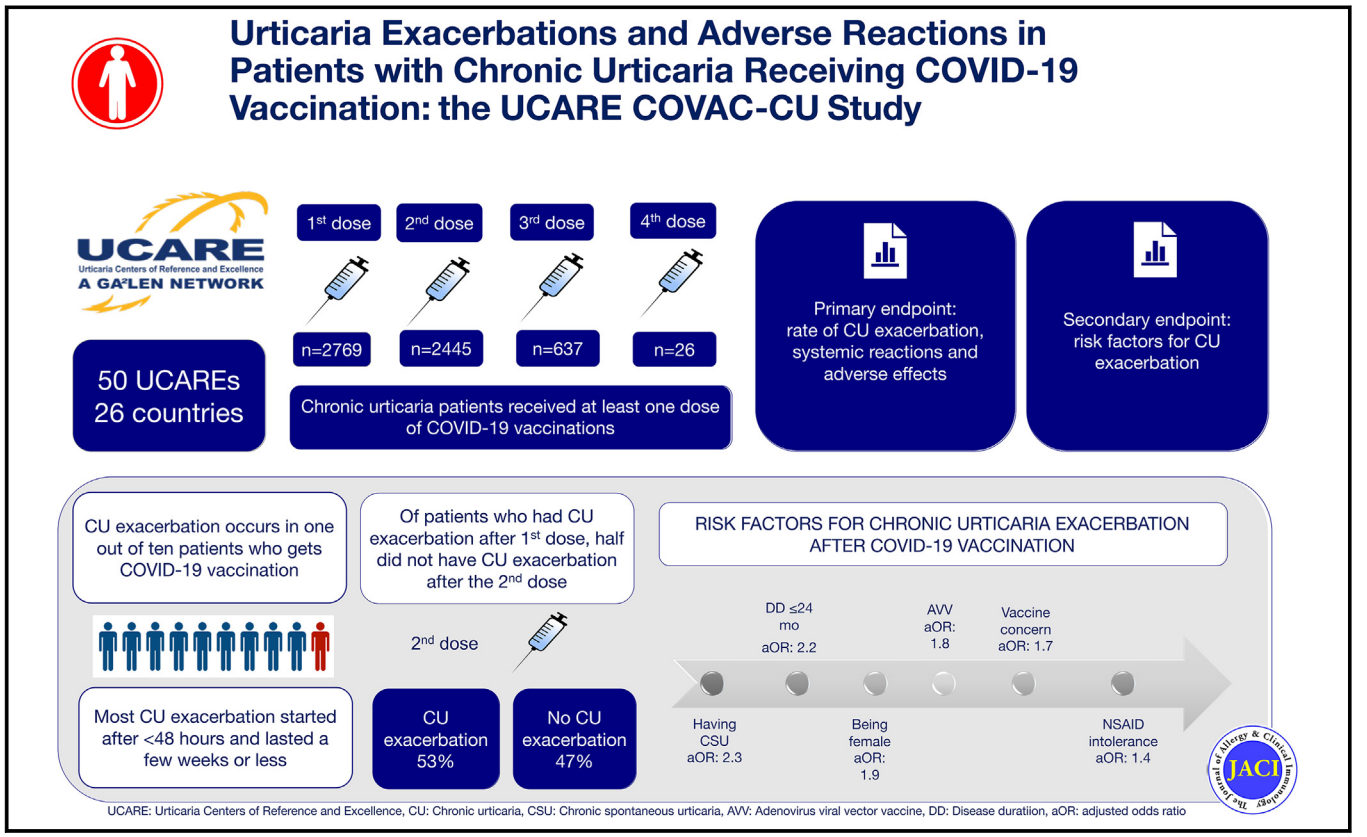
GRAPHICAL ABSTRACT



Background: Concern about disease exacerbations and fear of reactions after coronavirus disease 2019 (COVID-19) vaccinations are common in chronic urticaria (CU) patients and may lead to vaccine hesitancy.

Objective: We assessed the frequency and risk factors of CU exacerbation and adverse reactions in CU patients after COVID-19 vaccination.

Methods: COVAC-CU is an international multicenter study of Urticaria Centers of Reference and Excellence (UCAREs) that retrospectively evaluated the effects of COVID-19 vaccination in CU patients aged ≥18 years and vaccinated with ≥1 dose of any COVID-19 vaccine. We evaluated CU exacerbations and severe allergic reactions as well as other adverse events associated with COVID-19 vaccinations and their association with various CU parameters.

Results: Across 2769 COVID-19–vaccinated CU patients, most (90%) received at least 2 COVID-19 vaccine doses, and most patients received CU treatment and had well-controlled disease. The rate of COVID-19 vaccination–induced CU exacerbation was 9%. Of 223 patients with CU exacerbation after the first

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dose, 53.4% experienced recurrence of CU exacerbation after the second dose. CU exacerbation most often started <48 hours after vaccination (59.2%), lasted for a few weeks or less (70%), and was treated mainly with antihistamines (70.3%). Factors that increased the risk for COVID-19 vaccination–induced CU exacerbation included female sex, disease duration shorter than 24 months, having chronic spontaneous versus inducible urticaria, receipt of adenovirus viral vector vaccine, having nonsteroidal anti-inflammatory drug/aspirin intolerance, and having concerns about getting vaccinated; receiving omalizumab treatment and Latino/Hispanic ethnicity lowered the risk. First-dose vaccine–related adverse effects, most commonly local reactions, fever, fatigue, and muscle pain, were reported by 43.5% of CU patients. Seven patients reported severe allergic reactions.

Conclusions: COVID-19 vaccination leads to disease exacerbation in only a small number of CU patients and is generally well tolerated. (J Allergy Clin Immunol 2023;152:1095-106.)

Key words: *Adverse effects, COVID-19, exacerbation, omalizumab, real life, treatment, urticaria, vaccination, vaccine, worsening*

Abbreviations used

AE: Adverse event
aOR: Adjusted odds ratio
ASST: Autologous serum skin test
AVV: Spike protein DNA carried by adenoviruses
CI: Confidence interval
CIndU: Chronic inducible urticaria
COVID-19: Coronavirus disease 2019
CsA: Cyclosporine A
CSU: Chronic spontaneous urticaria
CU: Chronic urticaria
GCS: Glucocorticosteroids
IVV: Whole inactivated SARS-CoV-2
mRNA: Spike protein mRNA carried by lipidic microparticles
NSAID: Nonsteroidal anti-inflammatory drug
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
UCARE: Urticaria Center of Reference and Excellence

Chronic urticaria (CU) is a systemic inflammatory disease that manifests with wheals and/or angioedema for longer than 6 weeks; mast cells are the main effector cells.[1] In most cases of chronic spontaneous urticaria (CSU), skin mast cell activation is presumed to be due to autoantibodies, IgE in autoallergic, and IgG or IgM in autoimmune CSU, the 2 established mechanisms.[2]

Many patients with CU, especially those with CSU, experience exacerbations of the disease. In many cases, the trigger for exacerbations is unknown, but in others, triggers such as stress, medications like nonsteroidal anti-inflammatory drugs (NSAIDs), or a viral infection can be identified.[3] The recent Urticaria Center for Reference and Excellence (UCARE)[4] COVID-CU study, for example, found that coronavirus disease

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2019 (COVID-19) causes CU exacerbation in almost 40% of the patients, with higher rates in patients with severe COVID-19.[5]

Exacerbation of CSU can also be triggered by antiviral vaccines, and additionally vaccinations can induce new-onset urticaria. As of now, little is known about how often this happens, and the underlying mechanisms remain ill characterized.[6,7] Although there are several case reports and small studies on post–COVID-19 vaccination new-onset urticaria,[8-14] little information exists on the characteristics of COVID-19 vaccine–induced exacerbations of already existing CU[15,16] or on specific features of CU patients who are at increased risk for postvaccination disease exacerbation.

This lack of information may lead to vaccine hesitancy. Respondents from the Massachusetts General Hospital Vaccine Allergy Registry, who experienced urticaria after COVID-19 vaccination, reported that they would be unlikely to receive future recommended COVID-19 vaccine doses,[17] even though the risk of recurrent urticaria with subsequent doses has been reported to be very low.[18] Also, self-reported allergic symptoms after mRNA (spike protein mRNA carried by lipidic microparticles) COVID-19 vaccination were associated with a 5-fold increase in incomplete vaccination, while most individuals with self-reported allergic symptoms safely completed the vaccination series.[19]

The need for information from real-life studies in large population of patients prompted us to investigate the rates and risk factors for CU exacerbation and the frequency of adverse reactions, including allergic reactions in CU patients vaccinated against COVID-19 in a worldwide, large, and diverse patient population.

METHODS

Study design

COVAC-CU was an international, multicenter, observational (noninterventional) UCARE study that included CU patients treated at member centers of the UCARE network. The study encompassed the period August 2021 through March 2022. An ambispective cohort study design was used. The prospective part of the study included delivering questionnaires to CU patients treated at participating UCAREs at any time during the study period who had recently been vaccinated against COVID-19. The retrospective part explored the responses to COVID-19 vaccinations and also included laboratory data from patient charts. Ethics approval was obtained by the coordinating UCARE, Koc University Hospital (July 28, 2021, 2021.308.IRB1.138), and by each participating UCARE as required. Written informed consent was obtained from all participants before enrollment. Inclusion criteria were as follows: adults aged ≥18 years with CSU, chronic inducible urticaria (CIndU), or both; and vaccinated with ≥1 dose of any COVID-19 vaccine.

Additional materials and methods are provided in the Methods section of this article's Online Repository available at www.jacionline.org.

COVAC-CU questionnaire

The questionnaire included 43 questions and comprised 3 parts: (1) demographic data, laboratory data, and clinical history (23 questions), (2) questions on COVID-19 vaccine (13 questions), and (3) questions on COVID-19 vaccine reactions, including urticaria exacerbation and severe allergic reactions, ie, anaphylaxis (7 questions) (see Table E1 in the Online Repository available at www.jacionline.org).

Patients completed the questionnaires in face-to-face interviews, by telephone, or via email. Study data were collected and managed using the REDCap electronic data capture tools hosted at Yale University.[20,21] Further information on the questionnaire is provided in the Methods section of the Online Repository.

Data analysis

The statistical analysis was performed by SPSS v28.0 (IBM, Armonk, NY). Descriptive statistics such as mean, standard deviation, and frequency were used to analyze the data. Inferential statistics, such as bivariate and multivariable analyses, were used to determine the risk factors for CU exacerbation.

The variables that were used to determine risk factors in the bivariate analysis are presented in Table E2 in the Online Repository available at www.jacionline.org. All variables were included in the bivariate analysis; afterward, the variables with the most important clinical value were included in the initial multivariable analysis model using exacerbation as the dependent variable, and a backward stepwise model was used to select the final model that was interpreted. The multivariable analysis was applied for CU exacerbation related to the first dose of vaccination. Further details of the data analysis are available in the Methods section in the Online Repository.

RESULTS

Study participants and COVID-19 vaccinations received

The COVAC-CU questionnaire was distributed to COVID-19-vaccinated CU patients treated at 50 UCAREs in 26 countries (see Table E3 in the Online Repository available at www.jacionline.org). The study analyzed a total of 2769 CU patients; 70.9% had CSU, 12.2% had CIndU, and 16.9% had both. The median age of patients was 43.7 years (range, 18-91 years), and 71.7% were female (Table I). Comorbidities and laboratory values are shown in Tables E4 and E5 available in the Online Repository.

Most CU patients (90%) received at least 2 COVID-19 vaccine doses; the most commonly delivered vaccine was Pfizer-BioNTech (BNT162b2), followed by Oxford/AstraZeneca (see Table E6 in the Online Repository available at www.jacionline.org).

Treatments for CU and level of CU control before COVID-19 vaccination

Complete CU control before the first through fourth vaccinations ranged from 54.8% to 61.5%, respectively, with most patients receiving urticaria treatment (84.2% to 100%) before all vaccine doses (see Table E7 in the Online Repository available at www.jacionline.org).

CU treatments while receiving the first dose of COVID-19 vaccine were second-generation antihistamines (n = 1707; 61.7%), omalizumab (n = 924, 33.4%), cyclosporine A (CsA) (n = 40, 1.4%), and glucocorticosteroids (GCS) (n = 78, 2.8%) (Table E7). The average time between omalizumab injection and COVID-19 vaccine was 8 to 14 days. The time interval between omalizumab injection and vaccinations as well as the

TABLE I. Patient demographics and clinical characteristics and total CU exacerbation rates

Characteristic	Total (n = 2769)	CU-exa (n = 456)
Sex		
Female	1984 (71.7)	356 (78.1)
Male	785 (28.3)	95 (20.8)
Age (years), median (range)	43.7 (18-91)	42.51 (33-51)
Disease duration (months), mean ± SD	68.3 ± 80.5	57.17 ± 81.66
BMI (kg/m^2), mean ± SD	26.7 ± 5.8	26.0 ± 4.89
Diagnosis		
CSU	1963 (70.9)	340 (75.5)
CSU + CIndU	467 (16.9)	74 (16.5)
CIndU	339 (12.2)	36 (8)
Delayed pressure urticaria	44 (1.6)	8 (1.8)
Cold urticaria	66 (2.4)	8 (1.8)
Symptomatic dermographism	118 (4.3)	8 (1.8)
Cholinergic urticaria	76 (2.7)	7 (1.6)
Aquagenic urticaria	6 (0.2)	2 (0.4)
Heat urticaria	4 (0.1)	1 (0.2)
Contact urticaria	7 (0.3)	0
Solar urticaria	13 (0.5)	1 (0.2)
Clinical presentation		
Wheals	1212 (43.8)	207 (46)
Wheals + angioedema	1498 (54.1)	234 (52)
Angioedema	59 (2.1)	9 (2)
Ethnicity		
White	1680 (60.7)	278 (61.0)
Middle Eastern	220 (7.9)	33 (7.2)
African	42 (1.5)	10 (2.2)
Latino/Hispanic	240 (8.7)	32 (7.0)
East Asian	222 (8.0)	58 (12.7)
South Asian	166 (6.0)	27 (5.9)
Caribbean	3 (0.1)	1 (0.2)
Other	196 (0.1)	17 (3.7)
Smoking status—yes	419 (15.1)	58 (12.9)
Alcohol intake—yes	818 (29.5)	123 (27.3)

Data are presented as nos. (%) unless otherwise indicated. Data are shown as available; some data were missing in a few cases. A total of 2769 CU patients were vaccinated, and 456 of them experienced CU exacerbation. *BMI,* body mass index; *CU-exa,* CU exacerbation; *SD,* standard deviation.

time and rate of CsA and GCS discontinuation before vaccination are shown in Table II.

CU exacerbation occurred in 1 of 10 CU patients vaccinated against COVID-19

A total of 5877 vaccine doses were administered to 2769 CU patients, and 456 patients experienced exacerbation of their CU, with a total of 527 cases (527/5877, 9%). Specifically, CU exacerbation occurred in 8% (223/2769) of patients after the first dose, in 9.6% (234/2445) after the second dose, in 11% (70/637) after the third dose, and none of 26 patients after the fourth dose (Fig 1). Across these 456 patients, 312 (68.4%), 104 (22.8%), and 25 (5.5%) had CU exacerbation with only wheals, both wheals and angioedema, and only angioedema, respectively (unspecified, n = 15). Exacerbation of CU most commonly occurred within 48 hours (n = 261, 59.2%) after vaccination, with 17.9% (n = 79) occurring in the first 0 to 6 hours (see Table E8 in the Online Repository available at www.jacionline.org).

The incidence of CU exacerbation was lower (9.6%) in patients who had received no premedication and were not receiving omalizumab or GCS compared to all other patients (13.6%) ($P < .001$).

Before their first vaccination, more than half (56.4%) of the patients had some degree of concern (from slight to extreme) about being vaccinated, with lower rates before consecutive vaccine administrations (47%, 35.5%, and 20%, respectively, for doses 2 through 4). Patients who had concerns about getting vaccinated before the first dose had a reduced likelihood of getting ≥2 vaccinations compared to patients who had no concerns (79.5% vs 93.2%; $P < .001$).

Patients who received adenovirus viral vector vaccines had the highest rate of CU exacerbation

Patients who received adenovirus viral vector (AVV) vaccines had a higher rate of CU exacerbation after the first dose compared to patients who received whole inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines (IVV) or mRNA vaccines (AVV vs IVV, 13.7% vs 8.0%, $P = .003$; AVV vs mRNA, 13.7% vs 7.0%, $P < .001$). Patients who received AVV vaccines also had a higher rate of CU exacerbation after the second dose compared to patients who received IVV vaccines, but not higher than the patients who received mRNA vaccine, and the rate was lowest for IVV vaccine types (AVV vs IVV, 11.7% vs 2.9%, $P < .001$; AVV vs mRNA, 11.7% vs 9.5%, $P = .134$; IVV vs mRNA, 2.9% vs 9.5%, $P < .001$). No difference was observed between vaccine types with respect to the rates of CU exacerbation after the third dose ($P < .05$) (Table III).

Time of onset and duration of CU exacerbation are similar across vaccine types

In most patients, CU exacerbation lasted for a maximum of a few days (46%), whereas 24.3% and 22.9% of patients were affected for a few weeks and months, respectively. The most common treatments administered for CU exacerbation were second-generation antihistamines (70.2%; n = 310) and systemic GCS (13.4%; n = 59), whereas 10% (n = 44) of patients received no treatment (Table E8). Time to onset of CU exacerbation was similar across vaccine types: ≤1 week in 21.2%, 20.4%, and 29.5% of patients who received AVV, IVV, and mRNA vaccines, respectively. The duration of CU exacerbation was also similar for AVV, IVV, and mRNA vaccines, lasting for a few days or less in 62.5%, 55.3%, and 48.6% of patients and for a few months in 14.9%, 9.4%, and 22.2% of patients, respectively. Time of onset, duration, and treatment provided for CU exacerbation after the first dose with respect to vaccine type are provided in Table IV.

COVID-19 vaccination–induced CU exacerbation is more frequent in patients who had CU exacerbation after a previous vaccine dose

Almost three quarters (73%, n = 163) of the 223 patients with CU exacerbation after the first vaccination dose received ≥1 subsequent doses. Of these, 53.4% (87/163) experienced CU exacerbation after the second dose, compared to 5.5% of patients (140/2282) without ($P < .001$). Similarly, patients with CU exacerbation after the second but not the first dose had a higher risk of CU exacerbation after the third dose (7/24, 29.2%) compared to patients without CU exacerbation after the first and second dose (55/560, 9.8%) ($P = .003$). Fifty-five patients (9.8%) did not

TABLE II. Intervals between COVID-19 vaccine and omalizumab, CsA, and GCS treatments

Characteristic	First dose	Second dose	Third dose	Fourth dose
Omalizumab (n = 975)				
Total number	887	861	277	15
<7 days	72 (8.1)	75 (8.7)	24 (8.7)	1 (6.7)
2-7 days	85 (9.6)	95 (11)	31 (11.2)	4 (26.7)
8-14 days	452 (51)	415 (48.2)	139 (50.2)	6 (40)
14-28 days	199 (22.4)	185 (21.5)	49 (17.7)	3 (20)
>28 days	75 (8.5)	86 (10)	34 (12.3)	1 (6.7)
CsA (n = 40)				
Patients ceased treatment	4 (10)	2 (4.9)	2 (15.4)	—
1-3 days before	1 (25)	—	—	—
4-7 days before	—	—	1 (50)	—
>7 days before	1 (25)	1 (50)	1 (50)	—
Other	2 (50)	1 (50)	—	—
GCS (n = 76)				
Patients ceased treatment	16 (21.1)	16 (26.7)	1 (12.5)	—
1-3 days before	4 (26.7)	4 (26.7)	1 (100)	—
4-7 days before	2 (13.3)	3 (20)	—	—
>7 days before	9 (60)	7 (46.7)	—	—
Other/unknown	1 (6.7)	2 (13.3)	—	—

Data are presented as nos. (%).

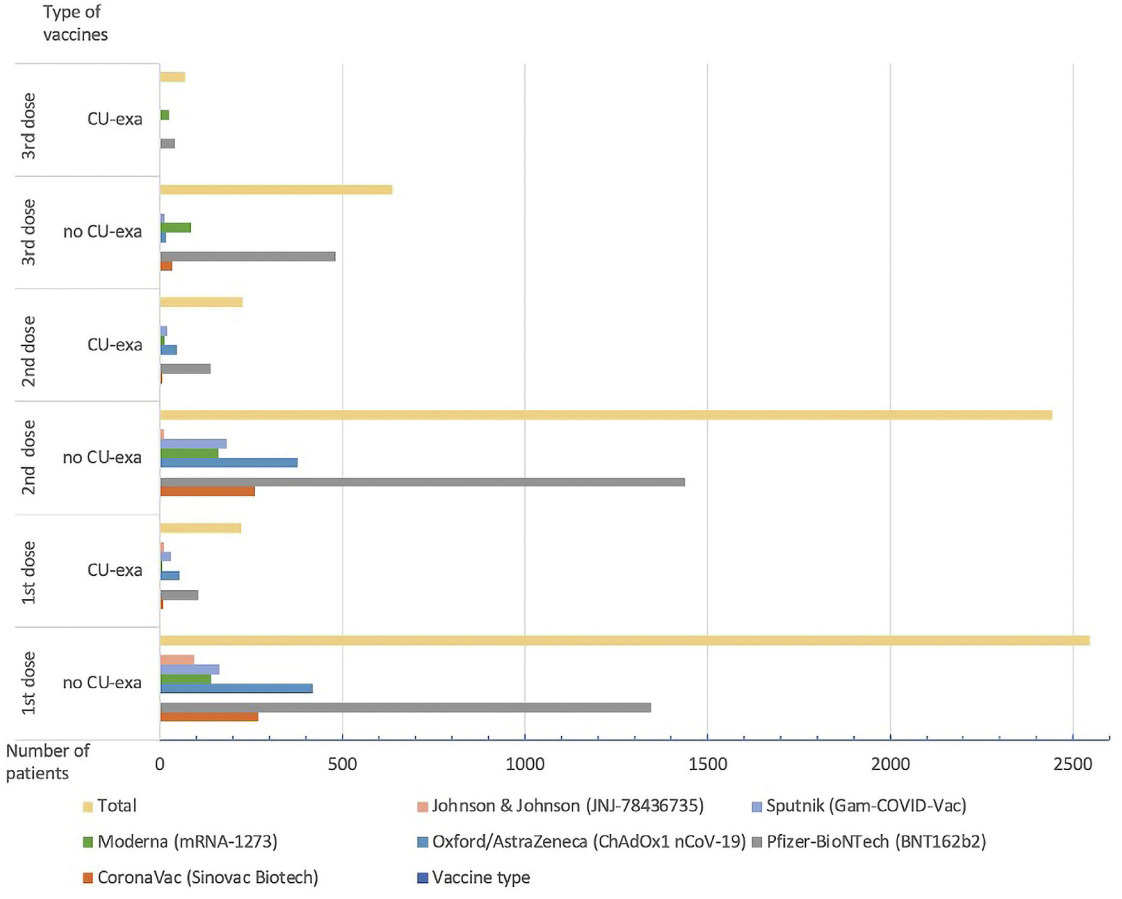

FIG 1. Distribution of CU exacerbation with respect to vaccines received in each dose. Most CU patients (90%) received at least 2 COVID-19 vaccine doses (2 doses in 67.2% [1861/2769], 3 in 22.7% [n = 622], 4 in 1% [n = 26]), with 9.1% (n = 252) receiving only 1 dose. Most patients were vaccinated with the Pfizer-BioNTech (BNT162b2) vaccine (52.4%, 58.8%, 75.5%, 96.2% for doses 1 through 4, respectively), followed by Oxford/AstraZeneca (ChAdOx1 nCoV-19; 17%, 15.4%, 2.7%, 0 for doses 1 through 4, respectively). CU exacerbation was reported in 3.2%, 0.3%, 0, 0 of patients who received CoronaVac (Sinovac Biotech), 7.2%, 9.6%, 8.9%, 0 of patients who received Pfizer-BioNTech (BNT162b2), 11.3%, 11.9%, 11.8%, 0 of patients who received Oxford/AstraZeneca (ChAdOx1 nCoV-19), 4.7%, 8.8%, 27.6%, 0 of patients who received Moderna (mRNA-1273), 15.9%, 11.5%, 0, 0 of patients who received Sputnik (Gam-COVID-Vac), and 10.4%, 8.3%, 0, 0 of patients who received Johnson & Johnson (JNJ-78436735) at the first, second, third, and fourth dose, respectively.

TABLE III. Vaccine types and CU exacerbations reported at each dose

Vaccine type	First dose	Second dose	Third dose	Fourth dose
mRNA	112 (7.0)	152 (9.5)	67 (11.8)	0
AVV	42(13.7)	67 (11.7)	2 (6.5)	0
IVV	69 (8.0)	8 (2.9)	0	0
Total	223 (8.0)	227 (9.3)	69 (10.8)	0
P value*				
AVV vs IVV	.003	<.001	.998	—
AVV vs mRNA	<.001	.134	.372	—
IVV vs mRNA	.375	<.001	.998	—

Data are presented as nos. (%) unless otherwise indicated. Percentages indicate percentage of CU exacerbations within patients who received that type of vaccine in specified dose of vaccination. Total percentage shows percentage of patients who had CU exacerbations among patients who received that particular dose of vaccine. Vaccines are classified into 3 types—AVV, IVV, and mRNA—as follows: *AVV,* spike protein DNA carried by adenoviruses (adenovirus viral vector vaccines, Sputnik, Astra-Zeneca, J&J); *IVV,* whole inactivated SARS-CoV-2 (Sinovac/Coronavac, Covaxin, Covivac); *mRNA,* spike protein mRNA carried by lipidic microparticles (Biontech, Moderna).
*All *P* values were adjusted to take into account multiple testing (Bonferroni adjustment).

experience CU exacerbation after the first or second dose but had CU exacerbation only after the third dose (Fig 2). The characteristics of second dose–induced CU exacerbation, including time of onset, duration, and treatment, were quite similar to those experienced by patients after the first dose (see Table E9 in the Online Repository available at www.jacionline.org).

COVID-19 vaccination–induced CU exacerbation is more frequent in patients who had constitutional symptoms after vaccination

COVID-19 vaccination–induced exacerbation of CU was more frequent in patients who developed constitutional symptoms such as fever (11.6% vs 7.2% without fever; $P < .001$), fatigue (11.3% vs 7.3% without fatigue; $P = .002$), muscle pain (11.4% vs 7.3% without muscle pain; $P = .002$), joint pain (15.3% vs 7.5% without joint pain; $P < .001$), or headache (13.6% vs 7.1% without headache; $P < .001$) but was not linked to local reactions (8.1% vs 8.0% in patients with and without local reactions, respectively; $P = .49$).

Several factors influence the risk of exacerbation of CU after COVID-19 vaccination

Of 22 categorical variables analyzed by univariate logistic regression (Table E2), 9 were associated with higher odds of having COVID-19 vaccination–induced exacerbation of CU (Table V). Six were identified to be risk factors by multivariable logistic regression analyses: female sex (adjusted odds ratio [aOR] 1.9, 95% confidence interval [CI] 1.3-2.7, $P < .001$), disease duration shorter than 24 months (aOR 2.2, 95% CI 1.4-3.2, $P < .001$), having CSU (vs CIndU) (aOR 2.3, 95% CI 1.3-4.0, $P = .005$), receipt of AVV vaccine (aOR 1.8, 95% CI 1.3-2.7, $P = .002$), NSAID/aspirin intolerance (aOR 1.4, 95% CI 1.0-2.0, $P = .038$), and being concerned about getting vaccinated (aOR 1.7, 95% CI 1.2-2.2, $P = .001$). Omalizumab treatment (aOR 0.5, 95% CI 0.3-0.7, $P < .001$) and Latino/Hispanic ethnicity lowered the risk (aOR 0.5, 95% CI 0.3-0.9, $P = .021$) (Table V).

Less than half of CU patients report vaccine-related adverse events, and these are mostly mild

Vaccine-related adverse effects were reported by 43.5% (n = 1124), 44.7% (n = 1043), 45.4% (n = 283), and 33.3% (n = 9) of patients after doses 1, 2, 3, and 4, respectively. The most common reactions reported were local reactions (30.3%; n = 839), fever (19%; n = 527), fatigue (19.2%; n = 532), muscle pain (18.5%, n = 511), joint pain (7.3%; n = 203), and headache (14.9%; n = 412) (see Table E10 in the Online Repository available at www.jacionline.org).

Histories of allergy/anaphylaxis and NSAID intolerance are common in CU patients who reported severe allergic reactions after COVID-19 vaccination

Severe allergic reactions were reported by 7 patients, all with CSU. These reactions occurred within 1 hour after vaccination in 4 of the patients. None of the patients reported receiving adrenaline treatment, and 4 of them also reported to have CU exacerbation. Further information on the patients who reported severe allergic reactions is provided in Table E11 available in the Online Repository available at www.jacionline.org.

Severe allergic reactions were found to be associated with (1) a history of allergy (ie, drug, dust, pollen, cat; 71.4% vs 31.9% with/without; $P = .038$), (2) previous episodes of anaphylaxis (28.6% vs 1.3% with/without; $P = .004$), and NSAID intolerance (57.1% vs 18% with/without; $P = .023$) in the univariate analysis, but had limited value as a result of the low number of patients.

DISCUSSION

In this study, even though more than half of CU patients had concerns about being vaccinated, only a minority (9%) experienced CU exacerbation after COVID-19 vaccination. Adverse reactions and CU exacerbation were rare despite the low rate of premedication before vaccination (~5%).

Real-world data are limited regarding exacerbation of CU after vaccination.[15,16,22-24] Grieco et al[16] and Picone et al[15] reported results that are similar to those of our study, with worsening of urticaria experienced by 8% of patients after COVID-19 mRNA vaccines, while Tuchinda et al[25] reported a higher rate (15%). Lascialfari et al[23] reported relapse or exacerbation of urticaria in 7.7% of pediatric CSU patients after COVID-19 vaccination. Another small study found no effect of mRNA COVID-19 vaccination on urticaria activity scores in 28 patients with CSU.[24] However, it is important to note that the rate of our patients affected by CU exacerbation after COVID-19 vaccination—9%—is markedly lower than the rate of CU patients who experience exacerbation of CU after COVID-19, which is approximately 40% in previous studies.[5,26]

TABLE IV. Time, treatment, and duration of CU exacerbations with respect to type of vaccines in first vaccination dose

	Time of onset of CU-exa at first dose								
Type of vaccine	**1 h**	**1-6 h**	**6-12 h**	**12-24 h**	**24-48 h**	**48 h to 1 wk**	**>1 wk**	**Other**	**Total**
mRNA	2 (2.6)	16 (20.5)	6 (7.7)	13 (16.7)	15 (19.2)	3 (3.8)	9 (11.5)	14 (17.9)	78 (100)
AVV	1 (3.0)	5 (15.2)	6 (18.2)	4 (12.1)	7 (21.2)	3 (9.1)	4 (12.1)	3 (9.1)	33 (100.0)
IVV	5 (10.2)	9 (18.4)	3 (6.1)	13 (26.5)	9 (18.4)	0	4 (8.2)	6 (12.2)	49 (100.0)
Total	8 (5.0)	30 (18.8)	15 (9.4)	30 (18.8)	31 (19.4)	6 (3.8)	17 (10.6)	23 (14.4)	160 (100.0)

	Treatment of CU-exa at first dose						
Type of vaccine	**Topical treatment**	**sgAH**	**GCS**	**No treatment**	**Unknown**	**Other**	**Total**
mRNA	2 (2.6)	53 (68.8)	10 (13.0)	6 (7.8)	1 (1.3)	1 (1.3)	73 (100.0)
AVV	0	25 (75.8)	3 (9.1)	3 (9.1)	0	0	31 (100.0)
IVV	1 (2.1)	32 (66.7)	6 (12.5)	6 (12.5)	0	0	45 (100.0)
Total	3 (2.0)	110 (73.8)	19 (12.7)	15 (10.0)	1 (0.6)	1 (0.6)	149 (100)

	Duration of CU-exa at first dose						
Type of vaccine	**A few hours**	**24 h**	**A few days**	**A few weeks**	**A few months**	**Other**	**Total**
mRNA	4 (5.6)	5 (6.9)	26 (36.1)	18 (25.0)	16 (22.2)	3 (4.2)	72 (100.0)
AVV	2 (6.3)	3 (9.4)	15 (46.9)	8 (25.0)	3 (9.4)	1 (3.1)	32 (100.0)
IVV	6 (12.8)	6 (12.8)	14 (29.8)	9 (19.1)	7 (14.9)	5 (10.6)	47 (100.0)
Total	12 (7.9)	14 (9.3)	55 (36.4)	35 (23.2)	26 (17.2)	9 (6.0)	151 (100.0)

Data are presented as nos. (%). "Other" indicates that no information was available about time of onset of CU exacerbations in this proportion of patients. Vaccines are classified into 3 types—AVV, IVV, and mRNA—as follows: *AVV,* spike protein DNA carried by adenoviruses (adenovirus viral vector vaccines; Sputnik, Astra-Zeneca, J&J); *IVV,* whole inactivated SARS-CoV-2 (Sinovac/Coronavac, Covaxin, Covivac); *mRNA,* spike protein mRNA carried by lipidic microparticles (Biontech, Moderna). *CU-exa,* CU exacerbations.

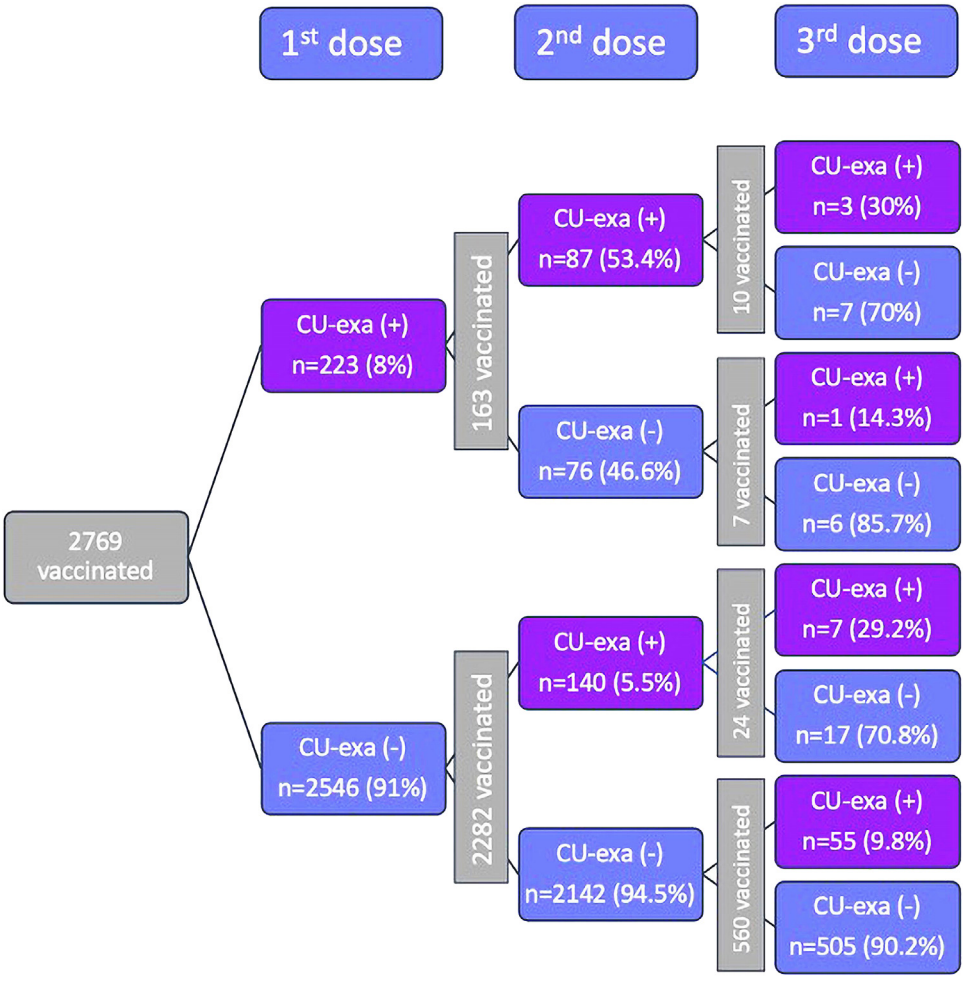

FIG 2. COVID-19 vaccination–induced CU exacerbation (CU-exa) increases exacerbation risk after subsequent vaccine doses. Numbers of patients who experienced CU-exa are 223 (8%), 234 (9.6%), and 70 (11%) after the first, second, and third doses, respectively. A fourth vaccination dose was received by only 19 patients; none experienced CU-exa after the first 3 as well as the fourth doses.

TABLE V. Factors associated with CU exacerbations after first dose of vaccination against COVID-19

	Univariate analysis				Multivariable analysis			
Factor	***P* value**	**OR**	**95% CI LB**	**95% CI UB**	***P* value**	**aOR***	**95% CI LB**	**95% CI UB**
Sex (female vs male)	.001	1.831	1.292	2.597	<.001	1.908	1.332	2.732
Duration ≤24 vs >25 months	.000	2.387	1.621	3.521	<.001	2.155	1.441	3.226
Diagnosis CSU† vs CIndU	.006	2.183	1.256	3.802	.005	2.257	1.279	3.984
Adenovirus viral vector vaccines	<.001	1.997	1.395	2.860	.002	1.830	1.251	2.676
Previous CU exacerbation after vaccination	.013	3.172	1.273	7.907	.055	2.629	0.978	7.067
NSAID/aspirin intolerance	.021	1.464	1.058	2.026	.038	1.445	1.020	2.047
Concern of getting vaccinated	<.001	1.980	1.501	2.610	.001	1.665	1.247	2.221
Omalizumab treatment	<.001	0.451	0.321	0.636	<.001	0.458	0.320	0.655
Latino/Hispanic ethnicity	.042	0.525	0.282	0.977	.021	0.473	0.252	0.894

Variables initially used in univariate analysis are shown in Table E2; some of them (ie, total IgE level, anti-TPO positivity, eosinopenia, prick test positivity, ASST positivity) were not included in the model because of their frequently missing values, and factors that did not show a significant association with the dependent variable are not shown. Multivariable analysis was applied for CU exacerbations related with first dose of vaccination. *LB,* Lower bound; *OR,* odds ratio; *sgAH,* second-generation antihistamines; *UB,* upper bound.

*Values >1 and <1 indicate increased and lower odds of exacerbation, respectively.

†CSU with or without CIndU.

Almost three quarters of the patients with exacerbation of CU after the first vaccine dose received ≥1 subsequent doses. Although half of the patients with CU exacerbation after the first dose did not experience exacerbation after the second dose, the rate of exacerbation of CU was higher in patients whose urticaria had exacerbated after a previous dose versus not. These observations are in line with a recent study that showed reoccurrence of CU exacerbation in 45% of patients after receiving the second vaccine dose.[25] Half of the patients with CU exacerbation after the first dose and one third of patients with CU exacerbation after the second dose experienced recurrence after the doses that followed, but the CU exacerbation rate overall was similar across doses—that is, 8%, 10%, and 11% after the first, second, and third vaccine dose, respectively. This is in line with real-life data from vaccine registries suggesting that the overall incidence of urticaria does not increase with subsequent vaccine doses.[18,27] It is also worth mentioning that in our study, CU exacerbation first occurred after the third dose in 10% of patients.

The risk factors we identified for CU exacerbation were female sex, disease duration shorter than 24 months, having CSU (vs CIndU), receipt of AVV vaccine, NSAID/aspirin intolerance, and being concerned about getting vaccinated. Interestingly, being female had previously been reported to increase the risk of new-onset urticaria after COVID-19 vaccination,[28] and female subjects in general more often experience adverse events (AEs) after vaccination than male subjects, with higher antibody responses and greater Toll-like receptor 7 activation.[29] That the risk of CU exacerbation is increased with AVV vaccines is another interesting finding of our study. A recent study also found higher CU exacerbation rates with AVV vaccines but did not identify AVV vaccines as a risk factor for this.[25]

Although our study did not investigate new-onset urticaria after COVID-19 vaccination, 2 comprehensive meta-analyses of cutaneous reactions after COVID-19 vaccinations showed a higher incidence of urticaria after receipt of the IVV vaccine.[30,31] A recent meta-analysis reported that the incidence of urticaria after COVID-19 vaccinations was higher in the Asian population compared to North American and European populations,[30] whereas our study found that Latino/Hispanic ethnicity was associated with a decreased risk of CU exacerbation. The reason for this ethnic difference remains to be clarified; humoral and cellular immune responses might vary among different races/ethnicities as well as among people from different geographical locations.[32]

COVID-19–induced CU exacerbation and new-onset urticaria may be different; however, the underlying immunologic mechanisms may be similar. Both CU exacerbation and new urticaria onset after COVID-19 vaccine may include triggering of autoimmunity, as suggested by Magen et al,[7] who reported that positive autologous serum skin test (ASST) results, concomitant allergic diseases, and basopenia were positively associated with the likelihood of CSU relapse within 3 months of BNT162b2 mRNA vaccination. Furthermore, a recent study from Korea that compared patients with COVID-19 vaccination–induced CU cases with controls found that levels of IgE–anti–IL-24, IgG–anti-TPO (but not IgE–anti-TPO), IgG–anti-FcεRI, IgG–anti-TYMS, and IgG–anti-THRA autoantibodies were elevated in patients with CU induced by SARS-CoV-2 vaccines.[33] In our study, we did not find that CU exacerbation was linked to markers of autoimmune CSU such as elevated anti-TPO levels, low IgE levels, eosinopenia, or positive ASST and basophil test results,[2] and there was no association with atopy. It is unlikely that urticaria exacerbations are associated with sensitization to vaccine compounds, as was suggested by Pescosolido and coworkers.[10] In our study, only 17.9% of patients with CU exacerbation experienced this within the first 6 hours after vaccination, and of these patients, only 36% experienced CU exacerbation after the following dose. It is more likely that urticaria exacerbation occurs as a result of immune and inflammatory response to COVID-19 vaccines, as suggested by Wang et al,[33] who found that cytokines and chemokines such as IL-2, IL-4, IL-6, IL-17A, TARC/CCL17, PARC/CCL18, and MIG/CXCL9 were elevated in patients with COVID-19 vaccine reactions including urticaria. Our finding that CU exacerbation was linked to higher rates of constitutional symptoms after vaccination also supports this notion.

Regarding ongoing CU treatments, current consensus recommendations were generally followed; of 887 patients who received omalizumab treatment, 452 (51%) had their first COVID-19 vaccination within 8 to 14 days of their last omalizumab injection. Oral CsA and GCS treatment was stopped before COVID-19 vaccination by only 4 (10%) of 40 patients and 16 (21%) of 76 patients, respectively. The German Society of

Allergology and Clinical Immunology recommends a 2-week interval between the application of omalizumab and COVID-19 vaccination,[34] the American College of Rheumatology recommends not to suspend oral GCS treatment before vaccination,[35] and the European Task Force on Atopic Dermatitis suggests suspension of CsA treatment for 1 week after COVID-19 vaccination.[36]

Importantly, receipt of omalizumab by CU patients was associated with a lower risk of CU exacerbation, confirming earlier reports that omalizumab can protect from CU exacerbation.[16] Other studies have shown that omalizumab did not increase the risk of COVID-19 infection[37,38] and that omalizumab can be safely provided to patients receiving COVID-19 vaccines.[37]

Notably, in our study, patients who had concerns about getting vaccinated (the result of fear of experiencing AEs or disease exacerbation) had a 1.7-fold higher risk of CU exacerbation. This finding is compatible with reports that the occurrence of vaccine AEs is associated with a prior negative attitude toward vaccination[39] and prevaccine adverse effect expectations.[40] The mechanisms that link concerns about vaccination and the occurrence of CU exacerbation remain unknown but may include immunization stress response syndrome.[41] Independent of the reasons that have patients concerned about getting vaccinated, the fact that concerns were linked to higher rates of CU exacerbation points to an opportunity for reducing the rates of vaccination-induced exacerbation of CU by taking these concerns seriously and addressing them with evidence-based information.

In our study, only 7 patients reported a severe allergic reaction after COVID-19 vaccination, and it is not clear how severe these reactions were and if these were *bona fide* hypersensitivity reactions or exacerbation of preexisting urticaria. The consistency of self-reported severe allergic reactions is often debated because the rates of self-reported allergic reactions tend to be higher than physician-confirmed rates.[42,43]

Across studies, AEs after COVID-19 vaccinations have been reported in 50% to 90% of participants, and most were mild.[44-47] The most common COVID-19 vaccine AEs are fatigue, muscle pain, headache, chills, redness/swelling at the injection site, joint pain, and fever. The rates of these AEs were somewhat lower in our CU study population compared to these rates in the vaccine trials, suggesting that treatments of CU may have a protective effect for these common AEs, but recall bias should be considered.

Our study has some limitations, which include the lack of information obtained with established patient-reported outcome measures. Also, in many patients, urticaria is a fluctuating disease; exacerbations can occur both spontaneously and in response to various triggers. Thus, some reported episodes of exacerbations may not have been triggered by the COVID-19 vaccinations. In addition, the variability in administration, lack of validation, and translation to multiple languages of the questionnaire are other potential limitations. Another important point is that the rate of patients with angioedema only and no wheals was very low in the present study: only 2.4%, compared to up to 25% in other studies.[48] The reasons for this are unclear but may include selection bias. Another limitation of the study is that patients were not assessed for their frequency of CU exacerbation independent of vaccination. Further studies should characterize CU patients for rate, frequency, trigger, and exacerbation course, including but not limited to COVID-19 vaccination–induced CU exacerbation. Of note, almost 20% of patients chose the "other" option to indicate a delay in onset of urticaria after vaccination; however, only 2 of them specified the delay, which was 7 weeks in one case and 2 months in the other. Apparently patients who chose "other" did not think that their delay was best described as >1 week, although this is technically correct. Also, the duration of CU exacerbation was not specified in 6.8% of patients.

Importantly, our study focused on the exacerbation of existing CU by COVID-19 vaccination, rather than new-onset urticaria after COVID-19 vaccination. The UCARE network has recently started the UNITACT study, which aims to characterize new-onset urticaria after COVID-19 vaccination or infection with SARS-CoV-2.

Conclusions

In our study, CU exacerbation were only observed in 9% of patients and were lower than the frequency that have been reported during COVID-19 infection.[5] CU exacerbation did not recur in half of the cases in the vaccinations that followed. Although we did not find disease control to be a risk factor for CU exacerbation, it is crucial to have CU under control in patients before receipt of COVID-19 vaccination because CU treatment possibly protected patients from CU exacerbation and from common AEs. However, it is also important to remind CSU patients to refrain from NSAIDs after COVID-19 vaccination; acetaminophen/paracetamol should be provided instead. Specifically, we observed that omalizumab treatment protected patients from urticaria exacerbations. Therefore, in patients who have disease deemed appropriate for omalizumab therapy, initiation should not be delayed as a result of concerns of interference with vaccination, provided there is a ≥1-week interval between omalizumab and vaccine administrations, as recommended.[33] Given that concerns about vaccination were found to be a risk factor for CU exacerbation, to relieve vaccine hesitancy, a dialogue between physicians and patients covering the potential for AEs is of the utmost importance.

DISCLOSURE STATEMENT

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Clinical implications: The risk of COVID-19 vaccination–induced worsening of CU is low.

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