

Development of immediate and chronic spontaneous urticaria following mRNA COVID-19 vaccination: Tolerability of revaccination and immunological study

Dear Editor,

Coronavirus 2019 (COVID-19) vaccination remains one of the key public health measures against the SARS-CoV-2 infection, significantly reducing illness severity and mortality rates. Urticaria and/or angioedema are cutaneous reactions that have been reported in response to messenger RNA (mRNA) COVID-19 vaccination and potentially affect fitness for revaccination.¹ The development of chronic spontaneous urticaria (CSU) post-COVID-19 vaccination² may further discourage patients from revaccination or preclude revaccination to keep vaccinations updated. We describe a Singapore case series of 64 patients with urticaria post-COVID-19 vaccination, studying patient tolerance to revaccination, immunological profile and development of CSU.

Patients who developed urticaria within 21 days following mRNA COVID-19 (Pfizer BNT162b2 or Moderna mRNA-1273) vaccination were recruited from outpatient allergy clinics at Tan Tock Seng Hospital, Singapore from February to September 2021. Cases were diagnosed by an allergist based on clinical evaluation after excluding other differential diagnosis. Onset of reactions were classified into immediate (<4 hours) or delayed onset (>4 hours).³ A single-point in-clinic urticaria activity score (UAS) was obtained. Reactions were graded into mild (UAS<3) or moderate-to-severe (UAS≥3).⁴

Patients were assessed for suitability for revaccination with the same Pfizer or Moderna mRNA vaccine or revaccination with a non-mRNA vaccine (Sinovac-CoronaVac), unless they declined revaccination. The choice of revaccination was a shared decision made by the allergist and the patient after weighing the benefits of completing the primary vaccination series or booster shot for protection against severe COVID-19 disease versus the risk of a subsequent reaction to revaccination.

They were followed up with a phone call or appointment to assess the patient's tolerability of revaccination—defined as either having no symptoms post-vaccination, or mild symptoms that were self-limiting or resolved with a short course (less than 1 week) of antihistamine. Patients were also assessed for development of post-vaccination CSU, defined as presence of recurrent or persistent urticaria/angioedema lasting or exceeding 6 weeks post-vaccination.⁴

Thirteen patients had blood samples taken within 4 weeks of their index reaction. The following biomarkers were assayed by enzyme-linked immunosorbent assay as described previously: complement 5a (C5a), intercellular adhesion molecule 1 (ICAM-1) for endothelial activation, C-reactive protein (CRP), and cytokines including interleukin (IL)-4, IL-5, IL-6, IL-10, IL-18, tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) and monocyte chemoattractant protein (MCP-1). IgE antibodies to Pfizer BNT162b2 vaccine were assayed against a standard (0.2–1000 ng/mL) based on the supplier's recommendation (Hu 6.3 IgE, Academia Sinica, Taiwan).⁵ This study was approved by the institutional review board (DSRB 2021/00174 and DSRB 2021/00878).

Among the 64 patients, median age was 40.5 (interquartile range [IQR] 30–56) years, 46 (72%) were female and 47 (73%) had a history of atopy (Table 1). Among patients who developed urticaria, 92% were attributed to the Pfizer-BioNTech vaccine and remaining 8% were to the Moderna vaccine. Of these, 77% reacted following the first vaccine dose, 19% to second dose and 5% to third dose. Sixty-two percent had moderate-to-severe urticaria.

Fifty-four (84%) patients received revaccinations; 33 with the same mRNA vaccine and 21 with non-mRNA vaccines. All patients tolerated revaccination well with no or mild symptoms, with the exception of 1 patient who developed recurrence of moderate-to-severe urticaria post revaccination with the same mRNA vaccine. Revaccination was not discussed with 3 (5%) patients as they had reactions occurring at the third dose with no further booster vaccinations being indicated as per prevailing vaccination guidelines at that time. Seven (11%) patients chose not to revaccinate (Supplementary Table S1).

Twelve patients developed chronic urticaria post-vaccination. The median age was 48 (IQR 36–60) years, 42% were women and 67% had a history of atopy. Eighty-three percent had been vaccinated with Pfizer-BioNTech vaccine and 17% with the Moderna vaccine. Five (42%) had a history of CSU, of which 2 patients had active CSU at the time of vaccination. Median time interval between vaccination and onset of urticaria was 24 (IQR 4–72) hours. The offending

Table 1. Demographics, characteristics and immunological profile of study population.

Variable	Result (n=64)
Age, median (IQR), years	40.5 (30–56)
Sex, no. (%)	
Female	46 (72%)
Male	18 (28%)
Ethnicity, no. (%)	
Chinese	46 (72%)
Malay	10 (16%)
Indian	5 (8%)
Others	3 (5%)
Brand of vaccine to which reaction occurred, no. (%)	
Pfizer-BioNTech	59 (92%)
Moderna	5 (8%)
Dose of vaccine to which reaction occurred, no. (%)	
1st	49 (77%)
2nd	12 (19%)
3rd	3 (5%)
Atopy history, no. (%)	
Any atopy history	47 (73%)
Chronic spontaneous urticaria	29 (45%)
Asthma	7 (11%)
Allergic rhinitis	12 (19%)
Eczema	10 (16%)
Food allergy	16 (25%)
Drug allergy	20 (31%)
Family history of atopy, no. (%)	13 (20%)
Timing and severity of reaction, no. (%)	
Immediate onset, mild	10 (16%)
Immediate onset, moderate-to-severe	9 (14%)
Delayed onset, mild	14 (22%)
Delayed onset, moderate-to-severe	31 (48%)
Development of chronic spontaneous urticaria post-vaccination, no. (%)	12 (19%)
Immunological biomarkers	No. (%) of patients with elevated biomarkers (n=13)
IL-6	5 (38%)
IL-18	13 (100%)
IFN- γ	12 (92%)
CRP	4 (31%)
MCP-1	6 (46%)
IL-4, IL-5, IL-10, TNF- α , ICAM-1, C5a	0

C5a: complement 5a; CRP: C-reactive protein; ICAM-1: intercellular adhesion molecule; IFN: interferon; IL: interleukin; IQR: interquartile range; MCP-1: monocyte chemoattractant protein; TNF: tumour necrosis factor

vaccine dose was the first dose in all 12 patients. Median duration of symptoms was 160 (IQR 74.5–285) days. All patients required treatment with antihistamines. Three patients received oral prednisolone exceeding 1 week duration (3, 5, 18 weeks). One patient required subcutaneous omalizumab injections.

Of the 13 patients who provided their blood samples, the following biomarkers were elevated comprising CRP (4), IL-6 (5), MCP-1 (6), IFN- γ (12), IL-18 (13). IL-4, IL-5, IL-10, TNF levels and ICAM-1 were normal (Table 1). IgE antibodies to the BNT162b2 vaccine were not detectable. The demographics of these patients were similar to the total study population. However, a higher

proportion (85%) had moderate-to-severe urticaria. Five patients developed CSU post-vaccine.

We observe that patients with mild urticarial reactions to mRNA COVID-19 vaccination tolerated revaccination well with mRNA vaccines. Patients with delayed-onset moderate-severe reactions tolerated revaccination well with non-mRNA vaccines; the subset who opted to revaccinate with mRNA vaccines (32%) also generally tolerated well. More importantly, after the shared decision-making between patient and allergist, most patients with immediate-onset moderate-to-severe reactions also tolerated revaccination with non-mRNA vaccines. We would recommend this over withholding further revaccination in such patients.

Notably, several international studies following our study period have demonstrated that most patients with severe immediate-onset reactions (including those with anaphylaxis) were also capable of tolerating COVID-19 revaccination with mRNA vaccines.^{6,7} This has also been our subsequent experience in our institution. This is likely due to the underlying mechanism of reaction being non-IgE mediated, for which there is increasing evidence.^{5,7,8}

Atopic conditions tend to induce a T-helper 2 (Th2) response, while T-helper 1 (Th1) response has been implicated in chronic inflammation and autoimmunity.⁹ The predominance of Th1 cytokines elevated in our patients with urticaria following COVID-19 vaccination further support these manifestations as unlikely to be IgE mediated.

The weaknesses of our report include the retrospective nature of the study with variability in allergist clinical assessment and recall bias. Our patient selection included more moderate-to-severe and chronic urticaria as this study was conducted in a tertiary referral centre.

In conclusion, revaccination with COVID-19 mRNA vaccines was generally well tolerated in patients who developed urticaria following mRNA COVID-19 vaccination. Patients with moderate-to-severe urticaria may be safely revaccinated with non-mRNA vaccines.

Keywords: chronic spontaneous urticaria, COVID-19, cytokines, urticaria, vaccines

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