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REVIEW

Adverse rare events to vaccines for COVID-19: From hypersensitivity reactions to thrombosis and thrombocytopenia

Natalija Novak[a], Leticia Tordesillas[b] and Beatriz Cabanillas[c]

[a]Department of Dermatology and Allergy, University Hospital, Bonn, Germany; [b]Department of Tumor Biology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [c]Department of Allergy, Research Institute Hospital 12 de Octubre, Madrid, Spain

ABSTRACT

Vaccines for the prevention of coronavirus disease 2019 (COVID-19) started to be developed since the initiation of the COVID-19 pandemic. Up to now, four vaccines have been authorized by international agencies such as European Medicines Agency (EMA). Two are DNA vaccines (ChAdOx1 nCov-19 and Ad26.COV2.S) and two mRNA vaccines (BNT162b2 and mRNA-1273). The administration of the vaccines has been associated with a strong decrease in the infections by SARS-CoV-2 and deaths associated with it. However, in parallel to these results, some rare adverse events have also been described. In that sense, events of thrombosis, thrombocytopenia, and hemorrhage have been described in close temporal proximity to the administration of the DNA vaccines ChAdOx1 nCov-19 and Ad26.COV2.S, but also mRNA vaccines. Recent scientific reports have been released with updated information on the possible association of thrombotic thrombocytopenia and COVID-19 vaccines. On the other hand, since the initiation of the vaccination campaigns, adverse hypersensitivity reactions have been described after mRNA and DNA vaccines administration for COVID-19. Although globally these adverse events are rare, a high proportion of the world population will be exposed to these vaccines. For that reason, their safety and tolerance should be carefully considered. In this review, we provide an updated review of the last scientific findings that can explain the rare side effects that the vaccines for COVID-19 can produce.

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1. Vaccines for COVID-19: DNA and mRNA vaccines

Four vaccines for the prevention of coronavirus disease 2019 (COVID-19) produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been authorized by European Medicines Agency (EMA) so far. Two are mRNA vaccines: BNT162b2 developed by Pfizer-BioNTech and mRNA-1273 developed by Moderna Therapeutics. The other two are DNA vaccines: ChAdOx1 nCov-19 produced by AstraZeneca and Ad26.COV2.S produced by Janssen-Johnson&Johnson. The approvals were based on randomized, blinded, controlled clinical trials [1–3, 52]. Both mRNA vaccines BNT162b2 and mRNA-1273 are based on a mRNA molecule that encodes the viral spike (S) glycoprotein of SARS-CoV-2. The mRNA molecule on these vaccines is surrounded by a lipid nanoparticle (LNP) that provides stability (Figure 1). In order to increase the vaccine efficiency and delivery, the LNP was subjected to a process of PEGylation, that is based on the chemical association of polyethylene glycol (PEG) to the LNP surface. On the other hand, the DNA vaccines ChAdOx1 nCov-19 and Ad26.COV2.S are based on adenovirus vectors (Figure 2). Ad26.COV2.S vaccine contains a replicant deficient human adenovirus type 26 vector and the ChAdOx1 nCov-19 vaccine (also named AZD1222, commercial name: Vaxzevria) is based on the replication-deficient chimpanzee adenovirus vector ChAdOx1 containing the gene that encodes the glycoprotein spike (S) antigen of SARS-CoV-2.

The administration of the vaccines for COVID-19 to the general population has been associated with an important drop in new infections with SARS-CoV-2 and a decrease in deaths due to COVID-19 [4,5]. However, since the initiation of the administration of the vaccines for COVID-19 in December 2020, adverse events have also been described. The mRNA vaccines were the first to be administrated and for those vaccines, some cases of adverse hypersensitivity reactions were reported [6]. The DNA vaccine ChAdOx1

CONTACT Beatriz Cabanillas bcabanillas.imas12@h12o.es Department of Allergy, Research Institute Hospital 12 de Octubre de Madrid, Avenida de Córdoba s/n, 28041 Madrid, Spain.

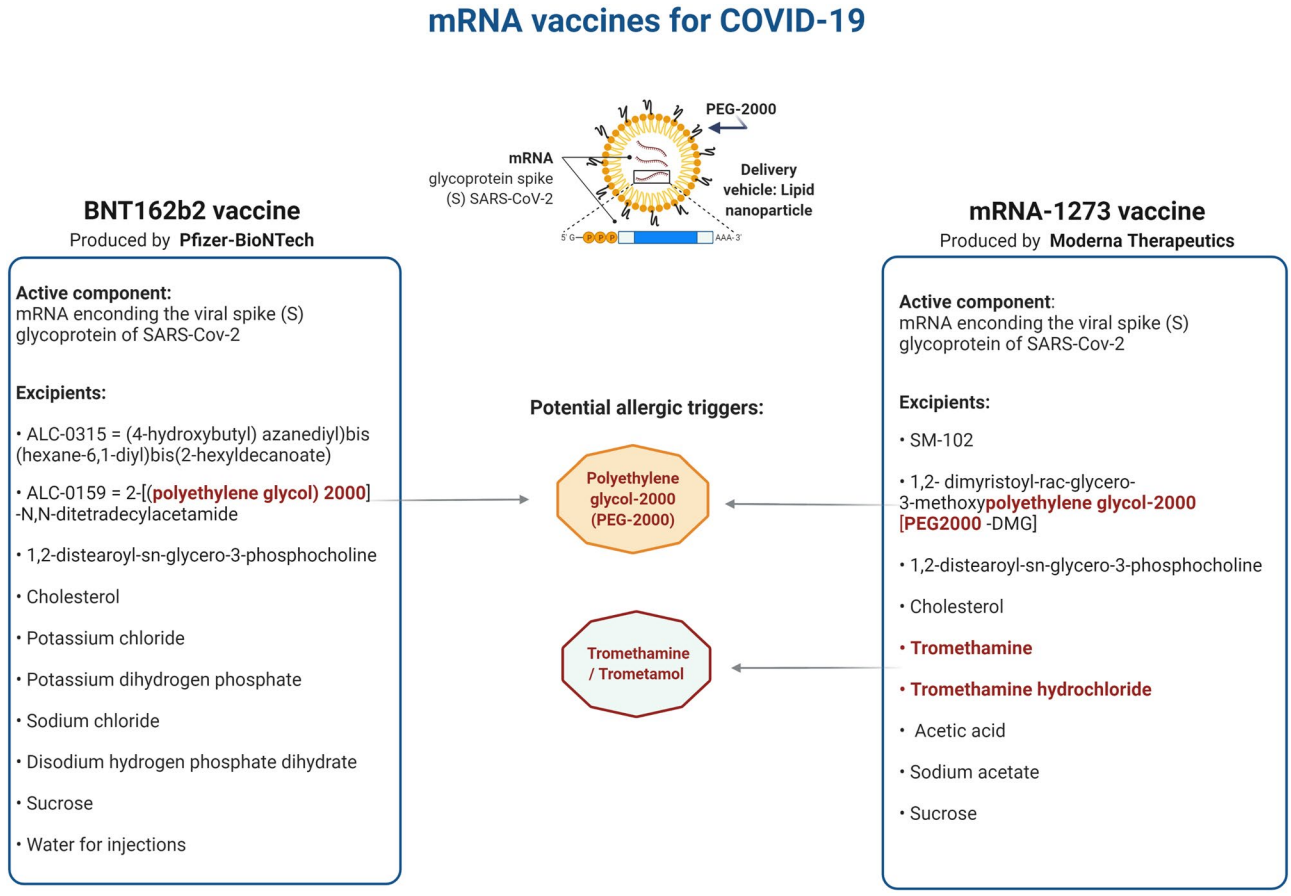

Figure 1. Graphic representation of the active component of the mRNA vaccines for COVID-19. BNT162b2 and mRNA-1273 (PEGylated LNP surrounding the mRNA molecule encoding the viral spike (S) glycoprotein of SARS-CoV-2). The list of ingredients of each vaccine is depicted and the components with allergic potential are highlighted in red color and represented in the center of the figure. Biorender software was used to create this figure under an academic license.

nCov-19 was also involved in hypersensitivity reactions, and it has been recently linked, together to the other DNA vaccine Ad26.COV2.S, to rare thrombotic events. Cases of thrombotic events have also been described in close temporal proximity with the administration of mRNA vaccines. In this review, we summarize the current knowledge regarding the safety of the currently available vaccines for COVID-19 with special attention to the last scientific advancements made on the adverse events that these vaccines might induce.

2. Thrombotic thrombocytopenia after administration of vaccines for COVID-19

Recent adverse events involving thrombocytopenia, thrombosis, and hemorrhage, that include a few cases of deaths, in temporal proximity to the administration of ChAdOx1 nCov-19 vaccine, promoted the temporary suspension of the administration of the vaccine by different European countries on March 15, 2021, and a reevaluation of the vaccine safety by EMA [7]. EMA concluded that although the causal link of very rare events of thrombosis and ChAdOx1 nCov-19 vaccine has not been proven, the connection cannot be excluded. Consequently, the safety information of the vaccine was updated including the warning on the rare events of thrombotic thrombocytopenia as a potential rare side effect. EMA highlighted that the benefits of the ChAdOx1 nCov-19 vaccine continue to outweigh the risks. However, the agency advised that the scientific bases of the potential side effects require investigation [8]. Cases of thrombosis in close temporary proximity to the administration of the vaccine Ad26.COV2.S have also been recently reported in the USA [9–11], which prompted FDA to halt the administration of the vaccine and to stop its distribution in Europe in order to perform a reevaluation of the possible side effects linked with the cases of thrombosis. Recent scientific reports have deepened onto the possible link of the adverse events of

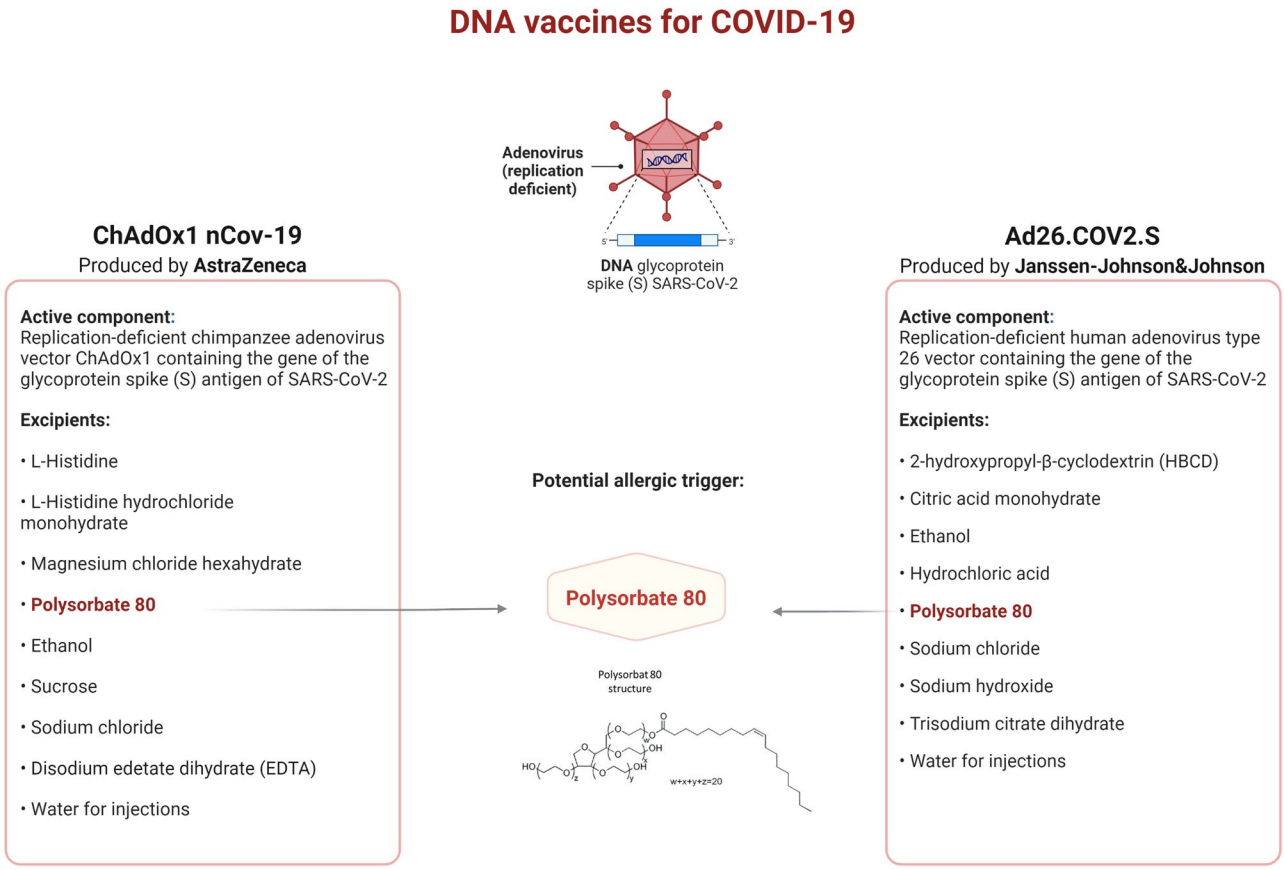

Figure 2. Graphic representation of the active component of the DNA vaccines for COVID-19. ChAdOx1 nCov-19 and Ad26.COV2.S (replicant deficient adenovirus vector containing the DNA molecule encoding the viral spike (S) glycoprotein of SARS-CoV-2). The list of ingredients of each vaccine is depicted and the component with allergic potential is highlighted in red color and represented in the center of the figure. Biorender software was used to create this figure under an academic license.

thrombotic thrombocytopenia and COVID-19 vaccines [10,12,13].

2.1. Vaccine-induced immune thrombotic thrombocytopenia: a rare new syndrome

Initial studies described a syndrome potentially induced by the ChAdOx1 nCov-19 vaccine, or at least in close temporary proximity to the administration of the vaccine, that consisted of severe thrombocytopenia and thrombosis. The studies were based on three case series of 39 patients in total recently published in the New England Journal of Medicine [12–14]. The first one described 5 health workers in Norway, (age: 32 to 54. Female: male 4:1) that experienced venous thromboembolism and concomitant severe thrombocytopenia after 7 to 10 days of receiving the first dose of ChAdOx1 nCov-19 vaccine. Four of these patients had thrombosis in cerebral veins experiencing intracranial hemorrhage which was fatal for three of them. Immunoassays detected in all the patients high levels of IgG antibodies against the complex formed by platelet factor 4 (PF4) and the heparin analogue poly(vinyl sulfonate) [13]. The second case series involved 11 patients in Germany and Austria (age: 22 to 49. Female: male 9:2) that developed thrombocytopenia and thrombosis after 5 to 16 days of receiving ChAdOx1 nCov-19 vaccine. The patients presented one or more thrombotic events and one patient experienced intracranial hemorrhage. The most common type of thrombosis among the patients was cerebral venous thrombosis. Six of the patients had a fatal outcome. All patients in which antibodies against PF4-heparin were tested (9 out of 11) had positive results that went along with positive platelet-activation assay [12]. The third study included 23 patients (age: 21 to 77. Female: male 14:9) in the United Kingdom that experienced thrombosis and thrombocytopenia 6 to 24 days after receiving ChAdOx1 nCov-19 vaccine. The thrombotic events were mainly cerebral venous thrombosis. Antibodies against PF4 were positive in 22 patients and 7 out of 23 patients had a fatal outcome [14].

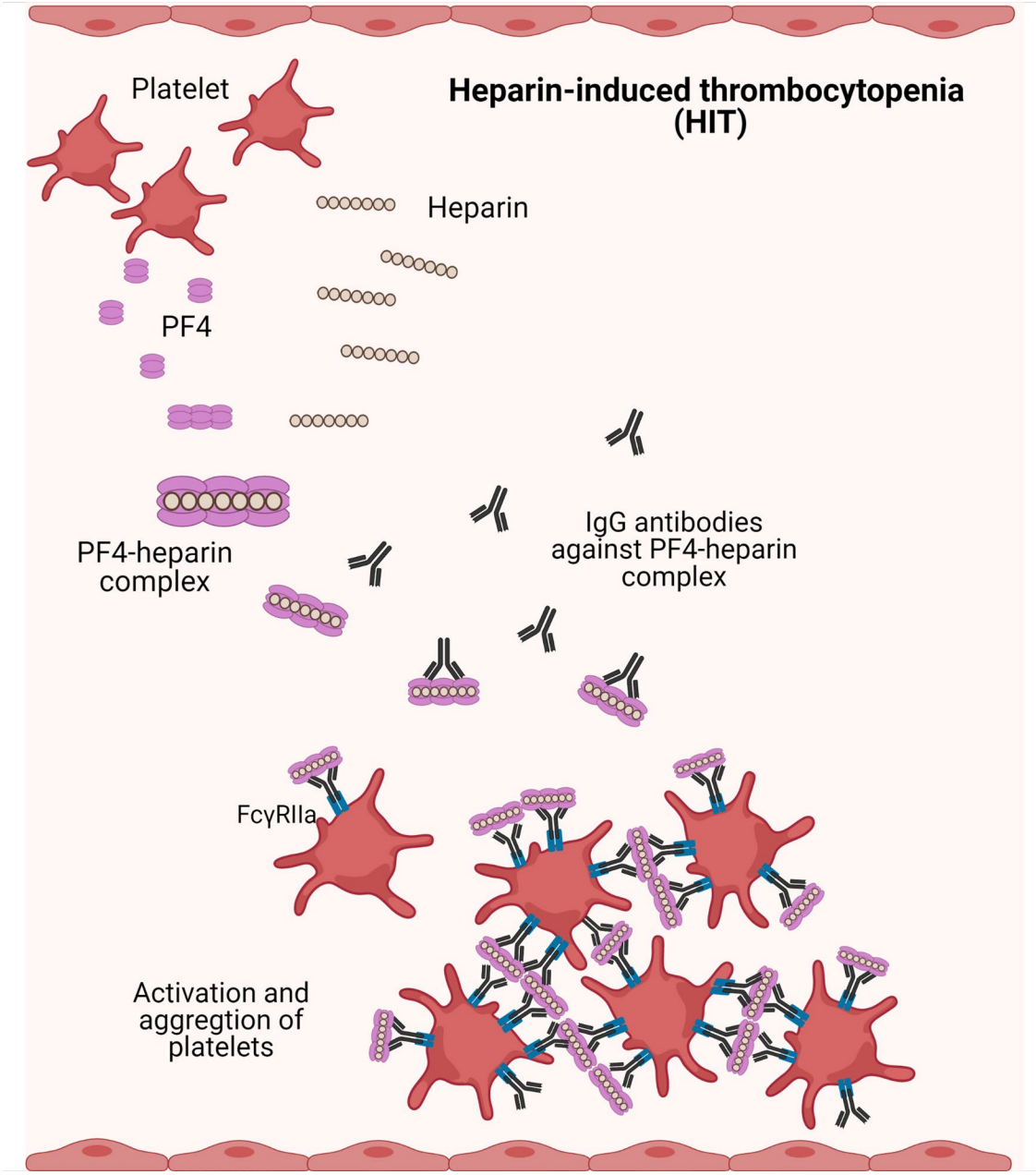

Figure 3. Immune mechanism involved in heparin-induced thrombocytopenia (HIT). In the presence of heparin, complexes between PF4 (which is released from platelets) and heparin or polyanions can be formed. HIT is characterized by the presence of IgG antibodies against the complexes formed by PF4-heparin or PF4-polyanions. These antibodies can bind to the FcγRIIa receptor of platelets promoting their activation, aggregation, and release of procoagulant platelets microparticles with the potential to induce thrombosis. Biorender software was used to create this figure under an academic license.

The presence of such antibodies against PF4-heparin and the clinical associated picture in close temporal connection with the vaccine administration prompted the authors of the studies to define the adverse events as a new syndrome named vaccine-induced immune thrombotic thrombocytopenia (VITT), which seems to be a variant of heparin-induced thrombocytopenia (HIT) (Figure 3). None of the 39 cases in the three studies were administrated with heparin before the initiation of the symptoms [12–14]. HIT is a well-defined prothrombotic disorder triggered by the administration of heparin in different forms (unfractionated heparin or low-molecular-weight heparin), and it is caused by IgG antibodies against complexes of heparin bound to PF4. Such antibodies can activate and aggregate platelets by binding to the FcγRIIa receptor, which can induce a decreasing number of platelets, by platelet consumption, and elicit the release of procoagulant platelets microparticles that can lead to thrombosis (Figure 3). HIT antibodies

can also bind to the FcγRI receptor in monocytes which seems to be associated with thrombin generation. When the thrombocytopenia leads to thrombosis the syndrome is called heparin-induced thrombotic thrombocytopenia (HITT) which can be life-threatening [15,16]. Antibodies against PF4-heparin are not uncommon in patients that receive heparin, but HITT is only developed in rare cases. Other triggers different from heparin can also induce similar prothrombotic syndromes that clinically and serologically resembles HIT. That is the case of specific polyanionic drugs or infections produced by bacteria or viruses.

Since the publication of the studies described above, several individual cases of cerebral venous thrombosis or ischemic stroke in close temporal proximity with the administration of the vaccine ChAdOx1 nCov-19 have been published. Most of the cases were accompanied with thrombocytopenia and were described in patients under 60 years of age [17–23].

For the vaccine Ad26.COV2.S, a case series of cerebral venous sinus thrombosis after receiving the vaccine between March 2 to April 21, 2021 and extracted from the US database VAERS (Vaccine Adverse Event Reporting System), has been reported. The clinical information of the cases was reviewed by physician investigators following standard methods. The case series included 12 patients (age: 18 to 59. Female: male 12:0) that had cerebral venous sinus thrombosis and thrombocytopenia beginning 6 to 15 days after receiving Ad26.COV2.S vaccine. Seven patients out of 12 also experienced intracerebral hemorrhage. Three patients had a fatal outcome. Similar to the cases described for ChAdOx1 nCov-19 vaccine, most of the patients (n = 11) with reactions after Ad26.COV2.S vaccination, had antibodies against PF4 [9,11]. Additionally, individual cases have also been reported, in that sense, one recent article has reported a case of extensive thrombosis and severe thrombocytopenia in a 48-year-old woman that received the vaccine 14 days before the onset of the symptoms. The patient presented antibodies against PF4-polyanion. Similar to the adverse events produced by ChAdOx1 nCov-19, the symptoms potentially induced by the Ad26.COV2.S resembles HIT [10].

Facing the question of whether there is a possible association between the thrombotic events and the administration of the DNA vaccines for COVID-19, studies have started to evaluate if causation between both facts can be established. In that respect, a study performed in Denmark and Norway compared the rates of thromboembolic events after vaccination with ChAdOx1 nCov-19 and with those produced in the general population. An excess of 11 events per 100,000 individuals was found in the vaccinated cohort compared with the expected events in the general population in relation to venous thromboembolism, which included cerebral venous thrombosis. The authors argued that although such events indeed exceed those of the general population, the absolute risk remained relatively low if the benefits of the vaccines for COVID-19 are considered [24].

2.1.1. mRNA vaccines and thrombotic events

mRNA vaccines for COVID-19 have also been liked with some cases of thrombosis. In that respect, a case of distal deep vein thrombosis (with the implication of peroneal vein) in a 66-year-old woman or acute coronary tree thrombosis in an 86-year-old man after administration of BNT162b2 have been reported [53,54]. Cases of thrombocytopenia within 2 weeks from the administration of BNT162b2 and mRNA-1273 have also been reported [55]. In this context, a descriptive analysis of the thrombotic events in close temporal proximity with the administration of the vaccines BNT162b2, mRNA-1273, and ChAdOx1 nCov-19 reported to the World Health Organization Global Database for Individual Case Safety Reports (VigiBase) from December 13, 2020, to March 16, 2021, found a rate of 0.21 cases of thrombotic events including cerebral venous thrombosis, per 1 million individuals vaccinated-days. The events were described in association with both mRNA vaccines (BNT162b2 and mRNA-1273) and the DNA vaccine analyzed (ChAdOx1 nCov-19) [25]. However, there is still a lack of studies analyzing if a causation can be established. Initial data on the association of thrombocytopenia and mRNA vaccines seem to indicate a lack of association (Lee et al. 2021), while the rate of thrombotic events in individuals administrated with DNA vaccines for COVID-19, although low, seems to be higher than the rate that is expected in the general population [24]. Further studies will be necessary to deep on this important aspect.

2.2. Potential triggers

In the adverse events potentially produced by DNA vaccines for COVID-19, authors speculated that the antibodies against PF4-heparin found in the patients, could correspond to autoantibodies induced by the inflammation produced by the vaccination or could correspond to antibodies triggered by the vaccine itself having those antibodies cross-reactivity properties with PF4 and platelets [12]. From the list of vaccine

components of ChAdOx1 nCov-19 and Ad26.COV2.S, it has been proposed that the active component itself (ChAdOx1 adenovirus vector or adenovirus type 26 vector containing the DNA of spike) and/or the mechanism that derives from it could have a role in the aforementioned adverse reactions in certain individuals. In that sense, it is known that certain replication-deficient adenovirus vectors derived from human adenovirus are linked with thrombocytopenia through binding and activation of platelets that are lately removed by tissue macrophages [26]. However, the role of the specific adenovirus vector of the vaccine ChAdOx1 nCov-19 or Ad26.COV2.S in the thrombotic events should be further analyzed and elucidated. Greinacher et al., proposed that the DNA component in the vaccine in a free form could also have a role in the reactions since they have previously shown that DNA and RNA can form different complexes with PF4 that can bind and induce antibodies to PF4-heparin in mice [27]. The potential trigger that could be implicated in the thrombotic events in relation to the mRNA vaccines should be also elucidated.

2.3. Clinical implications

The Pharmacovigilance Risk Assessment Committee (PRAC) from EMA, which is the committee responsible for assessing and monitoring the safety of human medicines, stated on 29th March 2021, that ChAdOx1 nCov-19 vaccine could be associated with thrombotic events and thrombocytopenia. Although the causal link was not proven at that time the agency mentioned that the link cannot be excluded. The information on the potential side effects of the vaccine was updated including the warning on the rare events of thrombotic thrombocytopenia. In relation to this, EMA advised that in the case of presentation of symptoms such as severe or persistent headache, blurred vision, persistent bleeding, leg swelling, shortness of breath, chest or persistent abdominal pain, and skin bruising or round, pinpoint spots beyond the site of vaccination after vaccination with ChAdOx1 nCov-19, medical attention should be sought [8]. Similar recommendations were issued for the vaccine Ad26.COV2.S [28]. Greinacher et al. advised that clinicians should be aware of these rare thrombotic events that can be clinically apparent after 5 to 20 days of vaccination with ChAdOx1 nCov-19 vaccine. They propose that ELISAs for the detection of antibodies against PF4-heparin, which are widely available, could be used to investigate potential VITT. A positive result in such a test in patients without recent exposure to heparin could give a hint of potential VITT [12]. The Society of Thrombosis and Haemostasis Research (GTH) has recently issued a guide for the recognition, diagnosis, and treatment of COVID-19 vaccine-related thrombosis [29].

3. Hypersensitivity reactions to the COVID-19 vaccines

3.1. Immediate type reactions: anaphylaxis

The vaccines for COVID-19 have also been associated with adverse immediate hypersensitivity reactions. The Center for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) through the Vaccine Adverse Event Reporting System (VAERS) have analyzed the suspected anaphylactic cases to the mRNA vaccines BNT162b2 and mRNA-1273 in the USA during different periods in December 2020 and January 2021 [30,31]. The reports found a prevalence of 11.1 cases of anaphylactic reactions per million of administrated BNT162b2 vaccines and 2.5 cases per million of administrated mRNA-1273 vaccines. In contrast to the potential side effect of thrombotic events, for the anaphylactic reactions to mRNA vaccines for COVID-19 no deaths were reported. The anaphylactic reactions to these vaccines usually occurred within 45 minutes of the vaccine administration and most of the patients required emergency room care. Most of the patients that experienced anaphylaxis due to the COVID-19 vaccine administration had a history of allergic reactions to medicaments, routine vaccines, contrast media, insect stings, etc. Interestingly, most of the adverse allergic reactions were described in women (100% in the case of the mRNA-1273 vaccine and 90% in the case of the BNT162b2 vaccine), a fact that can be partially explained by the circumstance that the proportion of women vaccinated at the time of the reports was higher [30,31]. Reports from CDC on the anaphylactic reactions after the administration of the DNA vaccines ChAdOx1 nCov-19 or Ad26.COV2.S have not been released so far, however, cases of allergy-like reactions have been described [32] and advisory statements in the product information of all the COVID-19 vaccines regarding severe allergic reactions have been included.

3.2. Delayed type reactions

Delayed hypersensitivity reactions after the administration of vaccines for COVID-19 have also been described and those reactions seem to occur more frequently than anaphylactic reactions. In that sense, an international registry study analyzed 414 cutaneous

reactions after the administration of the mRNA vaccines BNT162b2 and mRNA-1273 from 24th December 2020 to 14th February 2021. The study found a wide variety of reactions, being the most frequent delayed large local reactions mainly after the administration of mRNA-1273 vaccine. Other frequent reactions consisted of local reactions at the site of injection, urticaria, and morbilliform eruptions. Other less usual cutaneous manifestations were also described in this study [33]. Some of these manifestations mimicked previously described cutaneous manifestations that the virus SARS-CoV-2 itself can induce [51]. In the international registry, more than 50% of the patients that had a delayed hypersensitivity reaction did not experience a reaction to the second dose [33]. Further reports have described similar manifestations in individual cases, such as a case of a morbilliform rash after the administration of both the first and second doses of the BNT162b2 vaccine [50] or a case series from Italy including 11 patients with transient cutaneous manifestations after the administration of BNT162b2 vaccine [34]. In another case, the same vaccine in its first dose induced a persistent maculopapular exanthema involving 30% of the body. The patient also presented with liver damage, although its connection with the BNT162b2 vaccine was not explored and will need a deeper study. The patient was not administrated with the second vaccine dose due to the persistency of the reaction induced by the first dose [35]. Delayed inflammatory skin reactions after the administration of the DNA vaccine ChAdOx1 nCov-19 has also been described [36].

3.3. Potential triggers

Some components of the vaccines for COVID-19 have been pointed out as the possible responsible(s) of the hypersensitivity reactions, due to scientific data on their potential as allergenic compounds. In that sense, some of the excipients contained in the mRNA and DNA vaccines have been previously involved in hypersensitivity allergic reactions and some studies are beginning to analyze their possible role in the reactions to the COVID-19 vaccines ([37,49]. Excipients such as **PEG** contained in the mRNA vaccines BNT162b2 and mRNA-1273 as part of the PEGylated LNP has been previously described as a compound with the potential to induce severe allergic reactions. A recent study found that PEG was the culprit of the anaphylactic reaction that a 52-year-old woman experienced after receiving the BNT162b2 vaccine. Interestingly, the patient had a history of drug allergy and she was previously sensitized to PEG, although she was unaware of her PEG allergy, possibly due to a misdiagnosis of the specific excipient to which she was allergic to. The diagnosis of PEG allergy is usually difficult to establish due to the widespread use of PEG and its presence in multiple drugs and cosmetic products [37]. Despite this fact, a current revision of FDA data has found an average of four anaphylactic reactions to PEG per year in individuals exposed to PEG-containing drugs for colonoscopy or laxatives [38]. Sensitization to PEG seems to depend on the molecular weight (MW) of PEG and an individual threshold seems to exist [39]. PEG molecule contained in the mRNA vaccines for COVID-19 has a MW of 2000 g/mol and for that reason is denominated PEG-2000 (Figure 1). Another excipient contained in the mRNA vaccine mRNA-1273 denominated **tromethamine** (also named trometamol) (Figure 1) has been previously linked to allergic reactions. In that sense, adverse allergic reactions to tromethamine-containing iodinated contrast medium (IOM) or gadolinium-based contrast agents (GBCA) have been described [40]. In its CDC report, 20% of the patients with anaphylactic reactions to mRNA-1273 vaccine had a history of anaphylactic reactions to gadolinium, iodine, or intravenous contrast media [31].

An excipient contained in the DNA vaccines ChAdOx1 nCov-19 and Ad26.COV2.S denominated **polysorbate 80**, which is an emulsifier and stabilizer analogue of PEG, has been pointed out as a possible culprit of hypersensitivity reactions on the DNA vaccines for COVID-19 (Figure 2). In the scientific literature, allergic reactions to polysorbates, although rare, have been described in association with medicines and vaccines containing this compound [38,41–43].

3.4. Clinical implications

Safety statements on the potential side effect of hypersensitivity due to the administration of mRNA and DNA vaccines for COVID-19 have been updated in the product information by international regulatory agencies. Furthermore, the European Academy of Allergy and Clinical Immunology (EAACI) has issued a guideline on the diagnosis and management of potential allergic reactions after the administration of COVID-19 vaccines [44]. In that sense, only previous history of allergic reactions to any component contained in the vaccines for COVID-19 is a contraindication for the administration of the vaccines. However, a history of allergic reactions to aeroallergens, foods, or insect venoms is not described as a contraindication. In the cases of patients with allergy

to medicaments of routine vaccines, a careful assessment of the exact compound to which the patient is allergic should be performed.

4. Other vaccines for COVID-19

Other vaccines for COVID-19 are under rolling review by EMA, that is the case of CVnCoV (developed by CureVac AG), NVX-CoV2373 (developed by Novavax CZ AS), and Sputnik V (Gam-COVID-Vac, developed by Russia's Gamaleya National Center of Epidemiology and Microbiology). CVnCoV is a mRNA vaccine, NVX-CoV2373 is a protein-based vaccine, and Sputnik V is a DNA vaccine [45–47]. These vaccines contain among their ingredients excipients that have been pointed out as possible triggers of adverse events in the mRNA and DNA vaccines described in this review. In that respect, CVnCoV vaccine contains a PEG-ylated lipid, Sputnik V is based on adenovirus vectors and NVX-CoV2373 contains polysorbate 80. Some of these vaccines, such as Sputnik V have already been administrated in some countries after approval issued by their national regulatory agencies. In the phase-III-clinical trial with Sputnik V, there were adverse events in the same proportion in the placebo and the vaccine group. Three deaths in the vaccine group and in the placebo group occurred, none of them were considered related to the vaccine administration [48]. As these vaccines start to be approved by international regulators and their use spreads, possible adverse events should be monitored, and their causality should be studied.

5. Conclusions

Vaccines for the prevention of COVID-19 produced with novel technologies on the field of human vaccines are the most promising way to decrease the impact of the pandemic produced by SARS-CoV-2 worldwide. The administration of vaccines for the prevention of COVID-19 will surpass any other vaccine administration campaign, being a high percentage of the global population exposed to them. Side effects such as thrombotic thrombocytopenia or hypersensitivity reactions potentially associated with the administration of the vaccines should be carefully analyzed and understood and the possible causation should be established. Access to vaccines able to reduce the incidence of COVID-19 is essential. However, the safety and tolerance of such vaccines must be carefully considered and studied even when the benefits may outweigh the disadvantages of these COVID-19 vaccines.

Declaration of interest

The authors declare no conflicts of interest.

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ORCID

Beatriz Cabanillas http://orcid.org/0000-0002-5351-8140

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