Allergic reactions after administration of pfizer-biontech covid-19 vaccine to healthcare workers at a tertiary hospital

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Abbreviations

COVID-19 (Coronavirus Disease 2019); HR (Hypersensitivity reactions); PEG (Polyethylene glycol); ADR (Adverse drug reactions).

Comirnaty® is a mRNA-based coronavirus disease 2019 (COVID-19) vaccine manufactured by Pfizer-BioNTech. In a clinical trial of 43,548 participants the vaccine conferred 95% protection against COVID-19 and no severe allergic reactions were reported [1].

COVID-19 vaccines are contraindicated in patients that have suffered a previous severe allergic reaction to any component of the vaccine or to the first dose. Based on the experience with other vaccines, systemic allergic reactions would be expected within a range of 1-5 cases per million applications [2].

Clinically, drug hypersensitivity reactions (DHRs) are classified as immediate or nonimmediate/delayed depending on their onset during treatment. Immediate DHRs are induced by an IgE-mediated mechanism and occur within 1–6 h after the last drug administration while nonimmediate DHRs are associated with a T-cell dependent mechanism and occur at any time as from 1 h after the initial drug administration [3]. Systemic immediate DHRs were classified by severity [4].

Our objective is to report the clinical characteristics and the allergy assessment of all healthcare workers (HCW) from our hospital referred by the occupational health

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department after developing a suggestive DHRs [3] following the administration of the first dose of Comirnaty® during January 10-19, 2021. We conducted a retrospective review of HCW clinical charts. A thorough allergy study was conducted, including a detailed clinical history and cutaneous tests. We performed skin prick tests (SPT) with Comirnaty®, using the leftovers from vaccine vials, and to polyethylene glycol-2000 (PEG-2000) (Poly (ethylene glycol) BioUltra, 2,000 from Sigma-Aldrich), which is the excipient contained in this vaccine, at different concentrations (0.16 -160mg/ml). PEG has been reported as an antigen responsible for hypersensitivity reactions in drugs containing this excipient [5-6]. Basophil activation test with PEG2000 and Comirnaty® was also performed in patient 1, who had suffered a mild generalized urticaria after the second vaccine dose despite premedication. The study was approved by the ethics committee in our hospital (HULP- PI-4733).

A total of 8,446 first doses of Comirnaty® were administered, 6,393 (75.7%) in females, and the median age was 36.7 years (IQR 34-42.75). None had received a vaccine on the previous 7 days and did not have COVID-19 symptoms or an acute febrile disease at that moment.

Through a questionnaire, answered before vaccine administration, 127 HCW reported a history of allergic reactions to drugs, 40 to food allergens, 18 to aeroallergens, 11 to metals, 4 to latex and 65 to unspecified allergens. None referred history of allergic reactions to vaccines or to excipients as PEG or other ethylene oxide derivatives. Every health care worker was asked to call or to send an email to the occupational health department in the event any adverse reaction happened after the administration of the vaccine. A total of 207 adverse drug reactions (ADR) were reported to this department. Eleven (0.13%) suspected allergic reactions were reported after the first dose of the vaccine and were referred to the Allergy department for assessment (Supplementary Table 1). Nine (81.8%) were reported in female, and the median age of the subjects was 39 years (IQR 29.5-56.5). All were suspected cases of mild allergic reactions, 10 within the first 24h and 1 within 48h, and no severe allergic reactions were reported. Four

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patients were treated with systemic corticosteroids or H1-antihistamines, and none required hospitalization.

SPT were performed to 9 patients, with negative results in all of them. BAT was also negative in patient 1. Ten HCW (90.9%) received the second dose of Comirnaty® and no severe allergic reactions were reported. Five of them received premedication with H1-antihistamines, and two out of these five cases presented milder cutaneous symptoms. Five HCW did not receive premedication with H1-antihistamines, and three of them presented milder cutaneous symptoms. One HCW could not receive the second dose due to an intercurrent medical condition.

The Centers for Disease Control and Prevention (CDC) reported the allergic reactions presented after administration of the first dose of Pfizer-BioNTech COVID-19 vaccine in 1,893,360 subjects [7]. They described 83 cases of non-anaphylactic allergic reactions, with cutaneous or mild respiratory symptoms and 21 cases of anaphylaxis (11.1 per million of doses). Seventeen (81%) of these patients with anaphylaxis had a previous history of allergic reactions. Blumenthal et al. [8] observed that acute allergic reactions were reported by 1,365 health-care employees after 64,900 first doses (2.10% [95% CI, 1.99%-2.22%]), more frequently but not significantly with the Moderna vaccine compared with Pfizer-BioNTech (2.20% [95% CI, 2.06%-2.35%] vs 1.95% [95% CI, 1.79%-2.13%]; P = .03) [6]. With Comirnaty® (n=25,929), the number of anaphylaxis was low (7 confirmed cases, 2.47/10,000 vaccinations). In our series, we found no cases of anaphylaxis. However, there was a higher incidence of mild allergic reactions (0.13% vs. 0.0044%) than in the data reported by the CDC, although a lower incidence of acute allergic reactions (0.11% vs. 1.95 %) than in the study reported by Blumenthal [8].

Immediate DHRs related to vaccine administration are frequently associated with the inactive components or byproducts of the vaccine manufacturing process, such as egg or latex [9]. In the case of Comirnaty®, the presence of excipients as PEG-2000 has been considered as the potential agent causing immediate DHRs [5,6,9-11]. Furthermore, PEG-encapsulated nanomedicine can cause pseudo-allergic reactions in experimental models

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[12]. In addition, after endocytosis, the mRNA free PEG in lipid nanoparticles floating on the cell-surface interacts with IgE antibodies that bind to the FcƐR1-receptor on mast cells or basophils and can trigger immediate release of inflammatory mediators [12]. Although we cannot define the underlying mechanism of each reaction, it seems likely that non-IgE mediated mechanism are involved, as suggested by other groups [13]. In these mild cases in which an IgE-mediated reaction to PEG has been discarded, premedication with anti-H1 prior to the second dose could be helpful in blocking non-IgE mediated histamine release and may alleviate symptoms and improve tolerability.

It is important to carefully evaluate each patient with a possible allergic reaction to the vaccine to avoid being unnecessarily denied access to the vaccine [10]. In addition, all vaccinations centers should be prepared for the early diagnosis and treatment of allergic reactions related to COVID-19 vaccines [11].

In conclusion, after the administration of the first dose of Comirnaty®, there was no occurrence of severe allergic reactions in a large group of HCW. From those who presented mild allergic-like reactions, neither sensitization to Comirnaty® nor to its excipient PEG-2000 were found in the study. Although we cannot definitively rule out the occurrence of IgE-mediated reactions, it appears that most reactions could have a non-IgE-mediated mechanism. Finally, SPT with the vaccine and its excipients could be useful in the allergy work-up of hypersensitivity reactions to COVID-19 vaccines, but further studies will help clarify its real value.

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The authors declare that they have no conflicts of interests to disclose.

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