CoronaVac/Sinovac COVID-19 Vaccine-Related Hypersensitivity Reactions and Second-Dose Vaccine Administration: Tertiary Allergy Center Experience

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Abstract
Introduction: The COVID-19 pandemic has caused a global health crisis. To prevent the disease, the Ministry of Health of Turkey gained approval for the CoronaVac COVID-19 vaccine for emergency use as the first-line. This study aimed to evaluate patients who developed hypersensitivity reactions (HRs) due to the CoronaVac vaccine and to share our experience of administering the second dose of vaccine to these patients. Methods: The study group included the patients who presented to the Ege University Allergy and Immunology Division between January and May 2021. Demographic data, atopic status, allergic reactions to the first dose of the COVID-19 vaccine and the route of second-dose vaccine administrations were recorded. Results: A total of 7 patients (four healthcare professionals), 6 (86%) of whom were women, with an average age of 53.4 years, were included in the study. The rate of allergic reactions among Ege University health workers was 0.036% (2/5,558). Six of our patients had a history of additional allergic diseases and comorbid diseases. None had any allergic reactions to previous vaccinations and latex allergy. Reactions developed commonly on the skin, as generalized urticaria/angioedema and pruritus. The severity of the reactions was evaluated as mild in 2, moderate in 3, and severe in 2 cases. The second-dose CoronaVac was safely administered by using a gradually increase dose in a total of 6 patients. Conclusion: In patients with HRs due to Sinovac in the first dose, the second dose can be safely performed using a gradually increased dose.

Introduction
The SARS-CoV-2 pandemic, which started in Wuhan, China, in December 2019, has caused a devastating global crisis. No fully effective treatment for COVID-19 is known. There was an urgent need for a vaccine to control the pandemic. Vaccines continue to prevent millions of deaths worldwide each year by either completely protecting individuals from the disease or relieving symptoms associated with the disease. The first COVID-19 vaccine candidate entered clinical testing at speed on March 16th,
The CoronaVac vaccine was approved for emergency use in Turkey on January 14th, 2021, for healthcare workers, the elderly (age >65 years), and those with comorbid conditions. It was started to be administered in two doses in total at 4-week intervals.

The World Health Organization and independent experts have shown that vaccines are much safer than therapeutic drugs [2]. Albeit rarely, adverse reactions to vaccines may occur due to vaccine pharmacokinetics, toxicity, adverse effects, and interactions with other drugs, as well as hypersensitivity reactions (HR). Although HRs can be seen with allergic and non-allergic mechanisms, they are most frequently encountered as an immunoglobulin (Ig)-E-mediated allergic reactions [3]. Although anaphylaxis is the most severe HR and vaccine-related anaphylaxis that usually develops within 15–30 min is life-threatening and can lead to death, it can be treated with adrenaline without lasting effects [4]. Tryptase and complement terminal pathway C5b-9 levels can be helpful to confirm the diagnosis of anaphylaxis. Although tryptase is elevated within 60 min to 5 h during IgE-mediated anaphylaxis, it is not distinguished from non-IgE-mediated and non-IgE-mediated [5]. SC5b-9 is a measure of complement terminal pathway activation and has been proposed to be measured in non-IgE-mediated HR [6].

Rapid drug desensitization (RDD) is a frequently and successfully performed procedure when there are no alternatives and allows temporary clinical tolerance to the drug. In the literature, there are case reports of allergic reactions, including anaphylaxis, occurring after Pfizer – BioNTech and Moderna mRNA vaccines, but there are no HR data and RDD protocols for the use of the Sinovac vaccine [8, 9]. In the present study, the demographic characteristics, atopic status, laboratory characteristics, “type/kind” of reactions due to the first-dose vaccine, prick test results, and second-dose vaccine treatment approach, and the responses of patients were evaluated. We aimed to contribute to the literature by sharing our experiences.

**Materials and Methods**

Seven patients who presented to the Ege University, Department of Internal Medicine, Department of Allergy and Immunology between January 2021 and May 2021 with a preliminary diagnosis of HR after the first dose of Sinovac vaccine were evaluated retrospectively. Two of those were healthcare workers at the Ege University Hospital. The rest of the patients were referred to us from other hospitals. The Local Ethics Committee of Ege University School of Medicine, and the Ministry of Health approved the study and informed consent was obtained from all subjects (2021-05-07T15_25_12).

Demographic characteristics of patients (age, sex, healthcare worker status, history of allergic disease, and comorbidities), atopic status (SPT with aeroallergens and foods), and laboratory findings (absolute eosinophil count, total IgE, specific IgE, basal tryptase) were recorded. Onset time and symptoms of HR were obtained from medical records. HRs were categorized as mild, moderate, or severe according to the clinical severity grading system proposed by Brown [10].

**Skin Testing and Second-Dose Vaccine Administration in Reactive Patients**

Before the vaccine administration, SPT with the full concentration of vaccine was performed in 4 patients. In the other patients, SPT could not be performed due to antihistaminic use and refusal of the test. Histamine (10 mg/mL) was used as a positive control and saline solution was used as a negative control. A mean wheal diameter of 3 mm or larger than that obtained with the control solution was considered positive. IDT could not be performed because the registered vaccine is received in each patient’s name only once.

Informed consent was obtained from all patients. Montelukast 10 mg PO was given 1 day before the procedure and methylprednisolone (40 mg IV), H1 antihistamine (pheniramine 45.5), and H2 receptor blocker as premedication were administered 30 min before the procedure. The patients with a mild reaction were administered the second dose of vaccine intramuscularly in two steps at 45-min intervals and were observed for 2 h. In patients with moderate and severe reactions, it was planned to administer drugs in five steps with a gradually increasing dose after premedication. The protocol was performed via an intramuscular route with 15-min intervals in the intensive care unit under one-to-one nursing observation. The steps are shown in Table 3.

**Results**

Seven patients (6 females, 1 male) with a mean age of 53.4 (range 34–74) years were evaluated. Four were healthcare workers. Two out of 5,558 healthcare workers who were vaccinated in our hospital demonstrated HR to the vaccine. The rate of HRs among Ege University health workers was 0.036% (2/5,558).

None of the patients reacted to previous vaccines. Six had a history of allergic disease and additional comorbid disease, most commonly hypertension. SPT was performed with inhalant allergens, food allergens, and latex in 5 patients, but sensitization was detected only in 2 of them; it was clinically significant only for patient #2. SPT could not be performed because patient #6 had dermatographism and patient #7 refused the test. Mixed inhaled IgE values were positive in patient #2 and were consistent with the diagnosis.
with the history; whereas, in patient #7, grass mix, fish mix, and latex sIgE values were positive but inconsistent with the clinical history. The latex sIgE value was found to be negative in the other patients.

Eosinophil counts, basal tryptase levels, liver function tests, kidney function tests, C-reactive protein, and Ig G/A/M values were within normal limits. The demographics, atopic evaluations, and laboratory findings of the patients are presented in Table 1.

The mean interval from vaccine receipt to symptom onset was 30 (range, 2–120) min. Two patients had mild, 3 had moderate, and 2 had severe HRs to the vaccine. The most common symptoms were urticaria/angioedema and dyspnea (shown in Fig. 1). Adrenaline was not administered to any patients in the emergency department. Corticosteroids and antihistamines were administered to 6 patients. One patient (#4) was not treated in a healthcare setting. Table 2 lists the clinical characteristics of the patients with HRs to the CoronaVac vaccine.

All of the second doses of vaccines were administered 4 weeks after the first reactions because this interval was advised by the Turkish Ministry of Health. SPTs were performed using full-concentration CoronaVac (1/1) in 4 patients and each was negative. We could not perform SPTs in the others due to the use of antihistamines and refusal. After the premedication, a second dose of vaccine was administered with a gradually increasing dose in the intensive care unit. In 4 patients, the procedure was completed without any problems in five steps. Patient #2, who developed only upper lip swelling with the first dose, received the second dose in two steps. Upper lip swelling was also observed 45 min after the second dose. There were no additional findings. The patient was administered antihistamine and discharged after 4 h of follow-up. Patient #7 did not accept the second dose of the vaccine. The second dose of the CoronaVac vaccine was safely administered to all of the patients (shown in Table 3).

Discussion

In our case series, we evaluated the post-vaccine HRs of Sinovac COVID-19. The majority of our patients were female and had a concomitant allergic disease. Cutaneous symptoms and signs were the most common and were observed within an average of 30 min after vaccine administration. The reactions occurred within the first hour in 6 patients. Similar results have been reported with other COVID-19 vaccines [9].

In our study, the atopic conditions of 7 cases with HRs history to Sinovac vaccine were also evaluated. Respectively, drug allergy (n = 4), chronic spontaneous urticaria/angioedema (n = 3), contact dermatitis (n = 3), and most rarely, allergic rhinitis (n = 2) with inhalant allergens positivity in the skin and/or serum IgE tests were detected. Considering all cases, drug allergy is the most common accompanying atopic manifestation of HSRs against the Sinovac vaccine. Although statistical significance cannot be calculated due to the limited number of patients, the Sinovac vaccine should be administered with caution in cases with drug allergy.

The incidence of anaphylaxis in routine vaccination was reported as 1.31 cases/million doses (95% CI: 0.90–1.84) [11]. However, in clinical trials of the Pfizer-BioNTech and Moderna COVID-19 vaccines, excluding participants with a history of a severe allergy to any component of the vaccine or any vaccine, HRs were equally observed in the placebo (normal saline) and vaccine groups in both studies [12–14]. In real-life data, anaphylaxis is seen at a rate of 4.7 cases/million doses with the Pfizer-BioNTech vaccine and 2.5 cases/million doses with the Moderna vaccine as of January 18th, 2021 [15]. Confirmed allergic reactions to vaccines are not frequently attributed to the active ingredients, but rather to the inactive ingredients [16]. HR due to these vaccines are caused by components of the infectious agent, proteins in the biologic culture medium (chicken embryo cell) and eggs, cow’s milk, aluminum hydroxide, polysorbate 80, polysorbate 20, polyethylene glycol, gelatin, thimerosal, antibiotics (such as neomycin, gentamicin, polymyxin B),
Table 1. Characteristics of patients and results of SPT, specific IgE levels, and laboratory findings

| Patient | Age/sex | History of atopic disease | Comorbidity | Skin prick test of inhalant, food allergens, and latex | Specific IgE of aeroallergen mix, food mix, and latex, kUA/L | Total IgE, kU/L | Tryptase, µg/L |
|---------|---------|---------------------------|-------------|--------------------------------------------------------|-------------------------------------------------|---------------|--------------|
| #1 70/F | Rhinitis | DM, HL, HT, COPD, epilepsy, hypothyroidism | Negative | Negative | <16.9 | 5.87 |
| #2 70/F | AR, CSU-AE | D.F:5*20, D.P:6*15, olive: 5*15 | Aeroallergen mix: 5.07 | 234 | 4.44 |
| #3 45/F | CD (metals), DA (NSAID) | Negative | Negative | <16.9 | 3.82 |
| #4 47/F | AR, CD (metals), DA (pen) | Negative | Negative | 47.2 | 7.32 |
| #5 55/F | Rhinitis, CSU-AE, DA (Quin, TMP-SMX, CA) | Negative | Negative | 36.2 | 5.27 |
| #6 53/F | CD (metals), DA (pen, mxf, TMP-SMX, ery), CSU-AE | None | None | 102 | 3.11 |
| #7 34/M | None | None but his child had a solitary cutaneous mastocytoma | None | None | 102 | 3.11 |

F, female; M, male; AR, allergic rhinitis; CSU-AE, chronic spontaneous urticaria/angioedema; CD, contact dermatitis; DA, drug allergy; TMR-SMX, sulfamethoxazole/trimethoprim; Pen, penicillin; Mxf, moxifloxacin; Ery, erythromycin; Quin, quinolone; CA, contrast agent; DM, diabetes mellitus; HL, hyperlipemia; HT, hypertension; COPD, chronic pulmonary disease; AS, ankylosing spondylitis; ARA, acute rheumatic fever; D.F, dermatophagoides farinae; D.P, *Dermatophagoides pteronyssinus*; B.F, barley flour; O.F, oat flour; ND, not done.

Table 2. Characteristics of reported cases of HRs after the Sinovac vaccine

| Patient | Time to onset of Symptoms, min | Symptoms | Level of care | Treatment after first dose | Symptom resolution time | HR grade |
|---------|-------------------------------|----------|---------------|---------------------------|------------------------|----------|
| #1 10   | Chest tightness, dyspnea, tremor, dizziness, disoriented | ED, ICU  | O₂, Cp (20 mg), Pred (80 mg), IV hydration (%0.9 NaCl, 1,000 mL) | 24 h | Severe |
| #2 5    | Swollen lip, fatigue | ED       | Dxm (8 mg), Cpm (45.5 mg) for 2 days | 2 d | Mild |
| #3 2    | Nausea, dyspnea, minimal swelling of the uvula, hypertension, tachycardia | ED       | O₂, Cp (20 mg), Pred (80 mg) | 30 min | Moderate |
| #4 10   | Pruritus, urticaria, angioedema, throat tightness, dyspnea | Spontaneous | None | 12 h | Moderate |
| #5 5    | Pruritus, angioedema, throat tightness, dizziness, dyspnea | ED | Cpm (45.5 mg), Pred (40 mg), Dxm (8 mg) for 3 days | 3 d | Moderate |
| #6 120  | Pruritus, urticaria, throat tightness | ED | Cpm (45.5), Dxm (8 mg), Ace (500 mg) | 3 h | Mild |
| #7 60   | Tingling face and neck, flushing, dizziness, palpitation, hypotension | ED | Acute treatment: Cpm (45.5 mg), Pred (80 mg), Dxm (8 mg) Maintenance treatment: Pred (48 mg) and bilastine (40 mg) (PO daily for 1 week, then discontinue) | 5 d | Severe |

ED, emergency department; ICU, intensive care unit; O₂, oxygen; Cp, chlorphenoxamine; Pred, prednisolone; Dxm, dexamethasone; Ace, acetaminophen; Cpm, chlorpheniramine maleate.
and sensitivity to excipients [17]. Although the etiology of anaphylaxis in these cases is not fully understood, polyethylene glycol, a component of a lipid-based nanoparticle delivery system that prevents rapid enzymatic degradation of mRNA vaccines and facilitates in vivo delivery, seems to be the potential culprit [3, 18, 19].

The CoronaVac vaccine is produced by grafting the SARS-CoV-2 virus (CZ02 strain) into African green monkey kidney cells (Vero cell) and absorbing aluminum [20]. There were no other additives. Aluminum compounds are widely used in vaccines and mostly local reactions have been reported, but there is only one case report of anaphylaxis due to aluminum-containing drugs in the literature [21]. None of our patients had a history of reaction to previously administered vaccines, and further testing was not performed because there was no commercially available aluminum test material approved to investigate type 1 HRs. However, more research is needed to determine the role of aluminum in HRs associated with the CoronaVac COVID-19 vaccine.

In phase 1–2 clinical studies, 743 participants received at least one dose of the investigational product [22]. The most common symptom was injection site pain, most other reactions were mild and there was no significant difference between the placebo and vaccine groups. Urticaria, as an acute HR, occurred in only 1 patient. Urticaria lesions graded as severe, developed 48 h after the participant received the first 6 μg dose, and improvement was achieved within 3 days by

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**Table 3. Second-dose vaccine administration protocols and results**

| Patient | Histamine skin prick test | Vaccine SPT (undiluted) | Second-dose vaccine administration (step) | Symptoms with second dose |
|---------|---------------------------|-------------------------|------------------------------------------|--------------------------|
| #1      | 8 × 40 mm                 | Negative                | 1. Step 0.05 mL (1/10 concentration), 2. Step 0.05 mL (1/1 concentration), 3. Step 0.1 mL (1/1 concentration), 4. Step 0.15 mL (1/1 concentration), 5. Step 0.15 mL (1/1 concentration) (15-min intervals) | None                     |
| #2      | On-demand antihistaminics use | ND                      | 1. Step 0.25 mL (1/1 concentration), 2. Step 0.25 mL (1/1 concentration) (45-min intervals) | Swelling on the upper lip |
| #3      | 8 × 20 mm                 | Negative                | 1. Step 0.05 mL (1/10 concentration), 2. Step 0.05 mL (1/1 concentration), 3. Step 0.1 mL (1/1 concentration), 4. Step 0.15 mL (1/1 concentration), 5. Step 0.15 mL (1/1 concentration) (15-min intervals) | None                     |
| #4      | 6 × 15 mm                 | Negative                | 1. Step 0.05 mL (1/10 concentration), 2. Step 0.05 mL (1/1 concentration), 3. Step 0.1 mL (1/1 concentration), 4. Step 0.15 mL (1/1 concentration), 5. Step 0.15 mL (1/1 concentration) (15-min intervals) | None                     |
| #5      | 7 × 35 mm                 | Negative                | 1. Step 0.05 mL (1/10 concentration), 2. Step 0.05 mL (1/1 concentration), 3. Step 0.1 mL (1/1 concentration), 4. Step 0.15 mL (1/1 concentration), 5. Step 0.15 mL (1/1 concentration) (15-min intervals) | None                     |
| #6      | Dermatographism (+)       | ND                      | 1. Step 0.25 mL (1/1 concentration), 2. Step 0.25 mL (1/1 concentration) (45-min intervals) | None                     |

ND, not done.
administering chlorphenamine and dexamethasone. A similar reaction was not observed after the second dose of the vaccine [23]. Sinovac phase 3 clinical trials conducted in Turkey, Brazil, Indonesia, and Chile are ongoing. Phase 3 studies conducted in 24 centers in Turkey have been completed and preliminary data was released in a press conference [24]. Although no serious adverse effects were observed in the description, the most common adverse effects were fatigue (9.8%), headache (7.6%), muscle pain (3.8%), fever (2.5%), chills (2.4%), and pain at the injection site (1.6%) [25]. Although the data from Chile were not sufficient, the anaphylaxis rate was reported as 1.7/100,000 doses by the Strategic Advisory Group of Experts [26]. The rate of anaphylaxis as 1.7/100.00 is not low, but worse than Moderna and Pfizer. We do not have exact data on how many doses of the vaccine were administered in our city, but anaphylaxis to Sinovac vaccines have occurred at rates of 2 cases per 5,558 doses among healthcare workers at the Ege University Hospital.

Anaphylaxis to vaccines may be IgE or non-IgE mediated. The signs and symptoms are similar in both. IgE-mediated reactions occurred in sensitized individuals with a history of prior antigen exposure, but non-IgE-mediated reactions can occur with the first exposure through direct activation of mast cells, basophils, and complement kinin pathways. SPTs with the culprit agent is used to detect HRs. However, there is no consensus on test concentrations and evaluations for the CoronaVac vaccine. In our country, we did not have enough material to performed IDT because the vaccines are registered to individuals. The non-irritative concentration of the vaccine was also not certain. All of the performed SPTs were found negative in our cases. All of the negative vaccine SPTs were evaluated as true negative in our study. Our justification for this evaluation is that the histamine skin test response was detected as strongly positive with erythema and induration in all of our 4 patients. In addition, all of our patients use systemic corticosteroids and antihistamines for less than 5 days in the treatment of HSR after the Sinovac vaccine. Systemic medications were not administered to our patients for a period and/or dose that would impair the skin test response. Non-IgE-mediated mechanisms may be assumed to be involved in these cases. Sinovac-related reactions cannot be evaluated as IgE or non-IgE mediated based on the current findings and laboratory data because tryptase and SC5b-9 were not checked during the reaction.

RDD is used frequently and successfully in the management of both IgE and non-IgE-mediated HR. RDD is used when there is no alternative treatment allowing temporary clinical tolerance to a drug. However, there is little literature on vaccine desensitization and there is no RDD protocol for the Sinovac vaccine [27, 28]. The European Academy of Allergy and Clinical Immunology report on the diagnosis, management, and prevention of severe allergic reactions to COVID-19 vaccines recommended RDD with individual vaccine components and aimed to develop safe administration after primary vaccination [29]. Incremental dosing of the second injection usually involves fewer steps, is shorter in duration, and is not considered desensitization. However, if symptoms develop during the procedure, it is treated similarly to desensitization and, if successfully treated, the protocol can be continued, unlike drug provocation [30]. In this context, a 2-step gradual increase was performed on 2 patients with mild history, and a 5-step gradual increase was performed on 4 patients who had severe reactions.

Conclusion

To date, our case series is the first in the literature showing that the Sinovac vaccine can be administered safely and effectively with desensitization/partial dose provocation, under the supervision of an allergy and immunology specialist, in patients who experience an adverse reaction to the first dose.

Statement of Ethics

The study was conducted in accordance with the World Medical Association Declaration of Helsinki. The Local Ethics Committee of Ege University School of Medicine, and the Ministry of Health approved the study and informed consent was obtained from all subjects (2021-05-07T15_25_12). Written informed consent was obtained from parents and children aged 12 years and older.

Conflict of Interest Statement

The authors report no proprietary or commercial interest in any product mentioned, concept discussed, or personal relationships with other people or organizations that could influence their work and conclusions in this article.

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Author Contributions

R.G., C.T.D., E.N.M.G., and A.Z.S. contributed to conceptualization; R.G. and C.T.D. contributed to data acquisition; R.G., C.T.D., E.N.M.G., and A.Z.S. contributed to writing—original draft preparation; R.G. and E.N.M.G. contributed to writing—review and editing; R.G. and A.Z.S. contributed to supervision.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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