COVID-19 SPECIAL FORUM

# Cutaneous adverse reactions from 35,229 doses of Sinovac and AstraZeneca COVID-19 vaccination: a prospective cohort study in healthcare workers

Cutaneous adverse reactions (CARs) from mRNA-based COVID-19 vaccines have been reported in the literature.[1,2] On the contrary, information regarding Sinovac (CoronaVac), (SV) inactivated virus and adenoviral vector AstraZeneca (ChAdOx1 nCoV-19) (AZ) vaccines remains scarce. We have conducted this prospective cohort study to address this issue.

The participants were healthcare workers (persons who deliver services to the patients directly or indirectly[3]) at King Chulalongkorn Memorial Hospital, Bangkok, Thailand who agreed to be vaccinated with either SV or AZ COVID-19 vaccines. All participants with CARs were identified from the questionnaire sent out on day 1 and day 7 via mobile phone application, the self-reporting system, incident reports of reactions at the vaccination site, emergency room and Dermatology outpatient clinic. Photographic documentation of the skin lesions was obtained from the patients. These photos were assessed by three dermatologists and the skin findings were categorized.

A total of 35 229 injections, 29 907 of SV and 5322 of AZ were given during the study period. The number of cases with CARs was 204 from SV and 36 from AZ (total $n = 240$). The median (interquartile range (IQR)) age of the cases was 34 (28, 43.5) and 48 (35, 55), from SV and AZ, respectively. A female preponderance was observed (female $n = 169$ (82.84%) and 27 (75%), SV, AZ). Among 240 cases, there were 302 reactions reported. The number of participants experiencing 1 or more than one CAR from SV was 96.79% and 3.21%, and 97.73% and 2.27% from AZ. The incidence of CARs from SV was 0.94% and 0.70% from the first and second doses, whereas those of AZ were 1% and 0.52%, respectively.

Dermatologic findings were categorized only from cases with available clinical photographs ($n = 145$ reactions (48.01%)). Urticaria was the most common skin finding ($n = 104$, 34.44%) followed by eczematous reactions ($n = 21$, 6.95%) and angioedema ($n = 9$, 2.98%). Details are shown in Table 1.

When the first and second doses were analysed, 155 and 33 participants who developed CARs cases from the first doses of SV and AZ, respectively, went on to receive a second dose of the same vaccine. Skin reactions were found in 50 (32.26%) and 3 (9.09%) cases in these cases after the second dose of SV or AZ. Table 2 provides information on the recurrence. Compared to those who experienced urticaria >30 minutes after the first vaccination, those who experienced a first reaction within 30 min after the first vaccination had an increased risk of urticaria after the second vaccination (OR 2.9 (95%CI 0.44–19.3); $P = 0.27$). Although not statistically significant, the 95%CI was consistent with an increased risk of second reaction in this group with an early first reaction. For those with no skin reactions from the first injection, the incidence of CARs occurring only after the second dose was 0.39% (49/12,484) for SV and 0.15% (3/1935) for AZ.

There were no cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) in our cohort; however, a case with multiple ecchymosis as a sign of secondary immune thrombocytopenic purpura (ITP) was observed post-AZ. This is in keeping with the reports in the literature of ITP post-COVID-19 vaccination.[4] Dermatologists should be aware of the importance of these skin findings. Interestingly, types of CARs associated with SV and AZ are similar to those reported from mRNA vaccines including vasculitis, herpes reactivation and pityriasis rosea.[1,2] However, no delayed inflammatory reactions to filler was detected in our cohort. Form this study, we found that most CARs from SV and AZ were non-serious, and the incidence was ≤ 1%. Such skin reactions should not deter individuals from receiving vaccinations as soon as is practical when they are available.

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## Conflicts of interest

None.

## Funding sources

None.

**Table 1** Dermatologic findings reported after first and second Sinovac (CoronaVac) or AstaZeneca (ChAdOx1 nCoV-19) vaccinations

| Cutaneous reactions (*n* = number of incidence reports) | CoronaVac | | | | | | ChAdOx1 nCoV-19 | | | | | | Total *n* = 302 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dose 1 *n* = 162 (53.64%) | | | Dose 2 *n* = 95 (31.46%) | | | Dose 1 *n* = 34 (11.26%) | | | Dose 2 *n* = 11 (3.64%) | | | | | |
| | *n* (%) | Median onset (Q1, Q3) hours | Median duration (Q1, Q3) days | *n* (%) | Median onset (Q1, Q3) hours | Median duration (Q1, Q3) days | *n* (%) | Median onset (Q1, Q3) hours | Median duration (Q1, Q3) days | *n* (%) | Median onset (Q1, Q3) hours | Median duration (Q1, Q3) days | *n* (%) | Median onset (Q1, Q3) hours | Median duration (Q1, Q3) days |
| Urticaria | 55 (33.95) | 9 (2, 22) | 2 (0.2, 7) | 37 (38.95) | 6 (0.8, 24) | 1 (0.1, 7) | 9 (26.47) | 21 (7, 24) | 4 (2, 18) | 3 (27.27) | 4 (0.5, 5) | 3 (0.2, 29) | 104 (34.44) | 6 (1.5, 24) | 2 (0.2, 8) |
| Eczematous | 9 (5.56) | 24 (24, 120) | 8 (7, 16) | 8 (8.42) | 16 (4.5, 36) | 7 (3.5, 10.5) | 4 (11.76) | 72 (48, 96) | 4.5 (3.5, 6.5) | 0 | – | – | 21 (6.95) | 24 (16, 72) | 7 (4, 14) |
| Skin sign associated with the extravasation of blood (Ecchymosis, Petechiae, Purpura) | 5 (3.09) | 10 (3, 24) | 7 (3, 14) | 2 (2.11) | 8 (4, 12) | 13.5 (13, 14) | 3 (8.82) | 48 (6, 336) | 10 (6, 14) | 0 | – | – | 10 (3.31) | 11 (6, 48) | 11.5 (6, 14) |
| Angioedema | 5 (3.09) | 24 (20, 24) | 1 (1, 2) | 4 (4.21) | 24 (13.5, 48) | 1 (0.6, 1.5) | 0 | – | – | 0 | – | – | 9 (2.98) | 24 (20, 24) | 1 (1, 2) |
| Erythema reaction at/near injection site | | | | | | | | | | | | | | | |
| • Acute (< 8 days) | 4 (2.47) | 41.5 (5.8, 108) | 3 (1.3, 5.5) | 0 | – | – | 2 (5.88) | 13 (2, 24) | 4.5 (4, 5) | 1 (9.09) | 5 (–) | 7 (–) | 7 (2.32) | 11 (2, 72) | 4 (2, 7) |
| • Delay (≥ 8 days) | 0 | – | – | 1 (1.05) | 216 (–) | 5 (–) | 1 (2.94) | 240 (–) | 3 (–) | 0 | – | – | 2 (0.66) | 228 (216, 240) | 4.1 (3, 5.2) |
| Papule/Papulovesicle | 4 (2.47) | 72 (48, 108) | 7 (4, 12.5) | 2 (2.11) | 8 (6, 10) | 8 (3, 13) | 1 (2.94) | 240 (–) | 3 (–) | 0 | – | – | 7 (2.32) | 72 (10, 144) | 7 (3, 13) |
| Maculopapular | 4 (2.47) | 11 (9.5, 12) | 2.5 (1.3, 8.5) | 1 (1.05) | 168 (–) | 7 (–) | 0 | – | – | 1 (9.09) | 0.25 (–) | 1 (–) | 6 (1.99) | 11 (9, 12) | 2.5 (1, 7) |
| Anaphylaxis | 2 (1.23) | 0.2 (0.1, 0.3) | 1.5 (1, 2) | 0 | – | – | 0 (0) | – | – | 1 (9.09) | 0.25 (–) | 1 (–) | 3 (0.99) | 0.25 (0.1, 0.3) | 1 (2, 1) |
| Others | 7 (4.32) | | | 3 (3.16) | – | – | 2 (5.88) | | | 1 (9.09) | – | – | 20 (7.28) | 72 (24, 72) | 12 (3, 14) |
| • Herpes infection | 1 (0.62) | 72 (–) | 3 (–) | 0 | 108 | 5.5 (4, 7) | 1 (2.94) | 24 (–) | 14 (–) | 1 (9.09) | 72 (–) | 12 (–) | 3 (0.99) | 72 (48, 168) | 7 (4, 40) |
| • Insect bite like reaction* | 0 | – | – | 2 (2.11) | (48, 168) | – | 1 (2.94) | 72 (–) | 40 (–) | 0 | – | – | 3 (0.99) | 48 (6, 336) | 15 (7, 24) |
| • Pustule/ Acneiform lesion | 3 (1.85) | 48 (6, 336) | 15 (7, 24) | 0 | – | – | 0 | – | – | 0 | – | – | 3 (0.99) | 4 (–) | 36 (–) |
| • Vasculitis | 1 (0.62) | 4 (–) | 36 (–) | 0 | – | | 0 | – | – | 0 | – | – | 1 (0.40) | 24 (24, 24) | 9 (4, 14) |
| • Pityriasis rosea | 1 (0.62) | 24 (–) | 14 (–) | 1 (1.05) | 24 (–) | 4 (–) | 0 | – | – | 0 | – | – | 2 (0.66) | 2 (–) | 4 (–) |
| • Macular erythema | 1 (0.62) | 2 (–) | 4 (–) | 0 | – | – | 0 | – | – | 0 | – | – | 1 (0.40) | | |
| Unidentified** | 67 (41.36) | 8 (4, 24) | 0.5 (0.1, 2) | 37 (38.95) | 20 (7, 24) | 1 (0.5, 3) | 12 (35.29) | 48 (18, 120) | 1.5 (0.3, 2.5) | 4 (36.36) | 5 (2.8, 27) | 1 (0.6, 5) | 120 (39.74) | 10.5 (4.5, 24) | 1 (0.1, 3) |

*Insect bite like reaction was defined as an eruption of multiple discrete erythematous papules.

**Unidentified referred to cases without available photographs.

**Table 2** Characteristics of cutaneous adverse reactions of the 1st and 2nd dose vaccination in the same patient. (Unidentified rashes were excluded)

| 1st dose of CoronaVac (*n* = number of incident self–reports) | 2nd dose | Outcomes | Median Onset 1st Dose (IQR) hours | Median Duration 1st Dose (IQR) days | Median Onset 2nd Dose (IQR) hours | Median Duration 2nd Dose (IQR) days |
|---|---|---|---|---|---|---|
| Urticaria *n* = 45 | CoronaVac | Same reaction (Urticaria), *n* = 15 (33.33%) | 12 (3, 36) | 4 (1, 16) | 3 (0.6, 8) | 1 (0.1, 11.5) |
| | | Different reaction (Papulovesicles, Erythema at injection site), *n* = 2 (4.44%) | – | – | – | – |
| | | Negative, *n* = 26 (57.79%) | – | – | – | – |
| | ChAdOx1 nCoV-19 | Same reaction(Urticaria), *n* = 2 (4.44%) | 60.1 (30.1, 90) | 27.5 (27.3, 27.8) | 2.8 (1.6, 3.9) | 16 () |
| Angioedema *n* = 3 | CoronaVac | Same reaction (Angioedema), *n* = 2 (66.67%) | 16.5 (12.8, 20.3) | 6.5 (3.8, 9.3) | 48 (36, 60) | 0.6 (0.3, 0.8) |
| | | Negative, *n* = 1 (33.33%) | – | – | – | – |
| Anaphylaxis *n* = 1 | ChAdOx1 nCoV-19 | Same reaction (Anaphylaxis), *n* = 1 (100%) | 0.25 (–) | 1 (–) | 0.25 (–) | 1 (–) |
| Eczematous *n* = 9 | CoronaVac | Same reaction (Eczematous), *n* = 2 (22.22%) | 37.5 (20.3, 54.8) | 22.5 (18.3, 26.8) | 14 (9, 19) | 5 (4, 6) |
| | | Negative, *n* = 7 (77.78%) | – | – | – | – |
| Pityriasis rosea *n* = 1 | CoronaVac | Same reaction (Eczematous), *n* = 1 (100%) | 24 (–) | 14 (–) | 24 (–) | 4 (–) |
| Ecchymosis/purpura, *n* = 4<br>Erythema injection site, *n* = 3<br>Maculopapular, *n* = 3<br>Acneiform/pustule, *n* = 3<br>Papulovesicle, *n* = 2<br>Herpes reactivation, *n* = 1<br>Macular erythema, *n* = 1 | CoronaVac | Negative | – | – | – | – |
| **1st dose of ChAdOx1 nCoV-19 (*n* = number of incident self-reports)** | **2nd dose** | **Outcomes** | **Median Onset 1st Dose (IQR) hours** | **Median Duration 1st Dose (IQR) days** | **Median Onset 2nd Dose (IQR) hours** | **Median Duration 2nd Dose (IQR) days** |
| Urticaria *n* = 7 | ChAdOx1 nCoV-19 | Same reaction (Urticaria), *n* = 1 (14.29%) | 24 (–) | 53 (–) | 7 (–) | 18 (–) |
| | | Different reaction (Herpes infection), *n* = 1 (14.29%) | – | – | – | – |
| | | Negative, *n* = 4 (57.14%) | – | – | – | – |
| | CoronaVac | Negative, *n* = 1 (4.29%) | – | – | – | – |
| Eczematous, *n* = 3<br>Erythema at injection site, *n* = 1<br>Delayed, at injection site, *n* = 1<br>Papular, *n* = 1<br>Petechiae, *n* = 1<br>Ecchymosis, *n* = 1<br>Insect bite–like reaction, *n* = 1 | ChAdOx1 nCoV-19 | Negative | – | – | – | – |

## Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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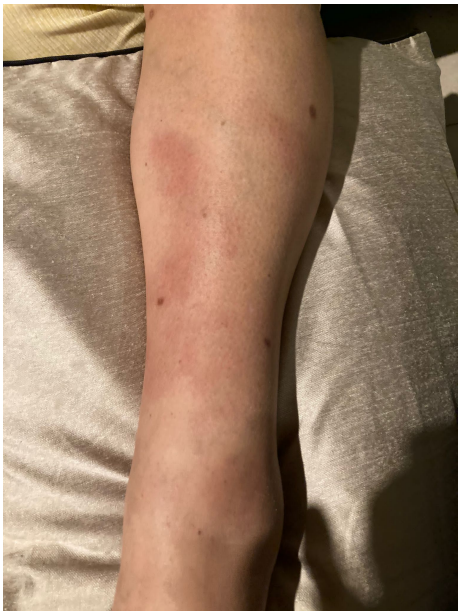

**Figure 1** Erythema nodosum on the left leg.

# Erythema nodosum following the first dose of ChAdOx1-S nCoV-19 vaccine

*Editor*

We present a case of erythema nodosum to ChAdOx1 nCoV-19 vaccine in a 64-year-old woman. The female patient complained of painful and erythematous skin lesions on both lower limbs 2 days after receiving the first dose of ChAdOx1 nCoV-19 vaccine (Fig. 1). Physical examination revealed erythematous plaques on pretibial surfaces, painful on palpation and compatible with the diagnosis of erythema nodosum (EN). The patient had no comorbidities except for heterozygous factor V Leiden mutation.

Laboratory and instrumental examinations performed to investigate the aetiology of EN resulted negative and included blood count, erythrocyte sedimentation rate, C-reactive protein, Mantoux test, antistreptolysin antibodies, viral hepatitis and HIV tests, angiotensin-converting enzyme, screening for connective tissue diseases and vasculitis, and chest X-ray. No skin biopsy was performed due to the classic clinical presentation of EN, which allowed for clinical diagnosis. Systemic therapy with methylprednisolone 16 mg was started with symptom improvement within 4 weeks.

The patient had no personal or family history of systemic or skin diseases and had not taken any drug related to the development of EN; therefore, it was hypothesized a causal correlation between COVID-19 vaccination and the appearance of skin manifestations.

EN is a panniculitis characterized by acute-onset inflammation of the dermo-hypodermic junction and interlobular septa of the hypodermic tissue; it can be idiopathic or associated with various clinical conditions such as infections, medications, pregnancy, inflammatory bowel diseases, sarcoidosis, autoimmune diseases and malignancies. The pathogenesis is unknown, but a delayed type IV hypersensitivity reaction to certain antigens is hypothesized.[1]

EN has been described as cutaneous manifestation of COVID-19 infection in many patients; the relationship between COVID-19 and EN can be explained by a dysregulated immune response induced by viral infection that can trigger the cutaneous manifestation.[2]

In the case described, the patient's clinical history and the temporal association between the administration of the first dose of ChAdOx1 vaccine and the onset of EN were compatible with the diagnosis of ChAdOx1 nCoV-19 vaccine-related EN. ChAdOx1 nCoV-19 consists of two doses given with an interval of 4–12 weeks and involves the production of antibodies to the spike protein.[3] The main side-effects reported were injection site pain, malaise, headache, fatigue, myalgia, pyrexia, chills, arthralgia and nausea, usually mild to moderate and self-limiting. Moreover, reports of thromboembolic events in young females have been reported and led to temporary suspension of ChAdOx1 nCoV-19 vaccine.[4]

The most common cutaneous adverse events reported after ChAdOx1 nCoV-19 vaccine were reactions at the injection site such as pain, redness, warmth, swelling, induration and tenderness[5]; delayed inflammatory reactions,[6] severe cellulitis, rosacea, psoriasis, vitiligo and Raynaud's phenomenon were also reported.[7]