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CASE REPORT

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# Successful fractionated undiluted doses of COVID-19 vaccine in five cases of suspected allergic reactions to the first dose

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**Abstract**

After a suspected allergic reaction to first dose of mRNA COVID-19 vaccine, given the PEG skin tests negativity and tolerance in vivo to PEG containing drugs, five patients were vaccinated with the second dose of Pfizer-Biontech undergoing a fractional protocol, with antihistamine premedication, without presenting immediate or delayed reactions.

**KEYWORDS**

allergy, anaphylaxis, COVID-19 vaccine allergic reaction, COVID-19, mRNA vaccine, polyethylene glycol, vaccine side effects, vaccine

## 1 | INTRODUCTION

Since the outbreak of the coronavirus disease (COVID-19), the implementation of public health practices and administration of the complete vaccination cycle helped to prevent the infection spread.[1]

Anaphylactic reactions, even if extremely rare, can occur with any vaccine (1.31 per million vaccine doses administered), but the incidence of these reactions to COVID-19 vaccination seemed to be more frequent.[2]

Last annual report drafted by the Drug Italian Agency records, for any million doses administered, the following anaphylactic events: 3 for BNT162b2 and 1.9 for mRNA-1273.[3]

The mechanisms underlying adverse reaction to mRNA vaccines are unknown, but the excipients have been suggested as a potential culprit, particularly polyethylene glycol (PEG, macrogol, E1521) and polysorbate (PS).[4] Cross-sensitization has been suggested between excipients, but the low molecular weight of PS led to suppose a little role in determining an allergic reaction. Furthermore, derivatives are widely included in drugs and everyday products. Several mechanisms have been hypothesized to cause adverse reactions to PEG more than an IgE-mediated mechanism. In fact, PEG triggers two other antibody classes, IgM and IgG, which can activate the complement system.[5]

This drug-induced reaction labeled complement activation-related pseudoallergy (CARPA) is a nonspecific immune response to nanoparticle-based medicines, often PEGylated, that could explain the severe reactions.[6]

There is no global consensus on the correct management of the patients with suspected reactions to COVID-19 vaccines. According to ENDA/EAACI Position Paper,[4] patients have to be investigated through a careful allergological history and by skin tests for the two excipients.[7,8]

In case of a history of anaphylaxis after the administration of a nonCOVID-19 vaccine or an injectable drug

potentially containing PEG or polysorbate, patients should be vaccinated in a hospital setting with fractionated doses after negative skin tests with vaccine excipients. COVID-19 vaccine needs a strict dose preparation protocol and performing more dilutions could alter pH, osmolarity, and lipid nanoparticles of the conjugated vaccine.[4]

## 2 | CASE SERIES

We report five cases of suspected allergic reactions to the first dose of Pfizer-BioNTech COVID-19 vaccine that finally underwent second COVID-19 vaccination in our allergological department during the Italian pandemic state of emergency.

Three patients experienced an immediate reaction within 30–60 min after vaccine administration: Two patients suffered from tongue angioedema and were treated immediately with an oral antihistamine drug, with the resolution of clinical signs in a few minutes, constantly monitored by the clinician; one patient suffered from dyspnea, hoarseness, and sensation of a lump in the throat, requiring an emergency treatment administered in the vaccination center (i.e., adrenaline by aerosol, corticosteroid intravenously, and antihistamine intramuscularly). The patient was discharged after 3 h of observation in the emergency room in good clinical status.

Two patients suffered from a delayed reaction (occurred from one to 4 h after the administration): One patient experienced laryngeal burning sensation, labial angioedema, and not-itchy skin rush localized at the chest; the other exhibited tingling in the tongue, a sensation of constriction in the jugule, and mild face edema. These reactions were treated with oral antihistamine therapy, with a complete resolution of symptoms in a couple of hours.

After these reactions, patients were referred for an allergological evaluation to our allergy outpatients department. As we supposed that our patient reactions to mRNA COVID-19 vaccine first dose were caused by an IgE-mediated mechanism, after a detailed clinical history about their PEG-containing drug tolerance, we performed skin tests with vaccine excipients.[7] As skin tests were negative, taking into account the nonserious reactions presented by our patients, we decided not to further dilute the vaccine and to administer fractionated doses of the undiluted extract (0.1 + 0.1 + 0.1 ml, cumulative dose 0.3 ml) every 30 min. After the vaccine administration, patients were kept under strict observation for 3 h in a hospital setting.

This off-label administration protocol was approved by the medical and health department and the clinical quality department. All the patients gave their informed consent.

## 3 | DISCUSSION

According to Italian Allergological Societies indications, given the negativity of skin tests with PEG and the tolerance in vivo to PEG-containing drugs, all patients were vaccinated with the second dose of Pfizer-BioNTech COVID-19 vaccine undergoing a fractional protocol described above. Before vaccination, all patients received a premedication with oral antihistamine from the day before to 5 days after vaccination. All five patients tolerated the second dose without presenting immediate or delayed reactions.

The purpose of our letter was to demonstrate that, pursuing an accurate drug history (based on the tolerance of drugs containing the same excipients of the vaccine) and excluding allergic sensitization to excipients using a skin test, a prudential fractionation protocol can be performed for the administration of COVID-19 vaccine second dose in patients who experienced suspected allergic reactions to the first dose. A limitation of our protocol is performing skin tests with commercial reagents of PEG 3500 as suggested by Italian Allergological Societies indication, because PEG 3500 was most similar in molecular weight to that contained in the vaccine and the vaccine itself was not available.

In our sample, we cannot exclude that the reactions classified as immediate may be caused by an immune mechanism other than hypersensitivity reactions. Furthermore, even in case of a suspected allergic reaction, the excipients of the vaccine are rarely the real cause of the reactivity, as reported in the literature.[9]

One mechanism proposed to explain "immediate" reactions is the complement activation-related pseudoallergy. On the basis that there may be a possible sensitization to PEG through the production of immunoglobulins G or M, due to the everyday wide exposure, these antibodies against PEG could activate the complement system. The subsequent generation of anaphylatoxins can then lead to mast cell degranulation, mimicking an allergic reaction.[10]

On the other side, the probability of a sensitization to other components of the vaccine not under investigation cannot be excluded, even though very low.

Unfortunately, we were not able to perform a prick test with the undiluted vaccine.

## 4 | CONCLUSION

The aim of this report was to strengthen that, after an allergological evaluation, a fractionated administration of undiluted vaccine seems to be safe and secure in patients with a suspected previous nonsevere allergic reaction to Pfizer-BioNTech COVID-19 vaccine. This protocol could be extended to other kind of COVID-19 vaccine.

## AUTHOR CONTRIBUTIONS

VP and FR provided the patient data regarding outpatients' clinical records. ACG, CC, and AS wrote the manuscript and made contributions to the interpretation of data. All authors critically read and approved the final manuscript.

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## CONFLICT OF INTEREST

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

## DATA AVAILABILITY STATEMENT

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

## ETHICAL APPROVAL

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT

Written informed consent was obtained from the patients to publish this report in accordance with the journal's patient consent policy.

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