

## REVIEW ARTICLE

# Allergenic components of the mRNA-1273 vaccine for COVID-19: Possible involvement of polyethylene glycol and IgG-mediated complement activation

Ludger Klimek<sup>1</sup> | Natalija Novak<sup>2</sup> | Beatriz Cabanillas<sup>3</sup> | Marek Jutel<sup>4</sup> | Jean Bousquet<sup>5,6</sup>  | Cezmi A. Akdis<sup>7</sup> 

<sup>1</sup>Center for Rhinology and Allergology, Wiesbaden, Germany

<sup>2</sup>Department of Dermatology and Allergy, University Hospital, Bonn, Germany

<sup>3</sup>Department of Allergy, Research Institute Hospital 12 de Octubre, Madrid, Spain

<sup>4</sup>Department of Clinical Immunology, Wrocław Medical University, Poland, ALL-MED Medical research Institute, Wrocław, Poland

<sup>5</sup>Comprehensive Allergy Center, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany

<sup>6</sup>MACVIA-France, Montpellier, France

<sup>7</sup>Swiss Institute of Allergy and Asthma Research (SIAF, University of Zurich, Davos, Switzerland

## Correspondence

Ludger Klimek, Center for Rhinology and Allergology Wiesbaden, An den Quellen 10, 65183 Wiesbaden, Germany.  
Email: ludger.klimek@allergiezentrum.org

## Abstract

Following the emergency use authorization of the mRNA-1273 vaccine on the 18<sup>th</sup> of December 2020, two mRNA vaccines are in current use for the prevention of coronavirus disease 2019 (COVID-19). For both mRNA vaccines, the phase III pivotal trials excluded individuals with a history of allergy to vaccine components. Immediately after the initiation of vaccination in the United Kingdom, Canada, and the United States, anaphylactic reactions were reported. While the culprit trigger requires investigation, initial reports suggested the excipient polyethylene glycol 2000 (PEG-2000)—contained in both vaccines as the PEG-micellar carrier system—as the potential culprit. Surface PEG chains form a hydrate shell to increase stability and prevent opsonization. Allergic reactions to such PEGylated lipids can be IgE-mediated, but may also result from complement activation-related pseudoallergy (CARPA) that has been described in similar liposomes. In addition, mRNA-1273 also contains tromethamine (trometamol), which has been reported to cause anaphylaxis to substances such as gadolinium-based contrast media. Skin prick, intradermal and epicutaneous tests, in vitro sIgE assessment, evaluation of sIgG/IgM, and basophil activation tests are being used to demonstrate allergic reactions to various components of the vaccines.

## KEYWORDS

COVID, SARS-CoV, vaccines

## 1 | INTRODUCTION

On the 18th of December 2020, an emergency use authorization (EUA) provided by the US Food and Drug Administration (FDA) permitted the immediate use of the mRNA-1273 vaccine developed by Moderna Therapeutics for the prevention of coronavirus disease 2019 (COVID-19). The EUA allowed the immediate distribution and use of the mRNA-1273 COVID-19 vaccine in the United States in subjects 18 years of age and older.<sup>1</sup> It is the second vaccine to be

granted an EUA by US regulators after the authorization received by Pfizer-BioNTech on the 11th of December 2020 for the use of the BNT162b2 vaccine.<sup>2</sup> The authorization of mRNA-1273 was based on early-phase trials<sup>3,4</sup> and on the revision of the results of an ongoing phase III trial that involved 33,000 adult subjects, randomized 1:1 to receive them RNA-1273 vaccine in a two-dose regimen or placebo. The assessment performed by the FDA demonstrated that the vaccine was 94.1% effective for the prevention of COVID-19 as determined 14 days after the administration of the second dose.<sup>1</sup> A total

Ludger Klimek and Natalija Novak participated equally in this paper.

© 2021 EAACI and John Wiley and Sons A/S. Published by John Wiley and Sons Ltd

of 196 cases were evaluated for the efficacy analysis of which 185 cases of COVID-19 were observed in the placebo group versus 11 in the mRNA-1273 group. The secondary endpoint involved the assessment of severe cases of COVID-19 and included 30 individuals. All of the severe cases occurred in the placebo group and none in the mRNA-1273 vaccinated group.<sup>5</sup>

The FDA stated that the potential benefits of mRNA-1273 outweigh the potential risks.<sup>1</sup>

Serious allergic reactions to the active components of the vaccine itself, or to other components, are one of the potential risks of every vaccination product. According to the New York Times<sup>6</sup> on the 25th of December, a physician in Boston developed an anaphylactic reaction to mRNA-1273 soon after vaccination started in the United States. He used his own adrenaline autoinjector, carried for his shellfish allergy, and recovered well. On the 10th of January 2021, 4,041,396 people had received the first dose of the mRNA-1273 vaccine and 1266 adverse events had been reported. A total of 10 cases were determined as being anaphylaxis, all of which recovered.<sup>7</sup>

Anaphylactic reactions to BNT162b2 were also reported in the United Kingdom (UK), Canada, and the United States.<sup>8,9</sup>

Allergic reactions to vaccines including severe anaphylaxis are generally IgE-mediated.<sup>10,11</sup> They usually occur within the first 30 min after vaccination and can be fatal. The symptoms include urticarial rashes, generalized pruritus, erythema, wheezing, coughing, dyspnea, throat, tongue, or eye swelling (angioedema), hypotension, dizziness, and vomiting. Furthermore, IgG- and complement-mediated anaphylaxis-like reactions have been described.<sup>12,13</sup> Clinical symptoms of this non-IgE-mediated hypersensitivity include, among others, hypo- and hypertension as well as airway obstruction with dyspnea.<sup>14</sup> Severe anaphylactic reactions to vaccines are rare, and the rate has been estimated at 1.31 (95% CI, 0.90–1.84) per million vaccine doses.<sup>15</sup>

The frequency of allergic reactions to BNT162b2 was nearly the same in both the verum and placebo groups (0.6% vs. 0.5%).<sup>16</sup>

Allergic reactions to the mRNA-1273 vaccine have not been reported in detail. During the phase I trial of the mRNA-1273 vaccine, one case of transient urticaria in the verum group treated with a vaccine dose of 25 µg was reported after the first injection. The total number of participants in this phase I trial was 45.<sup>17</sup>

Both BioNTech/Pfizer and Moderna excluded individuals with a history of allergic reaction to vaccines or their components from the phase III trials. The exclusion criteria for mRNA-1273 state: “History of anaphylaxis, urticaria, or other significant adverse reaction requiring medical intervention after receipt of a vaccine”.<sup>18</sup>

The anaphylactic reactions to the BioNTech/Pfizer vaccine during the routine vaccination prompted the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK to issue an alert stating that individuals with a history of severe allergic reactions to vaccines, medicines, food, or to any component of these particular vaccines should be advised against their administration and that a second dose should not be given to anyone having experienced anaphylaxis after the first dose.<sup>19</sup> Currently, the MHRA only

excludes those with a hypersensitivity to the active substance or to any of the excipients of the approved vaccines. Individuals having had a hypersensitive reaction to the first dose should not receive the second dose. For the PEG-containing vaccines, a warning was also issued for individuals hypersensitive to polysorbates, due to a potential cross-reactivity.<sup>20–22</sup> The EMA and the FDA both have the same recommendations for the BioNTech/Pfizer and Moderna vaccines.<sup>23–27</sup>

Although the culprit trigger has yet to be determined, initial reports pointed at the excipient polyethylene glycol 2000 (PEG-2000)—contained in the vaccine as a PEG-micellar carrier system—as the potential cause of the anaphylactic reactions.<sup>8,28</sup> PEGylated microsomes used as the carrier of the vaccine can cause anaphylactic reactions in individuals with preexisting PEG allergies, as has been previously observed for PEGylated drugs used in cancer therapy and treatment of chronic diseases.<sup>8,29,30</sup> PEG is also used as an excipient in other medicinal products as well as in everyday products, such as deposteroids, tablets, toothpaste, cosmetics, shampoos, and some biologicals.<sup>31</sup>

Lipid nanoparticles are similar to liposomes, which have been in use pharmaceutically for many years as carriers for drugs. Some of the approved liposome/LNP-containing drugs also contain a PEGylated lipid (e.g., in Caelyx pegylated liposomal<sup>®</sup> or Onpatro<sup>®</sup>). The PEG chains on the surface form a hydrate shell around the liposome/LNP. This increases stability and prevents opsonization, that is, the mechanism by which the surface of foreign cells (e.g., bacteria, viruses) that have invaded the body is covered with antibodies and factors of the complement system. In addition, the stability and half-life of the lipid particles are increased.

## 2 | PATHOPHYSIOLOGY

Allergic reactions to such PEGylated lipids are IgE-mediated.<sup>10,11</sup> However, non-IgE-mediated reactions should also be considered.<sup>32–34</sup>

IgE activates mast cells and basophilic granulocytes via cross-links of high-affinity IgE receptors, which is indirectly measurable in an increased expression of surface markers (CD63, CD203c) on basophils.<sup>9,35</sup>

The symptoms of anaphylactic reactions are particularly caused by mediators released mainly from mast cells and basophilic granulocytes such as histamine, prostaglandins, leukotrienes (LTB4, LTC4, and LTD4), tryptase, platelet-activating factor (PAF), heparin, proteases, serotonin, and cytokines.<sup>9,35</sup> Besides IgE, other antibody classes may trigger similar symptomatology or amplify an IgE-mediated reaction.<sup>9,35</sup> Possible non-IgE-mediated reactions include complement activation-related pseudoallergy (CARPA) and have been described in the context of liposomes.<sup>36–38</sup>

Updating the Gell and Coombs scheme of type I–IV hypersensitivity reactions (HSRs),<sup>39</sup> CARPA may be regarded as an independent category within type I reactions, representing “receptor-mediated” mast cell activations.<sup>38</sup>

CARPA is partly attributed to the binding of preexisting anti-PEG IgM to the liposomes with subsequent complement activation.<sup>40</sup> Clinical symptoms of this non-IgE-mediated hypersensitivity have been described as hypo- and hypertension, airway obstruction with dyspnea, and other anaphylaxis symptoms shortly after the intravenous administration of liposome-containing drugs.<sup>12,33,34,41,42</sup> Independent of PEGylation, liposomes have the potential to activate complement, non-specifically depending on their different surface structures and charge.<sup>12,36</sup> Complement products C3a, C4a, and C5a (anaphylatoxins) are considered to be particularly important mediators. In addition to basophils, neutrophils and macrophages are also considered to be relevant effector cells that can be activated via immune complex receptors (CD16, CD32, and CD64, respectively).<sup>9,12,13,35</sup> Anaphylatoxins are liberated during complement activation.<sup>38,43</sup>

Possible sensitization to PEG by previous use of cosmetics or drugs containing PEG is conceivable. Little is known about the prevalence of anti-PEG antibodies in the population. Certain reports state that as much as 72% of the population have at least some IgG or IgM antibodies against PEG,<sup>44</sup> while others report high levels in healthy people and even in those without documented treatment with PEGylated products.<sup>37,45,46</sup> However, there is no evidence for allergy or anaphylaxis depending on IgG in man. Evidence for a possible role of IgE in triggering PEG-induced hypersensitivity is also being discussed.<sup>47-49</sup> Allergic reactions following the use of PEG as an excipient in a variety of products have been described. This is also referred to as a “hidden” allergen.<sup>47-50</sup>

Similar to BNT162b2, the mRNA-1273 COVID-19 vaccine is a messenger ribonucleic acid (mRNA) vaccine encoding the viral spike (S) glycoprotein of SARS-CoV-2. The list of excipients of both vaccines shares certain components but also differs in others. Interestingly, PEG-2000 can also be found as an excipient in the mRNA-1273 COVID-19 vaccine (Figure 1). It should be noted that PEGs have never been used in any vaccine and that both Pfizer-BioNTech and Moderna are the first to apply this substance. PEG is a hydrophilic polyether compound used as an additive in medical products and cosmetics.<sup>51</sup> It is branded under different names, for example, macrogol. The molecular weight of the different PEG excipients varies from 300 to 10,000 g/mol or higher. Furthermore, hypersensitivity reactions may occur to the PEG of all molecular weights, with a higher rate of reaction to molecular weights of between 3350 and 6000 g/mol.<sup>47</sup> However, it has been suggested that the molecular weight threshold for PEG immediate reactions is still undetermined.<sup>48,52</sup>

Cross-reactivity between PEG and its derivatives—that is, structurally related polymers such as polysorbates—exists due to shared moieties ( $=\text{CH}_2\text{CH}_2$  and  $=\text{CH}_2\text{CH}_2\text{OH}$ ).<sup>47</sup> Severe allergic reactions to PEG, although rare, have been described after the administration of medications that contain this excipient. PEG has even been described as the high-risk hidden allergen, since it is difficult to detect as a possible cause of allergic reaction.<sup>30,47,48,52,53</sup> PEGylation is used successfully for drug delivery to protect the drug from any damage

by the immune system and to deliver it to the targeted location. In addition, PEG is an additive in cosmetics and shampoos. Both a primary cutaneous sensitization pathway and sensitization after systemic administration are possible.<sup>48</sup>

Additionally, and unlike the Pfizer-BioNTech vaccine, mRNA-1273 contains tromethamine, also called trometamol (molecular formula:  $\text{C}_4\text{H}_{11}\text{NO}_3$ ), an organic amine that is widely used in several medications for topical, enteral, or parenteral administration. Tromethamine/trometamol is also used in cosmetic products as an emulsifier, and contact sensitization and allergy to this compound have been described.<sup>54</sup> Recently, the first case of anaphylaxis to trometamol as an excipient in a gadolinium-based contrast agent (GBCA) was reported.<sup>55</sup> The reaction occurred immediately after the GBCA injection in a 23-year-old woman, and IgE-mediated trometamol allergy was detected in this patient.<sup>55</sup>

### 3 | DIAGNOSTIC OPTIONS

To avoid anaphylactic or anaphylactoid reactions to vaccines, individuals at possible risk should be identified by asking for their medical history and by diagnostic procedures. Reactions to PEG in substances such as depot steroids, laxatives, gels, wound dressings, lotions, toothpaste, mouthwash, cosmetics, and shampoos may be indicative.<sup>27,31,48,52</sup> Depending on the risk profile, a decision must be made as to the conditions under which vaccination is possible (Figure 2).<sup>35,56,57</sup>

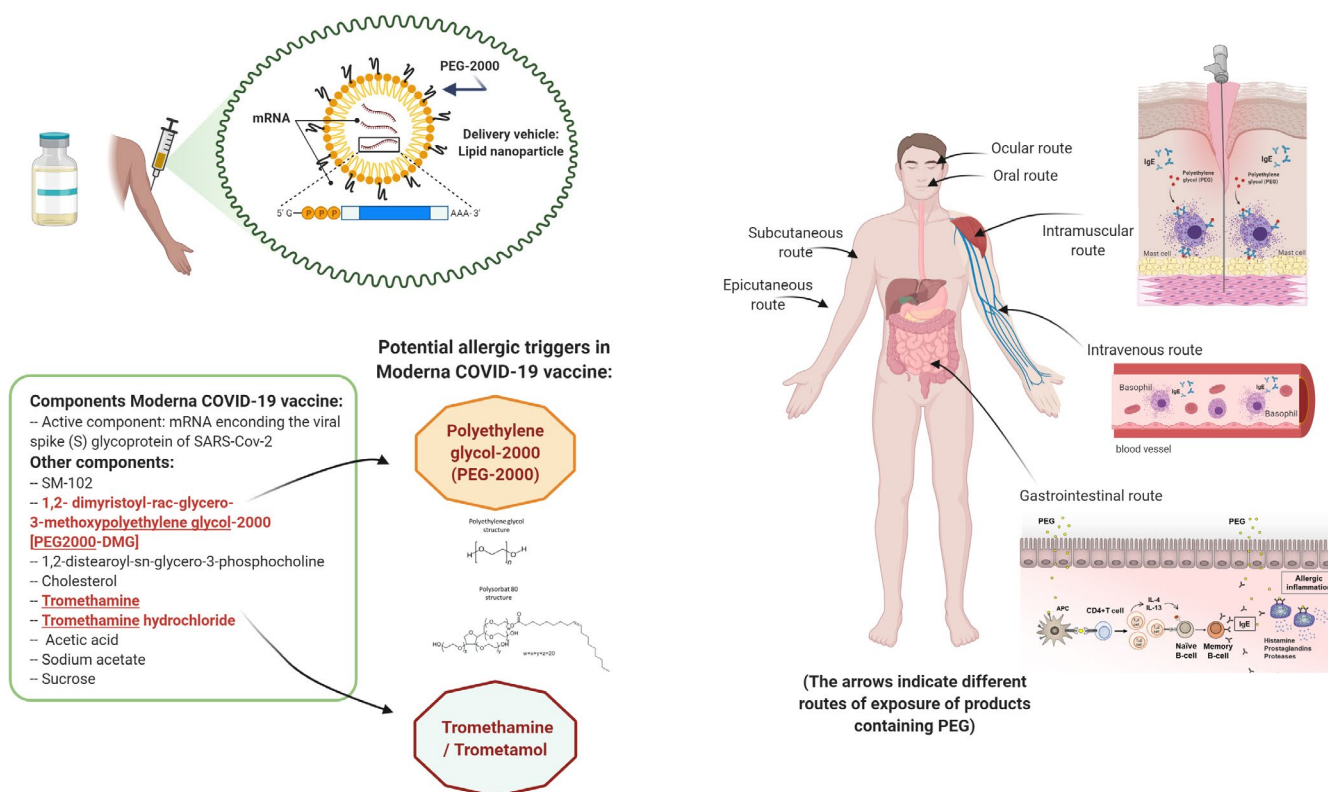
Risk factors exacerbating allergic reactions need to be taken into account when noting the medical history, such as previous anaphylaxis, mastocytosis, or other mast cell diseases (Figure 2).

Allergy testing should be performed in specialized allergy centers. Skin prick tests should be performed very carefully: initial dilutions from 0.001% up to 10% and a 30-minute observation period after every dose step to minimize the risk of a systemic reaction to PEG. Since it has been speculated that the individual threshold for positive reactions to PEG of different molecular weights varies,<sup>52</sup> testing should be performed with PEG excipients of 2000 g/mol molecular weight that are used in both vaccines. Published algorithms should also be followed.<sup>52</sup> Skin tests should be performed not earlier than 2 weeks after the hypersensitivity reaction. In addition, basophil activation tests (BATs)<sup>8,40</sup> and screening for specific IgE to PEG in blood serum<sup>8,40</sup> may be performed in high-risk individuals and in patients with suspected allergy to excipients of the vaccine.<sup>8</sup> If PEG allergy can be confirmed, an emergency kit should be prescribed, and a PEG-allergy information sheet provided. If not, intradermal testing with PEG of different molecular weights at a dilution of 0.01% can be carefully considered. High-risk patients should be excluded from those testing because systemic reactions can occur.<sup>8,52</sup> In some settings, oral provocation tests can be performed if necessary.<sup>47</sup>

Trometamol as a contact sensitizer is usually tested epicutaneously for allergic reactions of the delayed type. Testing for suspected type 1 reactions can be done by the skin prick procedure

## Moderna vaccine for COVID-19 (mRNA-1273)

## Allergic reaction due to PEG contained in drugs, intravenous substances, food additives, and other products



**FIGURE 1** Representation of the Moderna COVID-19 vaccine: The principle of the PEGylated-lipid nanoparticles as a delivery system for the mRNA is illustrated together with the full list of ingredients contained in the vaccine. PEG-2000 and tromethamine/trometamol as potential triggers of allergic reactions are indicated in red and shown on the left side. Different ways of exposition to PEG and PEG analogues are illustrated on the right side. Biorender software was used to create the figure under an academic license

(concentration 1:1) followed by intradermal testing with dilutions of trometamol from 1:1000 to 1:10.<sup>55,59</sup>

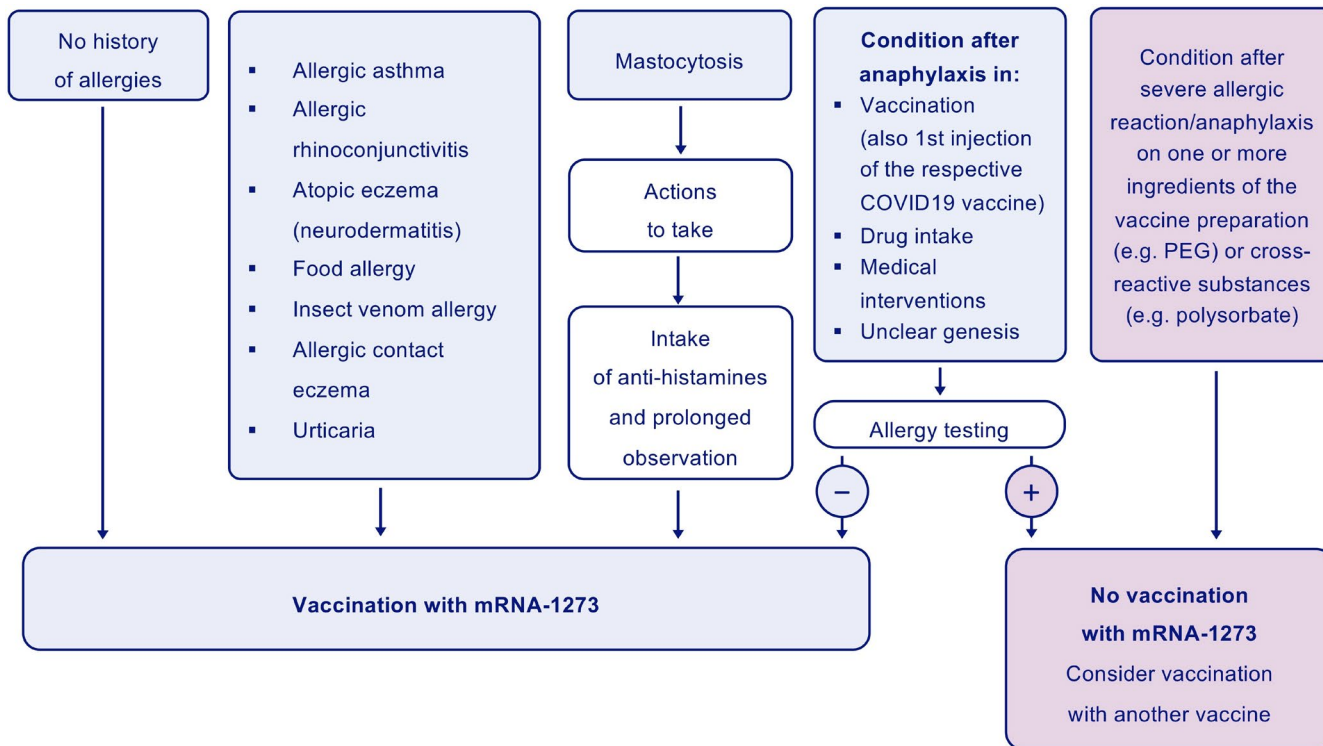
Although allergic reactions to mRNA-1273 components such as PEG and trometamol have not been frequently reported, the fact that the COVID-19 vaccines will be extensively administered worldwide to a high proportion of the population should caution health-care providers of the potential allergic reactions that may occur in individuals previously sensitized to the components of the vaccines, especially to PEG and PEG analogues as well as to trometamol in the case of mRNA-1273.<sup>60</sup>

#### 4 | THERAPEUTIC OPTIONS

This allergy is of particular interest since some of the drugs used to treat anaphylactic reactions, such as antihistamines or injectable corticosteroids, contain PEG or polysorbates. Substances that are cross-reactive to PEG, that is, polysorbates,<sup>27</sup> are widely distributed and commonly used in bread, pastry, chewing gum, ice cream, etc. They are also present in a high number of vaccines, biologics, and medications to

treat rheumatologic, cardiovascular, hematologic, gastrointestinal, or oncologic diseases, and during diagnostic procedures. It is very likely that hypersensitivity reactions to such agents have been underestimated in the past.

Two doses of the vaccine must be administered to achieve an effect. Sensitization might occur during the administration of the first dose, or individuals may develop allergic reactions to the second dose. Whether the new route of delivery of PEG via intramuscular injection plays a role in its allergenicity has yet to be determined. Since both mRNA-1273 and BNT162b2 contain PEG-2000, PEG-allergic patients, or patients allergic to components that are cross-reactive to PEG should be vaccinated with alternative COVID-19 vaccines. Physicians should be aware of this potential risk and should interrogate thoroughly for previous allergic reactions to PEG, PEG analogues, or tromethamine. They should also be trained to respond to potential anaphylactic reactions during vaccination. In these patients, the administration of emergency medications containing PEG should be avoided. Alternatives should be considered, such as clemastine solution for intravenous injection, cetirizine syrup for oral intake, soluble prednisolone or methylprednisolone for oral intake



**FIGURE 2** Algorithm for vaccination with the Moderna vaccine mRNA-1273 (modified according to Ref. [58])

or injection, and, of course, as recommended for all patients with severe anaphylaxis, most importantly, adrenaline.<sup>52</sup>

**CONFLICT OF INTEREST**

Dr. Akdis reports grants from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne—Center for Allergy Research and Education, European Commission’s Horizon’s 2020 Framework Programme, Cure, Novartis Research Institutes, Astra Zeneca,

Scibase, advisory role in Sanofi/Regeneron, grants from Glaxo Smith-Kline, advisory role in Scibase. Dr. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed Innov, outside the submitted work. Dr. Jutel reports personal fees from ALK-Abello, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay, HAL, during the conduct of the study; Astra-Zeneka, GSK, Novartis, Teva, Vectura,

**TABLE 1** Excipients listed in BNT162b2 and mRNA-1273 (according to Ref. [1,2])

BNT162b2 vaccine	mRNA-1273 vaccine
Active component: mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Active component: mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
Excipients	Excipients
ALC-0315=(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102
ALC-0159=2-[(polyethylene glycol)2000]-N,N-ditetradecylacetamide	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylen glycol-2000 [PEG2000-DMG]
1,2-distearoyl-sn-glycero-3-phosphocholin	1,2-distearoyl-sn-glycero-3-phosphocholin
Cholesterol	Cholesterol
Potassium chloride	<b>Tromethamine</b>
Potassium dihydrogen phosphate	<b>Tromethamine hydrochloride</b>
Sodium chloride	Acetic acid
Disodium hydrogen phosphate dihydrate	Sodium acetate
Sucrose	Sucrose
Water for injections	

UCB, Takeda, Roche, Janssen, Medimmune, Chiesi, outside the submitted work. Dr. Klimek reports grants and/or personal fees from Allergopharma, MEDA/Mylan, HAL Allergie, ALK-Abelló, from LETI Pharma, Stallergenes, Quintiles, Sanofi, ASIT biotech, Lofarma, Allergy Therapeut., AstraZeneca, GSK, Immunotk, Cassella med, outside the submitted work; and reports Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV, GPA, EAACI. Dr. Novak reports grants and/or personal fees from ALK-Abello, HAL Allergy, Stallergenes Geer, Leti Pharma, Novartis, Leo Pharma, Abbvie, Sanofi Genzyme, Lofarma, Bencard Allergy Therapeutics, outside the submitted work. Dr. Cabanillas has nothing to disclose.

## ORCID

Jean Bousquet  <https://orcid.org/0000-0002-4061-4766>

Cezmi A. Akdis  <https://orcid.org/0000-0001-8020-019X>

## REFERENCES

1. FDA. *United States Food and Drug Administration (FDA). Emergency use authorization for Moderna COVID-19 vaccine.* <https://www.fda.gov/media/144636/download>. Accessed December 28, 2020.
2. FDA. *United States Food and Drug Administration (FDA). Emergency use authorization for Pfizer-BioNTech COVID-19 Vaccine.* <https://www.fda.gov/media/144412/download>. Accessed December 28, 2020.
3. Anderson EJ, Roupheal NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med.* 2020;383(25):2427-2438.
4. Widge AT, Roupheal NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med.* 2021;384(1):80-82.
5. Moderna I. *Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization.* 30 November 2020. Cambridge, UK: Moderna, Inc.; 2020.
6. Wu KJ. *Boston Doctor Reports Serious Allergic Reaction After Getting Moderna's Covid Vaccine, in The New York Times.* New York, NY: The New York Times; 2020.
7. CDC. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine – United States. December 21, 2020–January 10, 2021, in *MMWR Morb Mortal Wkly Rep.* Druid Hills, GA: Centers for disease control and prevention; 2021;125-129.
8. Cabanillas B, Akdis C, Novak N. Allergic reactions to the first COVID-19 vaccine: a potential role of polyethylene glycol? *Allergy.* 2021;76(6):1617-1618
9. Klimek L, Novak N, Hamelmann E, et al. Severe allergic reactions after COVID-19-Vaccination with the Pfizer/BioNTech Vaccine in Great Britain and USA Position Statement of the German allergological Societies AeDA, DGAKI and GPA. *Allergo J Int.* 2020. <https://doi.org/10.1007/s40629-020-00160-4>.
10. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol.* 2018;141(2):463-472.
11. Nilsson L, Brockow K, Alm J, et al. Vaccination and allergy: EAACI position paper, practical aspects. *Pediatr Allergy Immunol.* 2017;28(7):628-640.
12. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. *J Allergy Clin Immunol.* 2017;140(2):335-348.
13. Szebeni J. Complement activation-related pseudoallergy: a stress reaction in blood triggered by nanomedicines and biologicals. *Mol Immunol.* 2014;61:163-173.
14. Stone CA, Rukasin CRF, Beachkofsky TM, et al. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol.* 2019;85(12):2694-2706.
15. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol.* 2016;137(3):868-878.
16. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New Engl J Med.* 2020;383(27):2603-2615.
17. Jackson LA, Anderson EJ, Roupheal NG, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. *New Engl J Med.* 2020;383(20):1920-1931.
18. ModernaTX, Inc. *A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19.* ClinicalTrials.gov. Massachusetts, MA: ModernaTX, Inc.; 2020. <https://clinicaltrials.gov/ct2/show/NCT04470427>
19. Gov.uk. *Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine.* Cheltenham, UK: Gov.uk; 2020. <https://www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine>
20. MHRA. *Information for Healthcare Professionals on COVID-19 Vaccine Moderna.* <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna>. Accessed January 28, 2021.
21. MHRA. *Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca.* <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca>. Accessed January 28, 2021.
22. MHRA. *Information for Healthcare Professionals on Pfizer/BioNTech COVID-19 vaccine.* <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>. Accessed January 28, 2021.
23. EMA. *SUMMARY OF PRODUCT CHARACTERISTICS: Comirnaty concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified).* [https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf). Accessed January 28, 2021.
24. EMA. *SUMMARY OF PRODUCT CHARACTERISTICS: COVID-19 Vaccine Moderna dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified).* [https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-epar-product-information_en.pdf). Accessed January 28, 2021.
25. FDA. *FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS) EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19).* <https://www.fda.gov/media/144637/download>. Accessed January 28, 2021.
26. FDA. *FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS); EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19).* <https://www.fda.gov/media/144413/download>. Accessed January 28, 2021.
27. CDC. *Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States.* <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>. Accessed February 3, 2021.
28. Garvey LH, Nasser S. Anaphylaxis to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit? *Br J Anaesth.* 2021;126(3):e106-e108.

29. Krantz MS, Liu Y, Phillips EJ, et al. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macro-gol allergy. *J Allergy Clin Immunol Pract.* 2020;8(4):1416-1419 e3.
30. Zhou Z-H, Stone CA, Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. *J Allergy Clin Immunol.* 2020. <https://doi.org/10.1016/j.jaip.2020.11.011>.
31. Bruusgaard-Mouritsen MA, Johansen JD, Garvey LH. Clinical manifestations and impact on daily life of allergy to polyethylene glycol (PEG) in ten patients. *Clin Exp Allergy.* 2021. <https://doi.org/10.1111/cea.13822>.
32. Demoly P, Lebel B, Messaad D, et al. Predictive capacity of histamine release for the diagnosis of drug allergy. *Allergy.* 1999;54(5):500-506.
33. Fernandez CA, Stewart E, Panetta JC, et al. Successful challenges using native *E. coli* asparaginase after hypersensitivity reactions to PEGylated *E. coli* asparaginase. *Cancer Chemother Pharmacol.* 2014;73(6):1307-1313.
34. Rau RE, Dreyer Z, Choi MR, et al. Outcome of pediatric patients with acute lymphoblastic leukemia/lymphoblastic lymphoma with hypersensitivity to pegaspargase treated with PEGylated Erwinia asparaginase, pegcristaspase: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2017;65(3):e26873.
35. Ring J, Beyer K, Biedermann T, et al. Guidelines (S2) to acute therapy and management of anaphylaxis – update 2021. *Allergo J Int.* Online ahead of print, 2021:30:1-25.
36. Inglut CT, Sorrin AJ, Kuruppu T, et al. Immunological and toxicological considerations for the design of liposomes. *Nanomaterials.* 2020;10(2):190.
37. Mohamed M, Abu Lila AS, Shimizu T, et al. PEGylated liposomes: immunological responses. *Sci Technol Adv Mater.* 2019;20(1):710-724.
38. Szebeni J. Complement activation-related pseudoallergy: a stress reaction in blood triggered by nanomedicines and biologicals. *Mol Immunol.* 2014;61(2):163-173.
39. Gell PGH, Coombs RRA. *Classification of Allergic Reactions Underlying Disease.* Oxford: Blackwell; 1963.
40. EMA. *Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product, in EMA/CHMP/806058/2009/Rev. 02. C.f.H.M.P. (CHMP),* Editor. Amsterdam, Netherlands: European Medicines Agency; 2013. [https://www.ema.europa.eu/en/documents/scientific-guide-line/reflection-paper-data-requirements-intravenous-liposomal-products-developed-reference-innovator\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guide-line/reflection-paper-data-requirements-intravenous-liposomal-products-developed-reference-innovator_en.pdf)
41. Neun BW, Ilinskaya AN, Dobrovolskaia MA. Analysis of Complement Activation by Nanoparticles. In: McNeil SE, ed. *Characterization of Nanoparticles Intended for Drug Delivery. Methods in Molecular Biology.* New York: Humana Press; 2018.
42. Chanan-Khan A, Szebeni J, Savay S, et al. Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil): possible role in hypersensitivity reactions. *Ann Oncol.* 2003;14(9):1430-1437.
43. Hugli TE. Structure and function of the anaphylatoxins. *Springer Semin Immunopathol.* 1984;7(2-3):193-219.
44. Yang QI, Jacobs TM, McCallen JD, et al. Analysis of pre-existing IgG and IgM antibodies against polyethylene glycol (PEG) in the general population. *Anal Chem.* 2016;88(23):11804-11812.
45. Armstrong JK, Hempel G, Koling S, et al. Antibody against poly(ethylene glycol) adversely affects PEG-asparaginase therapy in acute lymphoblastic leukemia patients. *Cancer.* 2007;110(1):103-111.
46. Yang Q, Lai SK. Anti-PEG immunity: emergence, characteristics, and unaddressed questions. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2015;7(5):655-677.
47. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy.* 2016;46(7):907-922.
48. Stone CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract.* 2018;7(5):1533-1540.e8.
49. Wenande EC, Skov PS, Mosbech H, et al. Inhibition of polyethylene glycol-induced histamine release by monomeric ethylene and diethylene glycol: a case of probable polyethylene glycol allergy. *J Allergy Clin Immunol.* 2013;131(5):1425-1427.
50. Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. *Allergy Asthma Clin Immunol.* 2016;12(1):67.
51. EFSA. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to an application on the use of polyethylene glycol (PEG) as a film coating agent for use in food supplement products. *EFSA J.* 2006;414:1-22.
52. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (anaphylaxis). *J Allergy Clin Immunol Pract.* 2021;9(2):670-675.
53. Calogiuri G, Foti C, Nettis E, et al. Polyethylene glycols and polysorbates: two still neglected ingredients causing true IgE-mediated reactions. *J Allergy Clin Immunol Pract.* 2019;7(7):2509-2510.
54. Singh M, Winhoven SM, Beck MH. Contact sensitivity to octyldodecanol and trometamol in an anti-itch cream. *Contact Dermatitis.* 2007;56(5):289-290.
55. Lukawska J, Mandaliya D, Chan AWE, et al. Anaphylaxis to trometamol excipient in gadolinium-based contrast agents for clinical imaging. *J Allergy Clin Immunol Pract.* 2019;7(3):1086-1087.
56. Worm M, Francuzik W, Renaudin J-M, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from the European Anaphylaxis Registry. *Allergy.* 2018;73(6):1322-1330.
57. Sokolowska M, Eiwegger T, Ollert M, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. *Allergy.* 2021;76(6):1629-1639. <https://doi.org/10.1111/all.14739>
58. Worm M, Ring J, Klimek L, et al. Anaphylaxie-Risiko bei Covid-19 Impfung – Empfehlungen für das praktische Management. *MMW Fortschr Med.* 2021;163(1):48-51.
59. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy.* 2013;68(6):702-712.
60. Klimek L, Jutel M, Akdis CA, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines – an EAACI-ARIA Position Paper. *Allergy.* 2021;76(6):1624-1628.

**How to cite this article:** Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Allergenic components of the mRNA-1273 vaccine for COVID-19: Possible involvement of polyethylene glycol and IgG-mediated complement activation. *Allergy.* 2021;76:3307-3313. <https://doi.org/10.1111/all.14794>