ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines – an EAACI-ARIA Position Paper

Ludger Klimek 1* / +/**, Marek Jutel*,+ 2, Cezmi A. Akdis* 3, Jean Bousquet*/** 4-6, Mübeccel Akdis* 3, Maria Torres-Jaen15+, Ioana Agache 7+, Giorgio W Canonica 8 **, Stefano Del Giacco 9 +, Liam O'Mahony+ 10, Mohamed H. Shamji 11, Ruby Pawankar 12, Eva Untersmayr 13 +, Johannes Ring 14, Anna Bedbrook 6**, Margitta Worm 4, Torsten Zuberbier 4 **

*: the first 5 authors participated equally in this paper
**: Member of ARIA board
+: Member of EAACI Executive Committee

1. Center for Rhinology and Allergology, Wiesbaden, Germany.
2. Department of Clinical Immunology, Wrocław Medical University, Poland.
3. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.
4. Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany.
5. University Hospital Montpellier, France
6. MACVIA-France, Montpellier, France.
7. Transylvania University Brasov, Brasov, Romania.
8. Personalized Medicine Clinic Asthma & Allergy, Humanitas University, Humanitas Research Hospital, Rozzano, Milan, and Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy.
9. Department of Medical Sciences and Public Health and Unit of Allergy and Clinical Immunology, University Hospital "Duilio Casula", University of Cagliari, Cagliari, Italy.
10. Department of Medicine and Microbiology, APC Microbiome Ireland, University College Cork, Cork, Ireland.
11. Immunomodulation and Tolerance Group, Allergy and Clinical Immunology, Inflammation, Repair and Development, National Heart and Lung Institute, Imperial College London. Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom.
12. Department of Pediatrics, Nippon Medical School, Tokyo, Japan
13. Institute of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria
14. Department of Dermatology and Allergy, TUM, Munich, Germany.
15. AllergyClinical Unit, Hospital Regional Universitario de Málaga-UMA-ARADyAL, Málaga, Spain.

Abstract:
Coronavirus disease 2019 (COVID-19) vaccine BNT162b2 received approval and within the first few days of public vaccination several severe anaphylaxis cases occurred. An investigation is taking place to understand the cases and their triggers. The vaccine will be administered to a large number of individuals worldwide and concerns raised for severe adverse events might occur. With the current information, the European Academy of Allergy and Clinical Immunology (EAACI) states its position for the following preliminary recommendations that are to be revised as soon as more data emerges. To minimize the risk of severe allergic reactions in vaccinated individuals, it is urgently required to understand the specific nature of the reported severe allergic reactions, including the background medical history of the individuals affected and the mechanisms involved. To achieve this goal all clinical and laboratory information should be collected and reported. Mild and moderate allergic patients should not be excluded from the vaccine as the exclusion of all these patients from vaccination may have a significant impact on reaching the goal of population immunity. Health care practitioners vaccinating against COVID-19 are required to be sufficiently prepared to recognise and treat anaphylaxis properly with the ability to administer adrenaline. A mandatory observation period after vaccine administration of at least 15 minutes for all individuals should be followed. The current guidelines, which exclude patients with severe allergies from vaccination with BNT162b2, should be re-evaluated after more information and experience with the new vaccine develops. The current data has not shown any higher risk for patients suffering from allergic rhinitis or asthma and this message should be clearly stated by physicians to give our patients trust. The benefit of the vaccination clearly outweighs the risk of severe COVID-19 development including the more than 30% of the population suffering from allergic diseases.

On the 9th of December 2020, the British Medicines and Healthcare products Regulatory Agency (MHRA) reported two cases of anaphylaxis and one possible allergic reaction following the administration of the coronavirus disease 2019 (COVID-19) vaccine BNT162b2. Two health care workers with a history of anaphylaxis showed severe allergic reactions after vaccination and another individual experienced a possible allergic reaction. Since the vaccine component that could be eliciting these systemic reactions is unclear, an investigation has been initiated to improve our understanding of each of the three cases and their triggers.

As a precautionary measure, MHRA issued a temporary guidance to the National Health Service (NHS) [1]. *"Any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer/BioNTech vaccine. A second dose should not be given to anyone who has experienced anaphylaxis following administration of the first dose of this vaccine." "Anyone due to receive their vaccine should continue with their appointment and discuss any questions or medical history of serious allergies with the healthcare professional prior to getting the jab".*

Remarkably, the clinical trials carried out with the vaccine excluded patients who were potentially allergic to its components. The Summary of Product Characteristics (SmPC) for the vaccine BNT162b2 includes a statement on a contraindication for the use of the vaccine in any individual that experienced an allergic reaction to the vaccine or any of the components of the vaccine [2]. It can be assumed that the broad recommendations issued by the MHRA will exclude even more patients from vaccination. On the 11th of December 2020, the U.S. Food and Drug Administration (FDA) issued the first emergency use authorization (EUA) for BNT162b2 for the prevention of COVID-19 in individuals 16 years of age and older and has also been approved by Canada and Bahrain and probably the EU will shortly follow. Soon after immunizations started in the USA, two health care workers at the same hospital in Alaska developed anaphylaxis, one without any history of allergies [3].

Since it is expected that this vaccine will soon be administered to a very large number of individuals worldwide, concerns raise that other types of adverse events might occur,

Allergic reactions to vaccines

Epidemiologic data from different studies showed that allergic reactions to vaccines are rare but may occur as often as 1 per 1,000,000 or up to 30 per 100,000 vaccinations [4-8], and can cause anaphylactic reactions.

According to the World Health Organization (WHO) definition, anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening upper and lower airway obstruction, or circulatory problems (hypertension or shock) and is usually, although not always, associated with skin and mucosal changes [9, 10]. The lifetime prevalence of anaphylaxis is currently estimated at up to 5% in the USA and 3% in Europe [11-13].

Vaccine components described to cause allergic reactions include residual animal proteins, antimicrobial agents, preservatives, latex from sealing the vaccine ampoules, stabilizers, adjuvants and the active component, i.e. the antigen inducing the immune response [4-8]. Individual vaccine ingredients that may trigger anaphylaxis include egg protein, gelatin, milk proteins, other additives, and compounds present in trace amounts originating from the manufacturing process [5-8].

The novel BNT162b2 vaccine

BNT162b2 is "temporarily licensed" in the UK and the USA for active immunization to prevent COVID-19 disease caused by the SARS-CoV-2 virus in people 16 years of age and older [2]. This vaccine is administered intramuscularly at the 0.3 ml final volume twice at an interval of 21 days. COVID-19 protection cannot be expected earlier than at least seven days after the second dose of the vaccine [2, 14].

The vaccine is packaged in multi-dose vials and the concentrate must be diluted prior to use. Neither an adjuvant nor a preservative is included. The excipients listed are ALC-0315 (((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyl decanoate)), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 2-distearoyl-sn-glycero-3 phosphocholine, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose and water [2, 14].

One vial (0.45 ml) contains five doses of 30 µg of highly purified, single-stranded, 5'-capped mRNA (BNT162b2 RNA), which is produced by cell-free in vitro transcription on an appropriate DNA template and encodes the viral spike (S) protein of SARS-CoV-2 [2, 14]. This mRNA is embedded in lipid nanoparticles. mRNA is easily absorbed by mononuclear phagocytes and rapidly degraded by ribonucleases. Due to its negative electric charge and high molecular weight, it poorly penetrates cell membranes. Consequently, mRNA used in a vaccine requires a protective cove. In this case, lipid-based nanoparticles (LNP) are used as non-viral vectors. Cationic lipids coat the polyanionic mRNA with their tertiary or quaternary amines complemented with zwitterionic lipids that mimic the phospholipids of the cell membrane. Cholesterol stabilizes the lipid bilayer of the nanoparticle. Polyethylene glycol (PEG)-modified lipids provide a hydration shell that improves the aqueous solubility of the LNPs. PEG, also known as macrogol, is a polyether compound widely used as an additive in cosmetics, pharmaceuticals, and the food industry [15]. PEG molecular weight ranges from

200 g/mol to 10,000,000 g/mol. Allergic reactions have been reported after its use in a wide range of medications and cosmetic products [16, 17]. PEG may be a potential allergenic component included in the vaccine [18, 19].

In the pivotal phase 3 clinical trial, the vaccine BNT162b2 was generally well-tolerated with no serious safety concerns reported by the independent Data Monitoring Committee [14]. A total of 43,548 participants underwent randomization and of those 43,448 received injections: 21,720 with BNT162b2, 21,728 with placebo, and 18,556 received a second dose of BNT162b2 [14]. Considering the very low number of infected individuals (8 in the BNT162b2 group) assessed in the clinical trial, the risk/benefit of vaccination has to be redefined when more data become available. The most common adverse reactions were local pain at the site of injection (84.7%), fatigue (62.8%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%) and fever (14.2%)**.** Most reactions were mild to moderate. Severe adverse reactions occurred in 0.0% to 4.6% of participants and were more frequent after dose 2 and less frequent in adults >55 years of age. Lymphadenopathy was reported in 0.3%. Systemic adverse events were usually of mild or moderate intensity and generally occurred the day after the dose (more often after the second dose than after the first dose) and lasted 1-2 days after vaccination [2, 14]. The frequency of an allergic reaction was comparable in the vaccine and placebo groups (0.63% vs. 0.51%) [2, 14]. However, this large clinical trial used to support vaccine approval by the MHRA and FDA excluded those with a "*History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g. anaphylaxis) to any component of the study intervention(s)*" [2, 14]. The UK patient leaflet stated that the vaccine should not be administered to individuals who were allergic to the active substance or any of the other listed vaccine ingredients. In this respect, the patient information was similar to the clinical trial exclusion criterion, and the approved vaccine labelling corresponds to the data received and reviewed by the MHRA to date.

Assessment and outlook

Vaccines have been recognized as one of the most effective public health interventions. Although vaccination programs have the main goal to protect the individuals at risk, the protective effect extends to nonvaccinated persons as acquired by herd immunity (resistance to the circulation of contagious agents in a population that results if a sufficiently high proportion of subjects are immune to the disease, especially through vaccination) [20]. In the case of COVID 19, it is assumed that herd immunity requires protective immunity rates of approximately 60% of the total population [20].

With the information we have so far, we can state the following preliminary recommendations for wave 1 and these are to be revised as soon as we have more data:

- To minimize the risk of severe allergic reactions in vaccinated individuals it is urgently required to understand the specific nature of the reported severe allergic reactions, including the background medical history of the individuals affected and the mechanisms involved. To achieve this goal all clinical and laboratory information should be collected and reported (e.g., thorough description of the local and systemic reaction, serum tryptase levels, etc).

- Allergic patients should not be excluded from the vaccine as the exclusion of all these patients from vaccination may have a significant impact on reaching the goal of herd immunity. However, health care practitioners vaccinating against COVID-19 are required to be sufficiently prepared to recognise and treat anaphylaxis properly. This, besides a mandatory observation period after vaccine administration of at least 15 minutes for all individuals, includes the ability to administer adrenaline IM and in a sufficient dose, amongst others.

- If PEG sensitisation is confirmed as cause of the anaphylactic reactions described so far, sensitisation to PEG and to cross-reacting PEG analogues must be evaluated by an allergist to identify patients at risk and to decide on the indication and protocol of BNT162b2 administration.

- The current guidelines, which exclude patients with severe allergies from vaccination with BNT162b2, should be re-evaluated after more information and experience with the new vaccine is accumulated.

The prompt reporting of these adverse allergic events using the yellow card scheme and the rapid dissemination of additional information including quick updated patient characteristics, demonstrates a functioning safety monitoring system in the UK. In view of the public health urgency and the extensive vaccination campaigns foreseen worldwide, also the European Medicines Agency (EMA) and the national competent authorities (NCAs) in EU member states have prepared themselves for the expected high data volume by putting in place this pharmacovigilance plan specific for COVID-19 vaccines. This is to ensure that all new information
collected post-marketing will be promptly reviewed and any emerging new information will be shared

with the public in a timely manner [21]. Severe allergic reactions to vaccines are rare but may become life-threatening. Heightened awareness of this possibility among vaccination teams and sensible precautions are advisable until more information on the potential side effects of this vaccine becomes available. BNT162b2 safety monitoring will continue for 2 years after intra-study administration of the second dose of COVID-19 vaccine [14].

On 21st December the European Medicine Agency (EMA) has recommended granting a conditional marketing authorisation for the vaccine BNT162b2 (Comirnaty). Only those allergic people are excluded from vaccination that have *"… an already know allergy to one of the components of the vaccine …".* Since only *"… a very small number of cases of anaphylaxis (severe allergic reaction) have occurred since the vaccine started being used …, Comirnaty should be given under close medical supervision, with the appropriate medical treatment available"* [22].

In summary however the benefit of the vaccination clearly outweighs the risk for the very vast part of the population including the more than 30% of the population suffering from allergic diseases. The success in the fight against COVID 19 depends on giving the vaccination to as many people as possible and unwarranted anxiety created by news articles endangers this. The current data has not shown any higher risk for patients suffering from allergic rhinitis or asthma and this message should be clearly stated by physicians to give our patients trust.

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