Potential culprits for immediate hypersensitivity reactions to BNT162b2 mRNA COVID-19 vaccine: not just PEG

Anna Radice[1], Filippo Fassio[1], Elisa Meucci[1], Maria Loredana Chiara Iorno[1], and Donatella Macchia[1]

[1]Ospedale San Giovanni di Dio

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Title:

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Anna Radice[1], Filippo Fassio[1], Elisa Meucci[1], Maria Chiara Loredana Iorno[1], Donatella Macchia[1]

[1]Allergy and Clinical Immunology Unit, Ospedale San Giovanni di Dio, Azienda USL Toscana Centro, Florence, Italy

Corresponding Author: Filippo Fassio, email:*filippo.fassio@uslcentro.toscana.it*, tel: +39 329 7973033

To the Editor,

as severe allergic reactions to the first authorized COVID-19 vaccine, BNT162b2 developed by Pfizer and BioNTech, were reported [1], concern arose among clinicians and in the general population – especially among allergic patients – with the possible consequence of contributing to vaccination hesitancy.

The lipid nanoparticle (LNP) transporting the mRNA was immediately considered as the possible target of the allergic response, as it hides several potential culprits (Figure 1).

Among these, it has been noted that lipid ALC-0159 contains PEG-2000, that belongs to the polyethylene glycols family, which are known to be capable of inducing hypersensitivity reactions [1]. These are polymers with similar structures but different molecular weight, which are widely used in pharmaceuticals, cosmetics or foods thanks to their solubility and stability [2].

Despite their ubiquity, however, immediate hypersensitivity reactions are rare: thirty-seven cases were reported in the last 40 years [2]. Immunoglobulin E (IgE)-mediated hypersensitivity is one of the suspected mechanisms, and sensitization could have taken place during repeated exposure of offended skin/mucosa to cross-reactive PEGs [2], [3]. The PEGs' multivalent structure favors cross-linking of FcεR1, thus inducing mast cell degranulation.

Complement pathway activation by PEG has been proposed [5]; although PEGs prevent opsonization, they could induce IgM and IgG production [6]. Nevertheless is not a single PEG but the presence of highly repetitive domains in LNP resembling a pathogen surface that can induce the so-called complement activation-related pseudoallergy (CARPA) [4]. The same mechanism can be advocated when engineered nanomaterials, e.g. liposome and micellar drugs, bind on their surface proteins creating a "biocorona". And even more other pathways leading to mast-cells degranulation have been identified [5] or postulated, including direct mast cell activation and degranulation [6].

PEG could therefore be the culprit of hypersensitivity reactions to BNT162b2 vaccine, but it should be noted that other vaccines that contain PEG cross-reactive excipients (e.g. polysorbate 80) induce hypersensitivity reactions with significantly lower incidence than those reported for mRNA COVID vaccines.

Apart from PEG, another component of the LNP, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), should also be considered a potential culprit as it contains a quaternary ammonium (QA) ion (Figure 2) [7].

Steroidal ammonium neuromuscular blocking agents (S-NMBA), i.e. rocuronium and similars, also contain this ion, and it is known that IgE-mediate hypersensitivity reactions to QA (but also other possible mechanisms, e.g. activation of Mas-related G-protein-coupled receptor member X2 (MRGPRX2)) are implied in anaphylaxis that can occur even at first exposure with these drugs, thus resembling the aforementioned cases associated to Covid-19 vaccine [8].

The origin of such sensitization against QA was identified in previous exposure to QA-containing compounds, such as cosmetics and disinfectants, through damaged skin/mucosa [9]. Whether the BNT162b2 vaccine could exploit specific IgE to QA needs to be better evaluated.

No hypersensitivity reactions to the third component of the LNP, ALC-0315, have been reported to date to the best of our knowledge.

Apart from lipids, even the mRNA has immunogenic properties since it is capable of inducing an inflammatory response by itself. Toll Like Receptors (TLRs) and other Pattern Recognition Receptors (PRRs), such as RIG-I, can detect mRNA and activate the inflammation cascade [6][10][11]; however, it is not known if this kind of mechanisms triggered by mRNA can lead to mast cell degranulation [12].

In conclusion, the culprit involved in the cases of immediate reactions to mRNA BNT162b2 vaccine seems to be concentrated mainly in the LNP constituting the envelope.

Further research on this topic is crucial, as a better knowledge of the mechanism underlying adverse reaction to BNT162b2 could allow a better risk stratification and patient selection, thus increasing safety for people undergoing vaccination and, in turn, reducing vaccination hesitancy.

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Figure Legends

Figure 1. BNT162b2 Pfizer-BioNTech vaccine composition. Lipid nanoparticle (LNP) components: ALC-0159 (2-[(polietilenglicole)-2000]-N,N-ditetradecilacetammide); ALC-0315 (((4-idrossibutil)azanediil)bis(esano-6,1-diil)bis(2-esildecanoate)); DSPC (1,2-distearoil-sn-glicero-3-fosfocoline); cholesterol.

This envelope encloses the mRNA and allows its entrance in antigen presenting cells (APC), whose ribosomes translate the genetic sequence so that then viral Spike proteins can be expressed on MHC class I and class II of APCs, giving rise to the immune response [10].

Figure 2. DSPC (1,2-Distearoyl-sn-glycero-3-phosphocholine) chemical structure with its quaternary ammonium ion [7].

Author Contributions

All the Authors have contributed to conceptualization, writing, revision of this letter. Anna Radice and Filippo Fassio created the figures.