

Letter to the Editor



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A Case Series of Chronic Spontaneous Urticaria After COVID-19 Vaccination

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To the Editor,

Coronavirus disease 2019 (COVID-19) vaccines play an important role in overcoming the global COVID-19 pandemic. Various immediate or delayed types of cutaneous adverse reactions, such as local site reactions, urticaria, morbilliform rashes, and delayed large local reactions, have been noted after COVID-19 vaccination, which are usually treatable with time.^{1,2} Chronic spontaneous urticaria (CSU) is defined by recurrent hives lasting > 6 weeks.³ Some patients have developed CSU after COVID-19 vaccination.⁴⁻⁶ Here, we report 12 patients with CSU after COVID-19 vaccination in Korea. We describe the clinical characteristics, treatment, and prognosis of these patients.

The clinical characteristics of the patients are presented in **Table 1**. Of the 12 patients with CSU, five were male, and the median age was 41.5 years (interquartile range [IQR], 14.3). Eleven patients were vaccinated with Pfizer-BioNTech COVID-19 vaccine and 1 was vaccinated with the Oxford-AstraZeneca COVID-19 vaccine. The median latent period was 7 days (IQR, 10.5). The median CSU duration was 44 weeks (IQR, 33.3). Eight patients (66.7%) developed CSU after their first vaccination, 3 (25.0%) after the second booster vaccination, and 1 (8.3%) after a third booster vaccination. One patient had urticaria shortly after receiving previous COVID-19 vaccinations. One of the 4 patients who received a booster despite persistent urticaria after the first COVID-19 vaccination experienced aggravation of urticaria. Four patients also experienced angioedema. None of the patients had any previous history of CSU or drug allergies.

Table 2 shows the medical treatment and prognosis of each patient. Treatment responses were measured using the urticaria control test (UCT) score (0–16): well-controlled for UCT 12–15, completely controlled for UCT = 16. If a patient had been free of urticaria without any medication for at least 1 month, he/she was considered to be in remission. Four patients (33.3%) were well or completely controlled with up to 4-fold increases of H1-antihistamines (H1AH), one patient of whom achieved remission within 5 weeks. Eight patients (66.7%) who were refractory to 3- or 4-fold increases of H1AH took omalizumab treatment (150–300 mg every 4 weeks subcutaneously), all of whom reached well- or completely controlled status. Five of these patients (62.5%) achieved well-controlled status within 1 month, while the others achieved well-controlled after 3 months. Two of the patients took cyclosporine in addition to omalizumab to reach well-controlled status. One of the nine patients with omalizumab treatment achieved remission. In total, nine patients still suffered from chronic urticaria with omalizumab and/or H1AH although their urticaria was well or completely

Table 1. Clinical characteristics of the study subjects

Pt. No.	Sex	Age	COVID-19 vaccine	Latent period (day)	Duration (week)	CSU duration (week)	Number of vaccination on CSU development	Hx of urticaria in the previous vaccination	Booster shot after CSU development	Aggravation of urticaria after booster shot	Hx of CSU	Allergic disease	Presence of angioedema	T IgE (IU/mL)	ANA	Anti-TG Ab	Anti-TPO Ab	CRP (mg/L)	Atopy*
1	M	41	Pfizer-BioNTech	14	5	55	1	NA	No	No	No	Yes	No	1,009	Neg	Neg	Neg	3.6	ND
2	F	33	Oxford/AstraZeneca	3	1	52	1	NA	Yes	No	No	Yes	No	126	Pos	Neg	Neg	1.5	No
3	F	51	Pfizer-BioNTech	5	2	7	1	NA	Yes	No	No	No	Yes	ND	ND	ND	ND	ND	ND
4	F	39	Pfizer-BioNTech	1	1	44	1	NA	No	No	No	No	No	309	Neg	ND	ND	0.9	Yes
5	F	48	Pfizer-BioNTech	7	3	51	1	NA	No	No	No	No	No	106	ND	ND	ND	0.9	ND
6	F	46	Pfizer-BioNTech	10	5	39	2	No	No	No	No	No	Yes	37	Neg	ND	ND	24.5	ND
7	M	48	Pfizer-BioNTech	20	12	52	2	No	No	No	No	Yes	Yes	837	Neg	Neg	Neg	11.0	Yes
8	F	36	Pfizer-BioNTech	7	3	38	2	No	No	No	No	Yes	No	154	Neg	Neg	Neg	0.9	No
9	M	56	Pfizer-BioNTech	3	6	5	3	Yes	No	No	No	Yes	No	144	Neg	Neg	Neg	0.9	Yes
10	M	31	Pfizer-BioNTech	14	8	12	1	NA	No	No	No	Yes	No	788	Neg	Neg	Neg	0.9	Yes
11	M	42	Pfizer-BioNTech	14	26	44	1	NA	Yes	Yes	No	No	Yes	423	Pos	Neg	Neg	0.9	ND
12	F	28	Pfizer-BioNTech	5	4	50	1	NA	Yes	No	No	Yes	No	160	Neg	Neg	Neg	0.9	Yes

COVID-19, coronavirus disease 2019; CSU, chronic spontaneous urticaria; Hx, history; T IgE, serum total immunoglobulin E; ANA, antinuclear antibody; Anti-TG Ab, antithyroglobulin antibody; Anti-TPO Ab, antithyroid peroxidase antibody; CRP, C-reactive protein; ND, not done; NA, not applicable.

*Atopy was defined as 1 or more positive reactions to common inhalant allergens by simultaneous multiple-allergen tests (AdvanSure Alloscreen inhalant panel; LG, Seoul, Korea).

Table 2. Medical treatment and prognosis of the study subjects

Pt. No.	Medication history		Omalizumab treatment				Treatment response†		Remission‡
	H1AH	Cyclosporin	Duration till omalizumab injection (week)	Omalizumab dose and interval	Time period to well-controlled status (week)	Duration of omalizumab use (week)	Current status of omalizumab use		
1	Up to 4x	Yes (200 mg/day)*	7	150 mg q2 → 300 mg q4	20	48	Well-controlled	No	No
2	Up to 4x	No	4	150 mg q2 → q6 → q8	2	52	Completely controlled	No	No
3	Up to 4x	No	5	150 mg q2	4	6	Completely controlled	Yes	Yes
4	Up to 4x	No	7	150 mg q2 → q4 → q6 → q8	12	43	Completely controlled	No	No
5	Up to 4x	No	8	150 mg q3 → q4 → q5 → q6	16	46	Well-controlled	No	No
6	Up to 4x	No	5	150 mg q4 → q6	12	35	Well-controlled	No	No
7	Up to 4x	Yes (200 mg/day)*	13	150 mg q4 → q6	4	34	Well-controlled	No	No
8	Up to 4x	No	10	150 mg q2 → q4	2	34	Well-controlled	No	No
9	Up to 2x	No				5	Discontinued	Yes	Yes
10	Up to 4x	No				10	NA	F/U loss	F/U loss
11	Up to 2x	No				24	Still taking	No	No
12	Up to 2x	No				52	Still taking	No	No

H1AH, H1-antihistamines; NA, not applicable.

*Cyclosporin was added to omalizumab to reach well-controlled status; †Well-controlled: UCT = 12–15 and completely controlled: UCT = 16; ‡Remission was defined as no urticaria without any medication for 1 month.

controlled. When we compared clinical characteristics between H1AH-responsive group and H1AH-unresponsive group (omalizumab group), there were no significant differences (**Supplementary Table S1**).

Newly developed CSU has been reported following COVID-19 vaccination with Pfizer-BioNTech, Oxford-AstraZeneca, and Moderna, regardless of whether it is a messenger RNA vaccine or adenoviral vector vaccine. Latent periods were within 3 weeks in most of the previously reported cases.^{4,5} Hence we enrolled all patients who developed urticaria within 3 weeks after COVID-19 vaccination.

De Montjoye *et al.*⁵ reported 8 cases of newly developed CSU after COVID-19 vaccination, with a mean follow-up duration of 9.9 months. Three patients received omalizumab or cyclosporine in addition to H1AH for disease control, and 4 patients achieved remission. Our patients had a similar median duration of 44 weeks (up to 55 weeks), and 2 patients achieved remission within 6 weeks. We identified 8 severe cases that received omalizumab with or without cyclosporine. In Israel, Magen *et al.*⁶ recently reported 27 relapsed CSU patients in addition to 32 new-onset CSU patients within 3 months after Pfizer-BioNTech COVID-19 vaccination. They showed that positive results for autologous serum skin test, allergic comorbidities, and basopenia were positively associated with the likelihood of CSU relapse compared to new-onset CSU after vaccination.

The exact mechanism of CSU development after COVID-19 vaccination remains unknown. Although it might be a coincidence, vaccines have been frequently nominated as one of the most common causes of drug-induced urticaria.⁷ Mast cell activation by innate immune responses triggered by COVID-19 vaccines may contribute to the pathogenesis of newly developed CSU. Since CSU has a significant impact on the quality of life of patients,³ further investigation of the progress of these CSU patients is needed.

In conclusion, CSU can be triggered by COVID-19 vaccination. Careful observation is needed for CSU development as COVID-19 vaccine adverse reactions.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1

Comparison of clinical characteristics between H1AH-responsive group and H1AH-unresponsive group (omalizumab group)

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