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COVID-19 CORRESPONDENCE

Anaphylaxis to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit?

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Editor—The day after the world watched the first person receiving the coronavirus disease 2019 (COVID-19) vaccine on December 8, 2020, reports of three cases of suspected allergic reactions in connection with the vaccine emerged from the UK. Two were reports of anaphylaxis in healthcare workers, with onset within minutes of vaccination, responding well to treatment with epinephrine. Both recovered fully and were reported to have severe allergies to foods and drugs, respectively. The third case was less severe and did not require epinephrine.

Immediate-type life-threatening reactions to vaccines are exceedingly rare; they are reported to occur in 1.3 cases per million doses.[1] Therefore, two cases of anaphylaxis on the second day of a vaccination campaign with a new vaccine require further scrutiny. The first important task is to confirm that these cases were indeed anaphylaxis. If anaphylaxis is proved likely, the cause of the reaction should be identified.

The active ingredient is rarely the cause, and the focus should be directed at the many excipients usually present in vaccines.[2] A recent review of the literature showed that rare cases of immediate hypersensitivity reactions to excipients have been described for adjuvants/preservatives; antimicrobials; and a single case of a reaction to polysorbate 80, a polymer with structural similarities to polyethylene glycol (PEG).[3,4] Hypersensitivity reactions to vaccines containing gelatin and egg had only been described in patients with previous known hypersensitivity to gelatin and egg. In fact, large studies have shown a very low risk of immediate reactions to ovalbumin in influenza vaccines in patients with allergy to eggs,[5] and the recommendation to these patients is that the risk of anaphylaxis is no higher than for non-allergics.

The COVID-19 vaccine from Pfizer–BioNTech recently introduced in the UK, USA, and other countries is a messenger RNA (mRNA)-based vaccine (tozinameran, BNT-162b2) using lipid nanoparticles to facilitate the transport of mRNA into cells.[6] The vaccine contains a number of excipients and lipids, one of them based on PEG-2000. This is currently the only excipient in the vaccine with recognised allergenic potential. The severity and rapid onset of the two reported reactions to the vaccine further increase suspicion towards PEG.

Allergy to excipients is often overlooked because of a lack of knowledge about their allergenic potential. However, allergy to PEG, also often called macrogol, has been reported with increasing frequency over recent years,[7,8] Patients have usually had repeated systemic allergic reactions/anaphylaxis before diagnosis. A typical history is of severe allergic reactions to several classes of drugs, for example, penicillin, laxatives, injected corticosteroids, or antacids, all containing PEG. Symptoms are of rapid onset, usually within minutes, and typically result in severe generalised pruritus, urticaria, angioedema, hypotension, or difficulty in breathing. Reactions are more severe with higher doses and with higher-molecular-weight PEGs.

Polyethylene glycol is an ingredient in many laxatives, in about 30% of tablets and is used as a surfactant in many injectable formulations, where a prolonged effect is needed, such as in depot steroids. More recently, the technology of PEGylation has been introduced to enhance drug delivery in many areas of medicine. No reactions to PEG in vaccines have been reported, but PEG has not been a commonly used excipient in vaccines until now.

The mechanism of sensitisation to PEGs is unknown, but from the cases described in the literature[7,8] and our personal experience with a total of 18 patients with PEG allergy, there is no reason to believe that existing inhalational or food allergies predispose to PEG allergy. However, PEG allergy may be suspected in patients with very severe reactions to drugs where

the cause is unconfirmed, or patients with repeated immediate-type reactions to several structurally unrelated drugs or other products containing PEG.

The potential benefit of an effective COVID-19 vaccine is far reaching and a potential solution to a substantial threat to global health. The risk of hypersensitivity and ultimately anaphylaxis is present for all drugs, including vaccines, although usually low and is offset by the benefits of the drug. Randomised clinical trials of the Pfizer–BioNTech COVID-19 vaccine in >22 000 individuals receiving the active treatment were independently reviewed by the US Food and Drug Administration (FDA) and presented at an advisory committee meeting for emergency approval of the vaccine on December 10, 2020. The FDA found a small signal towards more hypersensitivity cases in the vaccine group, but none of the reactions were immediate, severe, or requiring epinephrine. Exclusion criteria for the clinical trials of the vaccine included individuals with known hypersensitivity to vaccines, or with a history of allergy, hypersensitivity, or intolerance to the COVID-19 vaccine or its excipients according to the registration of the trials on ClinicalTrials.gov. At the FDA advisory committee meeting, the cases of anaphylaxis in the UK were discussed at length. The advisory committee voted 17 to 4 in favour of granting Pfizer emergency approval for the vaccine, which was granted on December 11, 2020. The FDA requested that a warning be added to the product information that medication to treat immediate-type hypersensitivity reactions should be available where vaccinations take place. Also, the FDA advised that the vaccine should be contraindicated in patients with a severe allergic reaction to the first dose of vaccine, or with known hypersensitivity to any ingredient/component of the vaccine. Finally, a stringent surveillance system is to be initiated to monitor adverse effects of the vaccine with monthly reporting.

In the UK, based on the anaphylactic reactions reported, the present advice from the UK Medicines and Healthcare products Regulatory Agency (MHRA) is that 'any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer/BioNTech COVID-19 vaccine'.[9] This is very likely to be overly cautious, but understandable, to maintain public confidence in the vaccine until more detailed information about the reactions is available. The individuals who have had allergic reactions to the vaccine in the UK should be urgently investigated to determine the mechanisms behind the reactions and the potential involvement of PEG. The reported history of previous severe allergies should be scrutinised and their causes determined. Once details are available, it is very likely that more specific recommendations about at-risk groups can be made to modify the rather broad current MHRA recommendations. As a rule, allergy to foods, single drugs, or insect venom does *not* predispose to allergy to other drugs or vaccines.

Tryptase measurement taken 0.5–2 h after the reaction should help determine if this was indeed anaphylaxis.[10] As in all allergic reactions occurring in a hospital setting, other potential allergens, such as disinfectants (e.g. chlorhexidine[11]) and latex, should be excluded. Investigations for allergy to PEG currently include skin testing,[7,8] but *in vitro* tests may be in the pipeline.[12] As systemic allergic reactions have been reported in connection with skin prick testing in PEG-allergic patients, the development of a reliable *in vitro* test is urgently needed.

In conclusion, allergic reactions to vaccines are exceedingly rare, and there is no reason to believe that this has changed. PEG has not been used previously as an excipient in vaccines with this potential for wide dissemination, but even if PEG is concluded to be the cause, allergy to this excipient is also very rare. As soon as a plausible explanation for the suspected vaccine reactions has been found, clear recommendations can be made for a safe vaccination strategy. At this stage, it is important that events such as these do not lead to misinterpretations and detract from global implementation of the vaccine.

The fact that these severe reactions have appeared early in the implementation of the vaccine should remind us all that anaphylaxis is a rare risk of drug administration, including vaccines. Anaphylaxis has a good prognosis when diagnosed and treated promptly and correctly.[10] Vaccination centres should be made aware of the risk of anaphylaxis and have trained staff and equipment immediately available to treat anaphylaxis. If such precautionary measures are taken, combined with continued close surveillance of potential hypersensitivity reactions, then the benefits of the COVID-19 vaccine clearly outweigh the risks, and we can finally start hoping for an end to the COVID-19 pandemic.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Association of frailty and mortality in patients with COVID-19: a meta-analysis

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The retrospective study by Darvall and colleagues[1] examined the impact of frailty on mortality among patients with (non-COVID-19) pneumonia admitted for intensive care. The authors commented that clinical frailty score (CFS) alone is not useful for guiding the allocation of critical care resources because lesser degrees of frailty (CFS 5–6) were not associated with mortality.[1] Whether the findings could be extended to patients with coronavirus disease 2019 (COVID-19) is unknown. Many researchers have sought to determine if frailty predicts poor prognosis in hospitalised patients with COVID-19. We aim to summarise the available evidence from observational studies through meta-analysis regarding the association between frailty and mortality in patients with COVID-19.

We performed a comprehensive literature search in electronic databases that included PubMed, Scopus, Google Scholar, and preprint repositories (medRxiv and Research Square) from December 1, 2019 to November 26, 2020, using the following keywords: 'COVID-19' or 'SARS-CoV-2' or 'severe acute respiratory syndrome coronavirus 2' and 'frailty' or 'frail' with no language restriction. The reference lists of relevant articles were also hand-searched for additional studies.

Studies eligible for inclusion were those with observational study design, included patients aged 18 yr or older, with a positive diagnosis of COVID-19, assessed frailty with any validated frailty assessment tools, and reported mortality as related to frailty in acute hospital settings. We excluded studies without any adjustment of potential confounders for the measures of association between frailty and mortality, and article types such as comments, narrative reviews, conference papers, and case reports without reporting original data.

After removing duplicates, a pair of reviewers (CSK and SSH) independently reviewed the titles and full-text articles to identify articles potentially meeting eligibility criteria. Full-text screening was used to identify a final list of studies that met the inclusion and exclusion criteria. If multiple studies were available from the same cohort of patients, the study with the largest sample was included in the review. Two investigators (CSK and SSH) independently extracted relevant data from included studies: family name of the first author, publication year, study design, study setting (single centre, multicentre, or database review), age of participants, sample size, prevalence of frailty, frailty assessment scale, rate of mortality in patients with frailty, and adjusted effect size for the association between frailty and mortality. Two investigators (CSK and SSH) independently appraised the quality of observational studies using the Newcastle–Ottawa Scale with scores of >7 indicating high quality.

Disagreement between the two reviewers related to the inclusion of studies, extraction of data, and quality appraisal of included studies was resolved through discussions with the third investigator (KT). We used a random-effects model to estimate the association between frailty and mortality, with the results presented as pooled odds ratio or pooled hazard ratio and 95% confidence interval. For studies that presented independent effect measure of mortality with different categories of frailty score, we first pooled the effect measures in a single study before including the pooled effect measure for each study in the meta-analysis. We examined heterogeneity between studies using the I^2 statistic with 50% and using the χ^2 test with $P<0.10$, as the thresholds for statistically significant heterogeneity.

We retrieved 598 records from the combination of two independent searches. After removing duplications and irrelevant records, 25 full-text articles were assessed for eligibility. A total of 14 studies that met the inclusion and exclusion criteria were included for further analysis. Supplementary Table S1 depicts the characteristics of included studies (including the full reference list). Of the 14 included studies, six