Postvaccination anaphylaxis and mRNA-based SARS-CoV-2 vaccines — Much ado about nothing?

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Received: 19 December 2020 | Revised: 24 January 2021 | Accepted: 30 January 2021

DOI: 10.1111/bcp.14763

LETTER TO THE EDITOR

Postvaccination anaphylaxis and mRNA-based SARS-CoV-2 vaccines—Much ado about nothing?

On December 2, 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) has given approval to the mRNA SARS-CoV-2 vaccine developed by Pfizer and BioNTech for use in the United Kingdom, making it both the first SARS-CoV-2 vaccine as well as mRNA drug in general to be licensed for widespread use in the western world. The initial enthusiasm regarding the first COVID-19 vaccine unfortunately quickly declined, following 2 instances of postvaccination anaphylaxis being reported on the first day of widespread vaccination. Within 24 h, the MHRA issued a new guidance, in which it stated that individuals with a history of anaphylaxis to food, medicines, or vaccines should not receive the Pfizer/BioNTech vaccine. The news regarding the adverse events following vaccinations quickly filled the headlines of media around the world; however, after more than 1 month of vaccination in the United Kingdom and elsewhere and an analysis of anaphylaxis reports, the MHRA updated their guidance again by stating that only individuals with a known history of allergy to an ingredient of the vaccine should not receive it.[1]

Phase 3 trial results of the Pfizer/BioNTech BNT162b2 vaccine have been published in the *New England Journal of* Medicine.[2] Of the 43 448 trial participants, half received the BNT162b2 vaccine and half placebo and all were subsequently monitored for a median of 2 months. The trial results showed that the vaccine is 95% effective in preventing COVID-19 (95% credible interval, 90.3–97.6). When looking at the safety profile of the vaccine, adverse events were more common in the vaccine group (27% vs. placebo 12%) due to the inclusion of transient reactogenicity events, while the incidence of serious adverse events was similar in both groups, 0.6% in those vaccinated vs. 0.5% in the placebo group.[2]

As Stone et al. point out in their systematic literature review of immune-mediated vaccine adverse events published recently in the *British Journal of Clinical Pharmacology* (*BJCP*), severe adverse events are rare, but they possess the potential to spark doubt in the safety of vaccines and to increase vaccine hesitancy.[3] Local reactogenic reactions to vaccines such as prolonged warmth, redness, swelling, rash, or malaise are the most common type of immune-mediated adverse reactions after vaccination and are transient and harmless in nature. In contrast, reactions which can be classified as anaphylaxis or IgE-mediated reactions occur in less than 1 case per million doses administered and are most commonly caused by a preexisting allergy to an administered vaccine excipient.[3]

The exact anaphylaxis trigger in the BNT162b2 vaccine has yet to be identified, but looking at the list of ingredients of the vaccine, a possible culprit could be a polyethylene glycol compound: 2[(polyethylene glycol)-2000]-*N*,*N*-ditetradecylacetamide.[4] Polyethylene glycols (PEG) are widely used in household items, food, and medicines and are considered safe; however, rare cases of hypersensitivity reactions have been reported. A literature review on immediate type hypersensitivity to PEG published in the *Clinical and Experimental Allergy* journal in 2016 identified 37 reports of hypersensitivity reactions caused by PEG that were described between January 1977 and April 2016, out of which 76% (n = 28/37) fulfilled criteria for anaphylaxis.[5] The exact mechanism of PEGs' hypersensitivity remains elusive, but based on the results of basophile activation and histamine release tests, it is believed to be IgE mediated. Although it seems that hypersensitivity to PEG is rare, the possibility that it remains underrecognized and therefore underreported should be considered.[5]

The American Centre for Disease Control (CDC) reported the incidence of anaphylaxis following the first dose of the Pfizer/BioNTech vaccine to be 11.1 cases per million doses administered. It seems that postvaccination anaphylaxis is 10 times more common following the administration of the Pfizer/BioNTech vaccine than other vaccines, but it is still regarded as a rare occurrence and the CDC warns that the incidence may be overestimated as it is possible that anaphylaxis cases are reported faster than the exact number of vaccine doses administered.[6] Furthermore, Moderna's mRNA SARS-CoV-2 vaccine has been approved for use in the United Kingdom on January 8, 2021, and it also contains a similar PEG ingredient: polyethylene glycol 2000 dimyristoyl glycerol. Cases of postvaccination anaphylaxis with the Moderna vaccine have been reported as well, but it seems that the incidence is lower than that of the Pfizer/BioNTech vaccine, amounting to 2.5 cases per million Moderna doses administered, according to the CDC.[7]

As it was pointed out by Polack and al., the Phase 3 BNT162b2 vaccine trial was large enough to detect with 83% probability at least one adverse event with an incidence of 0.01%, but for the detection of rarer adverse events (like anaphylaxis), it lacked sample size, as well as follow up duration.[2] Such phase 3 trial limitations in general underline the importance of phase 4 trials or post-marketing surveillance, in which the true safety profile of any drug (vaccines included) is determined. As the number of individuals receiving the vaccine increases, so too will the number of reported rare adverse events that were not detected by the phase 3 trials. Although these events are rare, they must be evaluated and properly investigated on a case-by-case basis in order to determine potential causality. The public

should be aware of the process and scrutiny with which all safety concerns are evaluated, and that this is a normal ongoing process throughout the whole life cycle of every drug and vaccine.[8]

An example of such post-marketing safety surveillance regarding human papilloma virus (HPV) vaccines has recently been published in the *BJCP* by Bolando et al., where the authors analysed data regarding adverse events following HPV vaccination from 55 356 reports to the US Vaccine Adverse Events Reporting System in a 10-year period, between 2007 and 2017, and compared them to 224 863 corresponding vaccine-event pairs.[9] The most common and statistically significant events were dizziness (n = 6259; ROR = 2.60) and syncope (n = 6004; ROR = 6.28), but some new potential safety signals like alopecia (n = 491, ROR = 10.39), hyperacusis (n = 185, ROR = 7.13), and parosmia (n = 37, ROR = 4.77) were also identified and further investigated. All in all, the benefits of HPV vaccination heavily outweighed the associated risks, and the majority of reports were of non-serious nature and were already listed in the corresponding summary of the product characteristics.[9] Pharmacovigilance studies similar to that of Bolando et al. regarding SARS-CoV-2 vaccines will surely be published in the future. As significant number of potential vaccines are still in phase 3 trials, it will certainly be interesting to compare efficacy and safety data on the different types of COVID-19 vaccines that eventually get licensed.

COVID-19 vaccination in the United Kingdom is currently in the centre of global public attention and the way adverse events are reported could have negative, as well as positive impacts on vaccine hesitancy. Cohen et al. stressed the importance of transparency and proper information regarding COVID-19 vaccines.[10] All information regarding vaccine development, trials, and authorization should be made available to the public and adverse events should be clearly reported, along with all the necessary information about the possible risks those events pose to individuals in the context of benefits of vaccination for the society. This should serve to increase the trust towards vaccination.[10] The public must also become more aware that although every drug, intervention, or vaccine has potential side effects, the risks are largely outweighed by the benefits and rare adverse events should not be overemphasized.

COMPETING INTERESTS

There are no competing interests to declare.

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