

Allergic Reactions Caused by a COVID-19 Vaccine

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Two years have passed since the beginning of the global COVID-19 pandemic. People have been afraid of being severely affected by COVID-19 infection, but we have struggled bravely with this difficult virus. At present, we have no proven therapeutic agents against COVID-19, but one effective weapon against this virus is vaccination. There are various kinds of vaccine against COVID-19; our focus here is on allergic reactions following the BNT162b2 mRNA vaccine. The BNT162b2 vaccine does not use live virus, and this vaccine targets the viral spike protein of COVID-19. This spike protein is necessary for the virus to infect human cells. The mRNA molecules of the viral spike protein are surrounded by lipid nanoparticles attached by Polyethylene Glycol (PEG), which provides stability and increases efficiency [1]. The nanoparticles are unaffected by enzyme actions or treatments of diseases and are available to deliver mRNA to cells [2,3]. Virus spike protein produced under the direction of mRNA in cells can cause immune reactions, and this action produces antibodies against virus spike protein [4].

It is possible for most people to use this vaccine, however, a small number of people are not able to use it because of severe adverse side effects. The most common adverse side effects of BNT162b2 are fatigue, headache, muscle pain and fever. Severe reactions such as anaphylaxis occur rarely. From 14 December 2020 to 23 December 2020, 21 of 1,893,360 recipients of their first dose of BNT162b2 showed anaphylactic reactions, yielding a rate of 11.1 anaphylactic cases per million administered vaccines [5]. Severe allergic reactions occurred in 6 cases in North America in 272,001 vaccinations prior to December, 2020. The frequency of a severe allergic vaccine reaction was 1:1 million [6]. What kinds of ingredients in this vaccine cause allergic reactions? One

major excipient in this vaccine is PEG, which is a suspected origin of allergic reactions. PEG is widely used in cosmetics, drugs and therapeutic proteins because it is considered a non-immunogenic high polymer, and it improves the stability and solubility of medicines in the body [7]. The molecular weight of PEG is 300-6000 g/mol, and that of the PEG in BNT162b2 is 2000 g/mol [8]. One popular PEG is macrogol, and cases of allergic reactions due to macrogol at the time of colonoscopy have been reported [9-14]. Additionally, Garvey reports 37 cases of PEG hypersensitivity with macrogol [15], and 3 cases of anaphylaxis out of 7,935 registered cases are known to have been induced by macrogol alone [16]. The frequency of macrogol allergy has been increasing in recent years [15,17], but cases of immediate allergic reaction to a vaccine are rare, on the order of 1.3 cases/million [5,6,18].

The degree of allergic reactions to the BNT162b2 vaccine may be associated with the molecular weight of PEG. PEG has not been commonly used as an excipient in vaccines until recently. The mechanism for PEG hypersensitivity remains unknown. PEG is often used in cosmetics, detergents, medicines and food additives because it is non-toxic and non-ionic. PEG connecting with nanoparticles or proteins may induce anti-PEG antibodies in the form of haptens. The induction of anti-PEG antibodies is affected by the route of administration, applied dose, kinds of haptens and modified rate of PEG. Immunogenicity may develop when PEG connects with tissue proteins and induces antibodies [19]. There have been reports on the existence ratio of anti-PEG antibody [11,20-25], but anti-PEG antibody presents not only as an induced antibody but also as a natural antibody [26,27], and the reason for the presence of natural antibody remains unknown. PEG is a strong stimulator of humoral immune reactions in the form of Complement Activation-Related Pseudo Allergy" (CARPA) [28]. It is suspected that people may be exposed to

PEG in foods, cosmetics or medicines without their knowledge, and anti-PEG antibodies could develop. In the case of a local skin inflammation after using or eating something containing PEG, it appears that PEG penetrates to the inflammation site, immune cells are stimulated, and anti-PEG antibody is produced [20]. In the case of pre-existing anti-PEG antibody, the presence of the antibody triggers an immunologic reaction [29,30]. This cell immunological activation and CARPA could bring about anaphylactic reactions associated with PEG. Cases that suffer an anaphylactic reaction to the BNT162b2 vaccine are fewer than the positive ratio cases of natural anti-PEG antibody, and natural anti-PEG antibody is not responsible for all anaphylactic reactions. Anti-PEG IgE antibody has been detected in all anaphylactic cases that showed high titers of anti-PEG IgG [22]. At the least, methods to suppress the induction of anti-PEG antibody are important in order to decrease allergic reactions to this vaccine. People with a PEG allergy must be careful of polysorbate, which has potential cross-reactivity with PEG [15,22,31].

Skin testing with PEG2000 is one method of investigating a possible allergy to BNT162b2. People with an IgE-mediated allergy to PEG who show positive results on skin testing with the BNT162b2 mRNA vaccine should use a different vaccine in order to prevent anaphylactic reactions [15,31], and it is important for those with positive reactions to PEG2000 skin testing to use other vaccines as well. If the results of skin testing by using BNT162b2 are negative, this alone is not sufficient evidence for the subject to be able to use the vaccine because the negative results may be truly negative or pseudo-negative. If insufficient antigen infiltrates the skin because of the large molecular weight, this could cause a pseudo-negative result. Generally, the molecular weight of substances that are able to infiltrate the skin is 200 g/mol, while the molecular weight of PEG2000 is much greater and other substances with the same molecular weight are usually unable to penetrate the skin. If the results of skin testing are negative, the patient should be followed carefully after injection. Skin testing is very difficult for all people and would be an impractical way to identify those with a PEG2000 allergy before vaccination.

The global COVID-19 pandemic has not yet been stamped out, because variant strains of the virus may well emerge. Although the BNT162b2 vaccine is not perfect, vaccinations its recipients are generally able to avoid severe illness and prevent infection. We hope to find therapeutic agents that will help to bring an end to this pandemic.

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