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Safety of mRNA-based COVID-19 vaccination in paediatric patients with a PEG-asparaginase allergy

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ABSTRACT

Background: Children treated for a malignancy are at risk to develop serious illness from a COVID-19 infection. Pegylated *E. coli* asparaginase (PEG-asparaginase) is used in the treatment of acute lymphoblastic leukemia. Allergy to this drug is common and both asparaginase and polyethylene glycol (PEG) are identified as possible antigens. The mRNA-based vaccines against COVID-19 contain PEG as a stabilizing component.

Methods: We developed a protocol to be able to safely vaccinate children with a PEG-asparaginase allergy. All patients with a history of allergy to PEG-asparaginase have been included and skin prick testing for various PEGs was performed before vaccination with the mRNA Pfizer-BioNTech COVID-19 vaccine.

Results: Twelve children between six and 16 years old were vaccinated, without allergic reaction. None of them got a positive skin prick test for PEG. Ten patients had pre-existing IgG or IgM antibodies against PEG.

Conclusion: Children with a PEG-asparaginase allergy can be safely vaccinated against COVID-19 with mRNA vaccines containing PEG irrespective of IgG/IgM antibodies to PEG-asparaginase. Routine skin prick testing in patients with PEG-asparaginase allergy does not seem to be of added value.

Clinical implications

Children with a PEG-asparaginase allergy can be safely vaccinated against COVID-19 with mRNA vaccines containing polyethylene glycol.

1. Introduction

The pandemic with the SARS-CoV-2-virus has an enormous impact on global health. Most infected people will have mild or moderate symptoms, but vulnerable people such as patients on chemotherapy or after stem cell transplantation are at risk to develop serious illness [1]. One of the most important tools to prevent infection is vaccination [2]. Different groups of vaccines against the SARS-CoV-2-virus have been developed: mRNA-based and adenovirus-vector based vaccines. The mRNA-based vaccines from Pfizer-BioNTech and Moderna contain polyethylene glycol (PEG)-2000 as a stabilizing component of the lipid nanoparticle carrier molecule for the mRNA spike protein [3,4]. The adenovirus-vector based vaccines contain polysorbate 80 which is structurally related to PEG and could therefore lead to cross-reactive immediate hypersensitivity [3–5]. Currently the COVID-19 vaccine of Pfizer-BioNTech is the only vaccine registered for children [6,7].

Polyethylene glycols are widely used in both medical and commercial products such as cosmetics and tooth paste. PEG is manufactured with molecular weights ranging from 200 to 35,000 g/mol [5]. PEG with molecular weights between 3350 and 6000 g/mol are frequently used as excipient in medication. PEG 5000 is used in PEG-asparaginase [5]. This drug is an important component of the treatment of acute lymphoblastic leukemia (ALL) [8]. L-asparaginase catalyzes the cleavage of L-asparagine, an amino acid important for ALL cells, in L-aspartic acid and ammonia. Depletion of L-asparagine results in decreased protein, DNA and RNA synthesis which leads to cell apoptosis [9]. The conjugation of L-asparaginase with PEG improves the half-life and lowers the immunogenicity of the drug [9]. Despite this conjugation to PEG, hypersensitivity reactions to PEG-asparaginase remain common and are reported in 2–8% of the patients [10,11]. Besides the antigen asparaginase itself, PEG is also identified as an antigen for these reactions by Kloos et al. who found anti-PEG antibodies (IgG or IgM) in all patients with PEG-asparaginase hypersensitivity [12].

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The COVID-19 vaccination protocol of the Dutch Centre for Infectious Disease Control (RIVM) which was written in collaboration with the Dutch Association for Allergy and Clinical Immunology and the manufacturers of the vaccines state that patients with a confirmed IgE-mediated allergy for one of the excipients of the vaccine need referral to an allergist before vaccination leading to delay in vaccination and extra burden for patients [3,4,13]. We therefore developed a protocol to be able to safely vaccinate children with ALL with a history of an immediate, within 2 h after administration, allergic reaction to PEG-asparaginase, against COVID-19. In this report we present this protocol and the results of our vaccinations.

2. Materials and methods

Children with a history of an immediate allergic reaction on PEG-asparaginase were considered as high risk for a serious allergic reaction to the mRNA-based COVID-19 vaccine because of a possible allergy to PEG-2000, one of the excipients of the vaccine. At the time of the allergic reaction to PEG-asparaginase serum anti-PEG and anti-*E. coli* asparaginase antibodies (i.e. IgG and IgM) were determined with a multiplex bead-based assay [14].

IgE-mediated vaccine allergy can be evaluated by using skin prick testing (SPT) for the excipients of the vaccine and the whole vaccine. Before vaccination of children with a severe allergic reaction, CTCAE grade 3 or higher (bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated or life-threatening) [15], to PEG-asparaginase in the past, we performed a SPT with the following substances: polysorbate 80, PEG 80, PEG 400, PEG 1500, PEG 3350 and PEG 4000. Histamine solution and saline were used as a positive and negative control respectively. Antihistamine medication was stopped for at least 72 h before the test. The size of the wheals was evaluated 15 min after application. The test was considered positive when the wheal size was larger than the positive control or when the wheal size was larger than 3 mm. Besides, we reported tolerance of oral macrogol (PEG 3350) usage.

In patients with a negative SPT and a severe allergic reaction to PEG-asparaginase in the past, the mRNA vaccine (Pfizer-BioNTech) was administered in a tapered dosing schedule starting with 0.05 ml intramuscularly, if tolerated after 30 min observation time followed 0.25 ml intramuscularly. The patients were then observed for at least 2 h. When patients had a mild reaction CTCAE grade 1 (systemic intervention not indicated) or 2 (oral intervention indicated) [15], to PEG-asparaginase or when they had received a stem cell transplantation after the allergic reaction to PEG-asparaginase vaccine dose was administered full-dose. Vaccination was contra-indicated when the children had poorly controlled asthma or a bad lung function. Our protocol is summarized in Fig. 1. Everything in this protocol was carried out in the context of regular care and therefore our research was no subject to the Medical Research Involving Human Subjects Act (WMO). All patients and their parents gave informed consent for the use of the data.

3. Results

Nineteen patients with a history of an adverse reaction to PEG-asparaginase were referred to our allergy clinic. Two of them suffered from acute pancreatitis following administration of PEG-asparaginase,

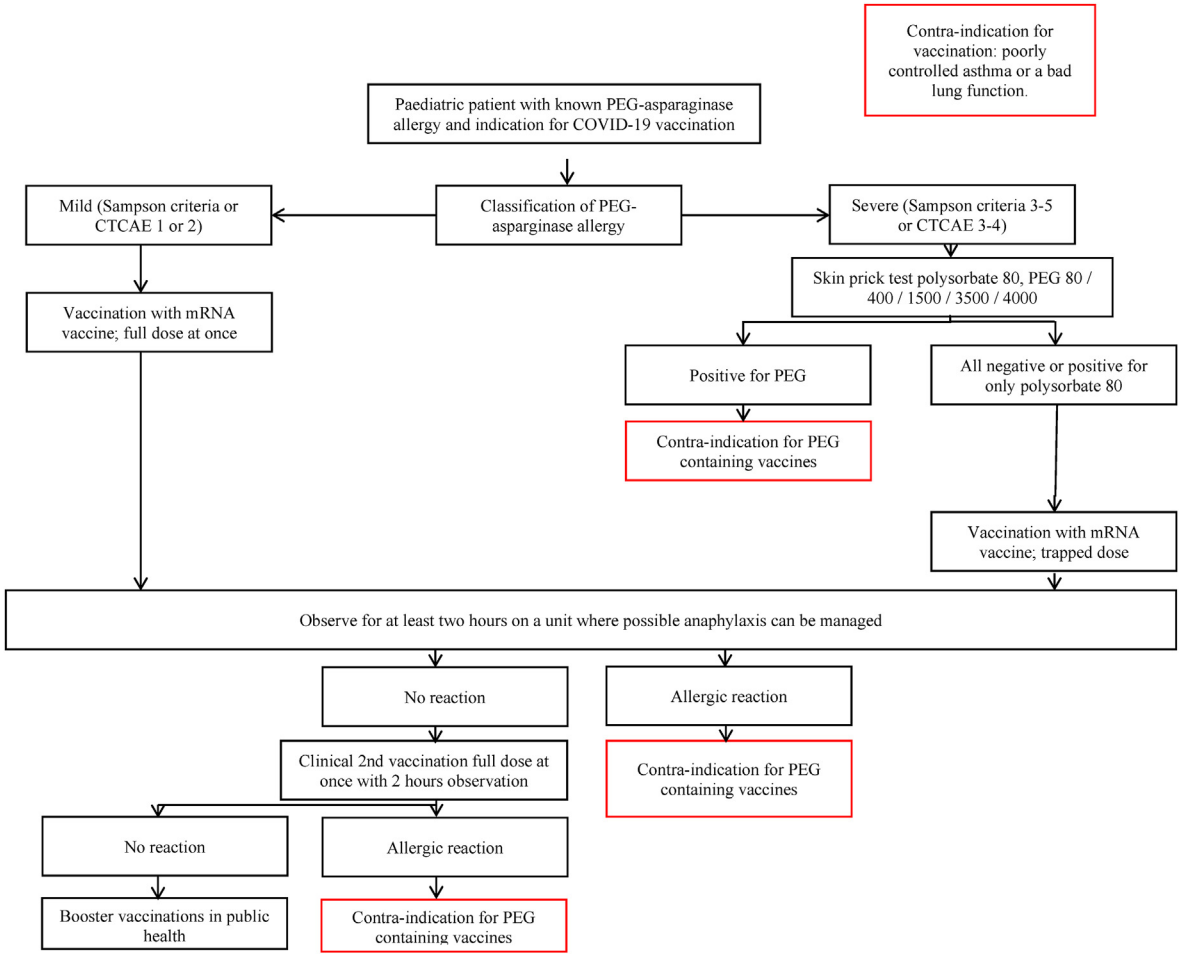

Fig. 1. Protocol: vaccination of paediatric patients with a known PEG-asparaginase allergy.

which is an adverse drug reaction, but no allergic reaction. Therefore, they were excluded from this protocol and vaccinated without special precautions. Seventeen patients had a history of an immediate, within to hours after administration, allergic reaction to PEG-asparaginase. The vaccination of five children was cancelled because of intercurrent COVID-19 infections or refusal of the vaccine. The characteristics of the 12 included patients are summarized in Table 1. Four patients were under 12 years old. Ten patients previously tested positive for anti-PEG antibodies (i.e. IgG or IgM). Nine children had a history of severe reaction to PEG-asparaginase and a SPT was performed that was negative for all tested substances in all patients. Three patients did not need a SPT: one only had a mild allergic reaction, CTCAE 1, on PEG-asparaginase, one had a stem cell transplantation after the reaction on PEG-asparaginase and one patient, who had a CTCAE 3 reaction to PEG-asparaginase, already got his first COVID-19 vaccination without side effects when he was referred to our center.

All 12 patients used and tolerated oral macrogol (PEG 3350). We did not observe any allergic reaction in all twelve patients after the COVID-19 vaccination. Therefore, the second vaccine dose was administered, at least 21 days after the first vaccination, all at once after which we observed the children for at least 2 h. The patients were followed up one day and one week after both vaccinations and no allergic reactions to the vaccinations were seen.

4. Discussion

We showed that children with ALL and a known PEG-asparaginase allergy can be safely vaccinated against COVID-19 with mRNA vaccines containing PEG. As all of our patients tolerated oral macrogol (PEG 3350) and SPT for PEG were negative we suspect that these children do not have an IgE-mediated PEG-allergy and therefore skin prick tests do not have added value. Although we did not perform a SPT on PEG 2000, the molecular weight that is used in these vaccines, but as we tested both smaller and larger molecular weights we suspect this would not add anything.

To the best of our knowledge, this is the first study that showed that children, also under the age of 12 years old, with IgG or IgM antibodies against PEG can be safely vaccinated with PEG-containing vaccines.

Our findings are in line with three previously published studies (n = 19–32) investigating children from 12 years old and adults with a PEG-asparaginase allergy who were all safely vaccinated with mRNA-based COVID-19 vaccines [16–18]. Zarnegar-Lumley et al. performed a survey under paediatric oncology providers and found that none of the 42 PEG-asparaginase allergic patients got an allergic reaction following vaccination with the COVID-19 vaccine [19]. None of these studies determined anti-PEG and anti-*E. coli* asparaginase antibodies (i.e. IgG and IgM) at the time of the allergic reaction on PEG-asparaginase.

Because of these findings the question rises whether PEG is the responsible antigen for a PEG-asparaginase allergy. Liu et al. administered PEG-asparaginase to 598 patients and they tested for IgG antibodies against PEG and asparaginase. 81 of these patients got a CTCAE grade 2 to 4 allergic reaction after administration of PEG-asparaginase of whom 66 patients had anti-PEG IgG. 107 patients also had anti-PEG IgG, but did not get an allergic reaction [20]. Kloos et al. found anti-PEG antibodies (IgG 100%; IgM 67%) in all 12 patients with a hypersensitivity reaction to PEG-asparaginase during the induction phase of the ALL treatment. Anti-asparaginase antibodies were detected in only 11% of these patients during induction [12]. Anti-PEG IgG or IgM-allergen complexes could, in susceptible patients, lead to a reaction via mast cell and basophil activation by complement C3a and C5a, which is called complement activation related pseudoallergy (CARPA). PEGylated nanodrugs can also activate the complement system themselves [20–24]. This immune reaction could explain the reactions seen on PEG-asparaginase. Since ten of our patients had anti-PEG IgG or IgM and none of them got a reaction to the PEG-containing vaccines, it cannot be solely the PEG in PEG-asparaginase that these children reacted on, but it has probably been

Table 1
Patient characteristics
All 12 patients had a medical history of acute lymphoblastic leukemia (ALL). Patient 3 had a stem cell transplantation. All patients had subsequent macrogol (PEG 3350) exposure. All patients were vaccinated with the mRNA-based COVID-19 vaccine of Pfizer/BioNTech.

Nr	Age (years)	Reaction to PEG-asparaginase	Sampson criteria	CTCAE	Treatment received	SPT	1st vaccination	2nd vaccination	Anti-PEG		Anti-asp	
									IgG	IgM	IgG	IgM
1	16	Vomiting, hypotension	5	3	Clemastine, volume substitution	Negative	Tapered	n/a	+	–	–	–
2	15	Swelling ears, dyspnoe	4	3	Adrenaline	Negative	Tapered	Full dose	+	+	+	–
3	13	Hypotension, tachycardia	5	4	Adrenaline	–	Tapered	Full dose	+	–	+	–
4	14	Mild	1–2	1	None	–	Full dose	Full dose	–	–	–	–
5	13	Itchy throat, redness skin	2	2	Antihistamine	Negative	Tapered	Full dose	–	–	+	–
6	6	Coughing, chest pain, dyspnoe, redness, swelling lips and eyes	4	3	Clemastine, hydrocortisone, adrenaline	Negative	Tapered	n/a	+	–	+	+
7	11	Red and itchy skin, swelling lips, dizziness, stomach pain, hypotension, tachycardia	5	4	Clemastine, hydrocortisone, volume substitution	Negative	Tapered	Full dose	+	+	+	+
8	11	Dyspnoe, redness and swelling face	4	3		n/a (1st vaccination before allergic reaction to PEG-asparaginase)	Full dose	Full dose	+	+	+	+
9	13	Redness, swelling throat, dyspnoe	4	3	Adrenaline	Negative	Tapered	Full dose	+	+	+	+
10	12	Anaphylactic shock	5	4	Adrenaline	Negative	Tapered	Full dose	+	+	+	+
11	15	Dyspnoe and vomiting	4	3	Salbutamol, clemastine, prednisolone	Negative	Tapered	Full dose	+	+	–	+
12	9	Dyspnoe, swelling face, respiratoiry distress, hypotension	5	4	Adrenaline (3x)	Negative	Tapered	Full dose	+	–	–	–

n/a = not applicable.

the whole 'anti-PEG-PEG-asparaginase complex'. CARPA was also described in a recent study from the United States that included 22 patients with suspected allergic reactions to mRNA COVID-19 vaccines from a cohort of almost 40,000 vaccinated patients. These 22 patients all received a SPT to excipients of the vaccine, a basophil activation test (BAT) and serum anti-PEG-IgE measurement was performed. The BAT is a diagnostic test that measures the degree of basophil degranulation following stimulation of an allergen in vitro. None showed IgE-mediated allergy to the components by SPT or had detectable PEG IgE levels, but most had positive BAT results to PEG and all had positive BAT results to their administered mRNA vaccine. The authors therefore also suggested that CARPA through plasma immune complexes with excipients of the vaccine may be responsible for mRNA vaccine allergy. Although reliability of SPT with PEGs and anti-PEG IgE measurements is uncertain it seems that CARPA is not IgE-mediated and therefore skin prick tests for PEG remain negative [25]. This suggests that the BAT might be of more value to predict the likelihood of developing an allergic reaction due to vaccination. Unfortunately the BAT is currently only available in research labs.

Our population taken together with the populations described in literature show that children with a PEG-asparaginase allergy can be safely vaccinated with COVID-19 vaccines that contain PEG irrespective of IgG/IgM antibodies to PEG-asparaginase. Also, routine skin prick testing in these patients does not seem to be of added value, but can be relevant for patients with a proven or highly suspected IgE-mediated PEG-allergy (mainly patients with a known immediate allergy for macrogol) [26]. Therefore, vaccination of these children does not necessarily need to be performed under supervision of a paediatric allergist which could lead to unnecessary delay of the vaccination.

Clinical trial registration

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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