

[Session1. 코로나 판데믹 이후 무엇이 달라졌나?]

코로나/독감 백신과 만성두드러기

예영민

아주의대 내과

코로나 / 독감 백신과 만성두드러기

2024.03.17
아주의대 알레르기내과
예영민

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Adverse Reactions to Vaccines

- 1. AEs directly caused by vaccine components**
 - viral antigen and other vaccine components
- 2. AEs d/t the host immune response**
 - Local inflammatory response: Ag/Adjuvants-TLR-induced inflammation
 - Systemic inflammatory response: fever, irritability, vomiting, myalgia
age, female, genetics, previous infection, increasing vaccine doses
- 3. Allergic reactions**
 - Type I: 0.65 cases / million doses
 - Type IV: peak between 72 and 96 h after vaccination (침가제)
- 4. Other Immune-related reactions:** Idiopathic, autoimmune response
 - 1/6000 measles, 1/3000 rubella, 1/30000 MMR vaccine

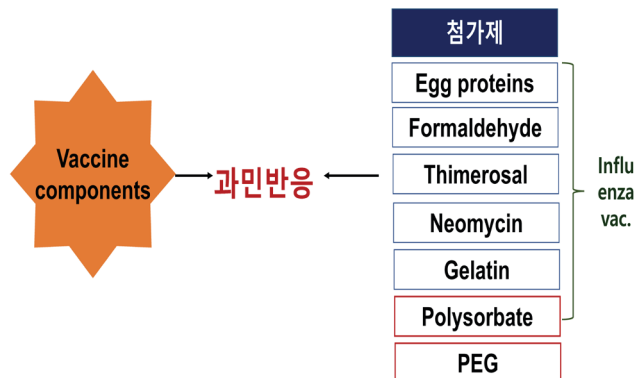
J Comp Path 2007;137:S46-S50

Vaccine-associated hypersensitivity

- Risk of **anaphylaxis** after all vaccines is estimated to be 1.31 (95% CI, 0.90-1.84) per million vaccine doses.
- Trivalent inactivated influenza vaccine (TIV)-triggered anaphylaxis: 1.35 (95% CI, 0.65-2.47) per million vaccine doses.
- MIV-induced anaphylaxis: 1.83 (95% CI, 0.22-6.63)
- Almost any vaccine can cause anaphylaxis,
 - additional component: egg (influenza), gelatin (MMR), alpha-gal (MMR, HZV), milk (DTaP)
 - adjuvants: aluminum hydroxide, gentamicin, tetracycline, neomycin, streptomycin, polymyxin B, thimerosal, 2-phenoxyethanol, phenol

J Allergy Clin Immunol 2018;141:463-72

Allergic components in Vaccines



Components in COVID-19 Vaccines

Pfizer	Moderna	AstraZeneca	Johnson & Johnson
<ul style="list-style-type: none"> • mRNA • KCl, NaCl • PEG-2000 • Sucrose • Saline 	<ul style="list-style-type: none"> • mRNA • Acetic acid • PEG-2000 • Dimyristoyl glycerol • Cholesterol • Phosphocholine • Sodium acetate • Sucrose • Tromethamine 	<ul style="list-style-type: none"> • Adenovirus vector • Histidine • Mg(Cl)₂ • Polysorbate 80 • Ethanol • Sucrose • Disodium edetate dihydrate 	<ul style="list-style-type: none"> • Adenovirus vector • Citrate monohydrate • Polysorbate 80 • 2-hydroxypropyl-B-cyclodextrin • Ethanol • Sodium hydroxide

N Engl J Med 2021; 384:643-649

Viral infections associated with Urticaria

Type of Urticaria	Viral infection
Acute urticaria	Parainfluenza, Herpes virus(HHV-1, HHV-2, HHV6, EBV, CMV), Coronaviruses including SARS-CoV-2, Hepatitis A, B, C, Adenovirus, RSV, Dengue virus, VZV, Parvovirus, Rotavirus, Norovirus, Enterovirus
CSU	Hepatitis A, B, C, HSV, HHV-6, Norovirus, Parvovirus
Cold urticaria	HIV, EBV, HBV, CMV
Cholinergic urticaria	SARS-CoV-2

Viruses 2023;15:1585. <https://doi.org/10.3390/v15071585>

Trends in AEs following immunization in Korea

the KAERS from 2005 to 2017

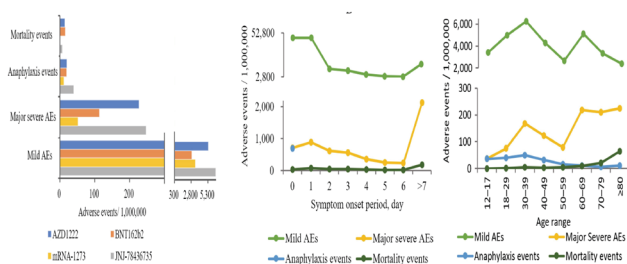
Vaccines	Neurologic reaction ^a		General systemic reaction ^a		Local reaction ^a		Allergic reaction ^b	
	aROR ^c	95% CI	aROR	95% CI	aROR	95% CI	aROR	95% CI
Influenza	0.88	0.83-0.93	0.95	0.91-0.99	1.32	1.27-1.38	0.85	0.77-0.92
Rotavirus	2.43	2.25-2.62	0.96	0.91-1.02	0.01	0.01-0.01	1.46	1.31-1.62
Pneumococcal	0.62	0.57-0.68	1.04	0.99-1.10	1.45	1.37-1.53	0.77	0.69-0.87
HPV	1.45	1.34-1.57	0.90	0.85-0.96	0.75	0.70-0.80	0.83	0.71-0.97
DTPaP	0.66	0.59-0.74	1.07	0.99-1.16	1.29	1.19-1.41	1.08	0.93-1.24
Meningococcal	1.41	1.27-1.56	0.52	0.49-0.56	2.88	2.63-3.16	0.37	0.30-0.46
Hib	0.96	0.89-1.08	1.29	1.19-1.41	0.66	0.59-0.76	1.78	1.55-2.03
BCG	0.07	0.04-0.11	2.20	1.91-2.53	3.15	2.69-3.68	0.17	0.11-0.27
Herpes zoster	0.73	0.61-0.87	0.97	0.87-1.08	1.13	1.01-1.26	0.63	0.44-0.89
Japanese encephalitis	0.87	0.72-1.05	1.36	1.19-1.56	0.29	0.22-0.38	2.38	1.99-2.87

generalized urticaria, anaphylactic reactions, allergy, hypersensitivity, etc

Yonsei Med J. 2020;61:623-30

Adverse events following COVID-19 vaccination in South Korea

- A nationwide observational study (2021.02.28~ 2021.08.21)
- Incidence of adverse reactions after COVID-19 vaccinations was <1%.
- Pain (63.5%), myalgia (32.2%), headache (29.4%), GI symptoms (25.3%), skin-related (22.4%), neurologic (17.6%), and arthritis (1.9%)



Int J Infect Dis 2022;118:173-82

Incidence of common cutaneous reactions related to COVID-19 vaccination

- A systematic review including 35 studies, 2549968 participants from 23 countries

- Overall systemic skin reactions: 3.8% (2.4%-5.5%)

- Urticaria 1.1% (0.7%-1.5%)

Urticaria				
Age groups				
Mean/median age <50 years	8	1.8% (0.6%-3.5%)	90	
Mean/median age ≥50 years	0	-	-	
Ethnic groups				
Asia	6	2.9% (2.1%-3.7%)	40	<0.001 [†]
North America	4	0.4% (0.2%-0.6%)	94	0.022 [†]
Europe	4	0.6% (0.1%-1.4%)	79	0.295 [‡]
Vaccine types				
mRNA vaccine	9	0.7% (0.4%-1.1%)	95	0.006 [†]
Inactivated vaccine	2	4.0% (2.2%-6.1%)	-	0.094 [‡]
A/V vaccine	3	3.1% (1.8%-4.6%)	-	0.130 [‡]
Vaccine doses				
The first dose	4	1.2% (0.5%-2.2%)	97	
The second dose	3	1.0% (0.3%-1.9%)	-	

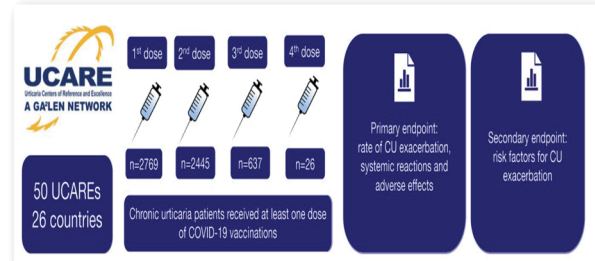
J Glob Health 2023;13:06008

COVID-19 Vaccination as a Cause of AU

- A recent meta-analysis reported that cutaneous ADR after COVID-19 vaccination
- acute injection site reaction (72.2%)**, rash/eruption (13.8%), **urticaria/angioedema (6.5%)**, pruritus (2.3%), delayed large local reactions (1.9%), maculopapular rash (0.5%), herpes zoster (0.4%), oral blister/ulcer (0.36%), pityriasis rosea (0.24%), vesiculobullous lesions (0.2%), petechia/purpura/ecchymosis (0.14%), and vasculitis (0.1%)
- AU after COVID-19 vaccination most often occurs **after the 1st dose** and tends to **not recur with subsequent doses** (17% recurrence after 2nd dose, non-severe).
- mRNA-based** COVID-19 vaccines were found to have a higher prevalence (**6.9%**)
- Moderna (3.9%) and Pfizer (3.9%) vaccines have a lower incidence of urticaria compared to the flu (5.5%), and HBV (6.4%) vaccines.

Dermatologic Therapy. 2022;35:e15391

CSU Exacerbation: COVAC-CU study

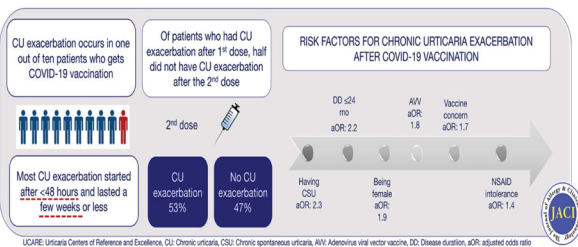


- An international multicenter **retrospective study** in CU patients **>18 years** and vaccinated with **>1 dose of any COVID-19 vaccine**
- 2769 COVID-19-vaccinated CU patients, 90% received at least 2 COVID-19 vaccine doses, and most patients had well-controlled disease

J Allergy Clin Immunol 2023;152:1095-106

The UCARE COVAC-CU study

- First-dose vaccine-related adverse effects, most commonly **local reactions, fever, fatigue, and muscle pain, were reported by 43.5% of CU patients**
- The rate of COVID-19 vaccination-induced **CU exacerbation was 9%**

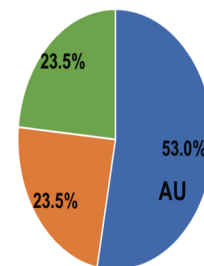


- ❖ **Urticaria exacerbation: 8% ~ 15% of CU patients** after COVID-19 vaccines *Dermatol Ther* 2022, *J Clin Med* 2022
- ❖ Relapse or exacerbation of urticaria in **7.7% of pediatric patients** after COVID-19 vaccination *Allergol Immunop* 2022

J Allergy Clin Immunol 2023;152:1095-106

132 patients reported with urticaria after COVID-19 vaccination

- Using ADR report system from June 2021 to February 2022



Variables	AU (n=70)	CU (n=62)
Age (yr)	42.2 ± 17.6	44.7 ± 13.5
Female	48 (68.6%)	39 (62.9%)
Angioedema (+)	12 (17.1%)	27 (43.5%)
mRNA-based V	50 (71.4%)	47 (75.8%)
Adenovirus V	20 (28.6%)	15 (24.2%)
1 st / 2 nd / 3 rd dose	44 (62.9%) 20 (28.6%) 6 (8.6%)	33 (53.2%) 26 (41.9%) 3 (4.8%)
Treated with		
H1AH	66 (94.3%)	61 (98.4%)
Steroid	60 (85.7%)	50 (80.6%)
Omalizumab	0	11 (17.7%)
Latent period (days)	4.9 ± 6.6	5.4 ± 14.3

Chun HS, et al. KAAACI 2022

	New onset of CU (n=31)	Exacerbation of existing CU (n=31)	P value
Age (year)	45.0 ± 14.4	44.5 ± 12.9	0.882
Female sex	18 (58.1%)	21 (67.7%)	0.430
Pfizer-BioNTech	22 (71.0%)	23 (74.2%)	
Moderna	1 (3.2%)	1 (3.2%)	
Oxford-AstraZeneca	8 (25.8%)	7 (22.6%)	
after 1 st / 2 nd / 3 rd dose	14 (45.2%) / 16 (51.6%) / 1	19 (61.3%) / 10 (32.3%) / 2	0.392
Past Hx of allergic disease	14 (45.2%)	11 (35.5%)	0.437
Interval between vaccination and symptom onset	9.1 ± 19.5 (days)	1.7 ± 2.8 (days)	<0.001
Angioedema	12 (38.7%)	15 (48.4%)	0.442
Anaphylaxis	4 (12.9%)	7 (22.6%)	0.319
Duration of symptom (days)	141.41 ± 62.2 (n=22)	72.48 ± 80.3 (n=23)	0.003
OMA treatment for	6 (19.4%)	3 (9.7%)	

Chun HS, et al. KAAACI 2022

Allergy Asthma Immunol Res. 2023 Sep;15(5):695-698
https://doi.org/10.4168/aiir.2023.15.5.695
pISSN 2092-7355 eISSN 2092-7363

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Letter to the Editor

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

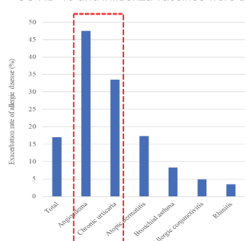
Pl. No.	Sex	Age	COVID-19 vaccine	Latent period (day)	Duration till first visit (week)	CSU duration (week)	Number of vaccination on CSU development	Allergic disease	Presence of angioedema	T IgE (IU/mL)	ANA (IU/mL)	Anti-TG Ab	Anti-TPO Ab	CRP (mg/L)	Atopy
1	M	41	Pfizer-BioNTech	14	5	55	1	Yes	No	1,009	Neg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

58.3%

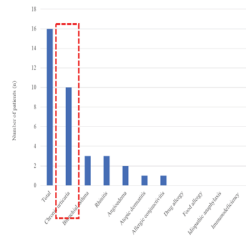
Omalizumab treatment

Effects of COVID-19 and Influenza Vaccination on Allergic Diseases

- Patients with allergic diseases who were diagnosed and followed up by allergy specialist were enrolled from 14 university hospitals in Korea.
- The 17 questionnaires about adverse reactions and exacerbation of underlying allergic disease after COVID-19 and influenza vaccines were answered.



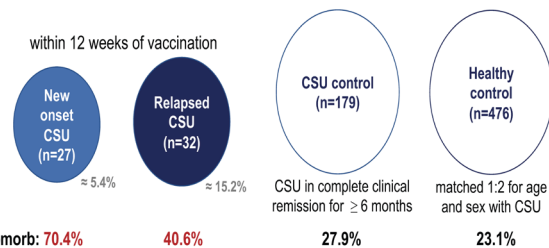
- Among 1680 vaccinated patients with COVID-19, 286 (17%) experienced exacerbation of allergic disease.



- Of 805 had influenza vaccination, **2%** (n=16) showed exacerbation of underlying allergic disease, and 62.5% (n=10) were chronic urticaria.

Ran GY et al. KAAACI 2022

COVID-19 Vaccination as a Cause of CU



- Allergic comorb: 70.4%
 - Multiple logistic regression analysis
 - ASST positivity 5.54 (2.36–13.02)
 - AR, BA, AD 6.13 (2.52–14.89)
 - Basopenia* 2.81 (1.17–6.72)
- * < 100 cells/mL

A retrospective study from Jan 2020 to Aug 2021 in Israel. *Allergy Asthma Proc* 2022;43:30–6

Clinical characteristics of patients with SARS-COV-2 vaccines-induced CU

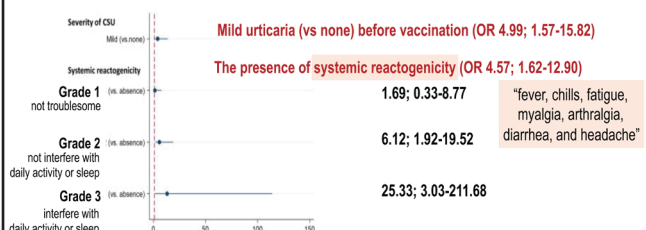
Characteristics	SARS-COV-2 vac-induced CU (n = 57)	SARS-COV-2 vac-tolerant controls (n = 115)	OR, P value
Age (years)	49.9 ± 16.5	47.5 ± 15.1	0.371
Female (%)	39 (68.4%)	64 (55.7%)	1.7 (0.9–3.4)
Received vaccine			
- AZD1222	13 (22.8%)	27 (23.5%)	
- mRNA-1273	34 (59.6%)	40 (34.8%)	
- BNT162b2	9 (15.8%)	19 (16.5%)	
<i>Asthma, AR, AD, CU, Drug allergy, Food allergy – no significant difference</i>			
Thyroid disease	5 (8.8%)	1 (0.9%)	11.0 (1.2–96.2)
Anti-TPO IgG Ab	16 (28.1%)	5 (4.3%)	8.6 (3.0–24.9)
Total IgE >100	20 (35.1%)	12 (10.4%)	4.6 (2.1–10.4)
D-dimer > 0.55	12 (21.1%)	6 (5.2%)	4.8 (1.7–13.7)

ANA, CRP, TSH, WBC, Eosinophil, Basophil – no significant difference

J Autoimmun 2023;138:103054

Exacerbation of CSU following COVID-19 vaccination

- A questionnaire-based cross-sectional study in a tertiary hospital
- **105 CSU patients (230 vaccination cases)** aged 18 to 80 years, who were **regularly treated with omalizumab**, had received at least one dose of COVID-19 vaccination and had no or mild CSU at the time of COVID-19 vaccination.
- ▶ **15 patients (14.3%) experienced a CSU exacerbation at least once after COVID-19**
- **Risk factors for CSU exacerbation:**



J Allergy Clin Immunol Pract 2023;11:2403-10

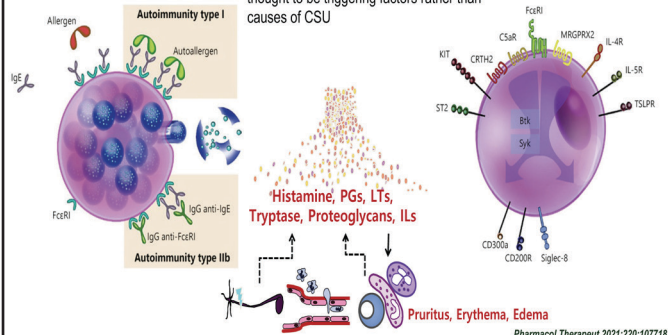
Safety of COVID-19 mRNA vaccination in children with chronic urticaria

- From December 2021 to March 2022, **101 children aged 5 to 18 years** from a registry of children with CU recruited from 3 allergy clinics in Canada and Israel.
 - For both the first and second BNT162b2 doses, **no patients reported any allergic reaction, including exacerbations of CSU.**
 - A total of 17 patients (17%) had been infected with COVID-19, and 9 of them (53%) were unvaccinated at the time of infection.
- Children with CU are **at minimal risk** of suffering from an **allergic reaction secondary to COVID-19 vaccination.**
- COVID-19 infection in children with CU does **not precipitate a CU flare.**

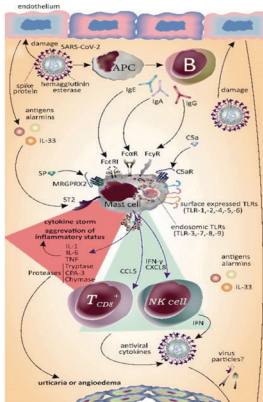
J Allergy Clin Immunol Pract 2023;11:1313

Urticaria is a mast cell-driven disease

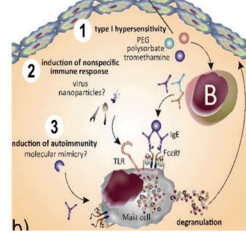
- ❖ Stress, hormones, infections (URI, GI infections), and pseudo-allergens are thought to be triggering factors rather than causes of CSU



How COVID-19 Infection and Vaccination are Linked to Urticaria ?

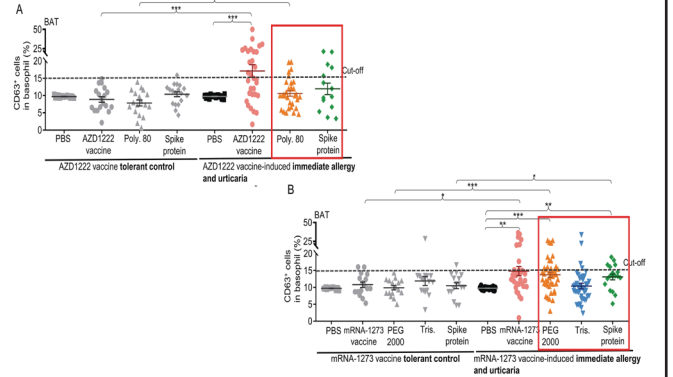


- **MC-orchestrated** sentinel responses to pathogens, including certain viruses, are generally protective but can lead to **enhanced inflammation or autoimmunity**.
- Viral infections may contribute to the development of AU which can then become **chronic in 5–39% with possibly circulating autoantibodies**



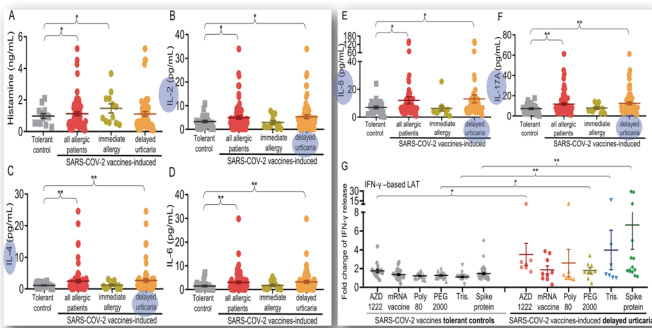
Viruses 2023;15:1583

Allergic urticarial reactions induced by SARS-CoV-2 vaccines



J Autoimmun 2023;138:103054

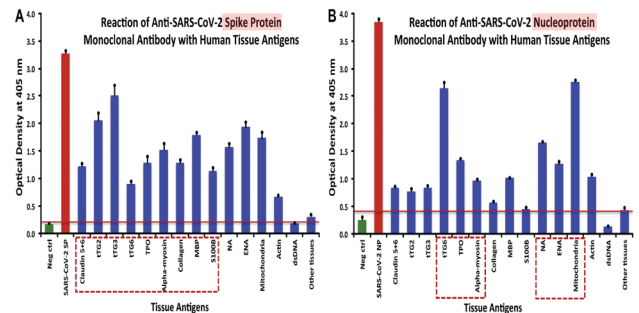
Mast cell and T cell-mediated cytokines



J Autoimmun 2023;138:103054

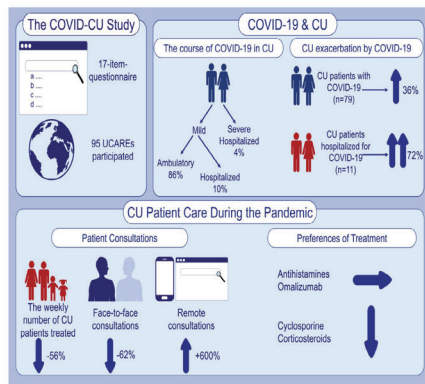
Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue

- A possible link to an increase in autoimmune diseases

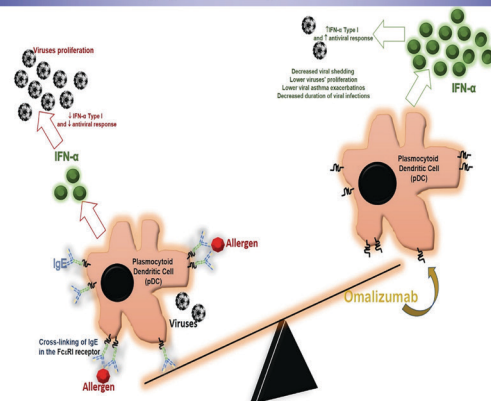


Clinical Immunology 2020;217:108480

The COVID-19 pandemic severely impairs CU patient care

Emek Kocatürk et al. *Allergy*. 2021;76:816–830.

Effects of omalizumab on the antiviral response produced by plasmacytoid dendritic cells



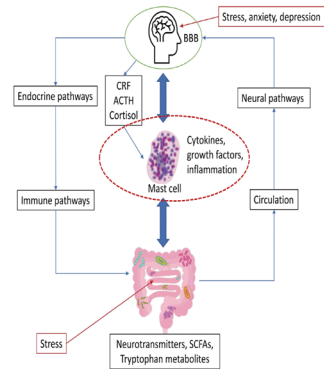
Dermatologic Therapy. 2020;33

Long COVID and Chronic Urticaria

Mast Cell Activation Syndrome

Organ system	Clinical symptoms
Systemic	Anaphylaxis, syncope, fatigue
Dermatologic	Flushing, skin rash, pruritus, urticaria
Cardiovascular	Hypotension, shock, chest pain, tachycardia
Respiratory	Wheezing
Musculoskeletal	Arthralgia, myalgia, degenerative disc disease, osteoporosis/osteopenia
Gastrointestinal	N/V, abdominal pain, gastroesophageal reflux, diarrhea, esophagitis, malabsorption
Neurological	Cognitive impairment, brain fog, dizziness, vertigo, migraine, paresthesia, peripheral neuropathy

J Allergy Clin Immunol 2017;140:349-355



Asia Pacific Allergy 2023;13:50-3, Virol J 2022;19:158

Summary

- 바이러스 감염이 두드러기 (급성 > 만성)의 유발요인이 될 수 있다.
- COVID-19 백신 접종 후 만성두드러기 발생이 보고되었다.
 - 소아에서는 거의 없으며,
 - 성인에서는 1.1%, 기저 알레르기 질환, 갑상선질환, ASST +, Basopenia, anti-TPO IgG, high IgE, high D-Dimer (potential risk)
- COVID-19 백신 접종 후 만성두드러기 악화가 보고되었다.
 - 8% ~ 15% of CU, incompletely controlled urticaria, systemic reactions, female, urticaria duration < 24 months, Adeno-viral vector, NSAID hypersensitivity
- COVID-19 백신 접종 후 만성두드러기 악화는 항히스타민제 증량, Omalizumab로 잘 치료
- 재접종 시 두드러기 악화의 반복 50% 정도이므로, 백신 접종을 기피할 필요 없다.
- 접종 전후 만성두드러기 유지치료가 COVID-19 감염 및 증증도에 영향을 미치지 않는다.