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REVIEW

COVID-19 vaccines adverse events: potential molecular mechanisms

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Abstract

COVID-19 is an infectious disease caused by a single-stranded RNA (ssRNA) virus, known as SARS-CoV-2. The disease, since its first outbreak in Wuhan, China, in December 2019, has led to a global pandemic. The pharmaceutical industry has developed several vaccines, of different vector technologies, against the virus. Of note, among these vaccines, seven have been fully approved by WHO. However, despite the benefits of COVID-19 vaccination, some rare adverse effects have been reported and have been associated with the use of the vaccines developed against SARS-CoV-2, especially those based on mRNA and non-replicating viral vector technology. Rare adverse events reported include allergic and anaphylactic reactions, thrombosis and thrombocytopenia, myocarditis, Bell's palsy, transient myelitis, Guillen-Barre syndrome, recurrences of herpes-zoster, autoimmunity flares, epilepsy, and tachycardia. In this review, we discuss the potential molecular mechanisms leading to these rare adverse events of interest and we also attempt an association with the various vaccine components and platforms. A better understanding of the underlying mechanisms, according to which the vaccines cause side effects, in conjunction with the identification of the vaccine components and/or platforms that are responsible for these reactions, in terms of pharmacovigilance, could probably enable the improvement of future vaccines against COVID-19 and/or even other pathological conditions.

Keywords COVID-19 vaccines · Adverse events · Side effects · Adverse drug reactions · Pharmacovigilance · Mechanisms

Abbreviations

ACE2	Angiotensin-converting enzyme 2
Ad26	Adenovirus serotype 26
ADE	Antibody dependent enhancement
APCs	Antigen presenting cells
CAR	Coxsackie/adenovirus receptor
CARPA	Complement activation-related pseudoallergy
CDC	Center for Disease Control and Prevention
CXADR	Coxsackie and adenovirus receptor
DC-SIGN	Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
DSPC	Distearoylphosphatidylcholine
EDTA	Ethylenediaminetetraacetic acid
HIT	Heparin induced thrombocytopenia
HLA-DRA	HLA class II alpha chain
HMW	High molecular weigh
HPA-1a/b	Human platelet antigen genotype
IFNα	Interferon-α
LMW	Low molecular weigh
LNPs	Lipid nanoparticles
MCAS	Mast cell activation syndrome
MW	Molecular weight
NETS	Neutrophil extracellular traps
NORSE	New-onset refractory status epilepticus
PECAM-1	Platelet endothelial cell adhesion molecule 1 gene
PEG	Polyethylene glycol
PF4	Platelet factor 4

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PMPs	Platelet microparticles
POTS	Postural orthostatic tachycardia
S protein	Spike protein
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SNPs	Single nucleotide polymorphisms
ssRNA	Single-stranded RNA
TLRs	Toll-like receptors
tPA	Tissue plasminogen activator
VITT	Vaccine-induced immune thrombotic thrombocytopenia
WHO	World Health Organization

Introduction

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA (ssRNA) virus. The virus was first observed in Wuhan, China, in December 2019, and quickly spread to other parts of the world. On 11 March 2020, the World Health Organization (WHO) declared a global pandemic. Fortunately, there are currently several vaccines widely available to confront the disease. Up to now, over twenty vaccines have been granted approval for emergency use. Among these vaccines, seven have been fully approved by WHO. The fully approved vaccines consist of the mRNA-1273 by Moderna, the BNT16b2 by Pfizer/Biontech, the Ad26.CoV2.S by Janssen/Johnson and Johnson, the AZD1222 which is also referred to as ChAdOx1 nCoV-19 by Oxford/Astrazeneca, an Oxford/Astrazeneca formulation known as Covishield, the BBIBP-CorV by Sinopharm and last Sinovac's CoronaVac [1].

COVID-19 vaccines are based on new technology (mostly mRNA and viral vector based platforms) and as a result, many people are hesitant to get vaccinated, especially due to reported adverse events. Among the most common reported side effects are fatigue, headache, myalgia, fever, pain, and/or redness at the injection site, with mild or moderate symptoms [2, 3]. On the other hand, there are some rare adverse events reported, such as allergic and anaphylactic reactions following mRNA vaccination, and thrombosis and thrombocytopenia following non-replicating viral vector vaccination [4–6]. Other rare adverse events described were myocarditis, Bell's Palsy, Transient Myelitis, Guillen-Barre syndrome, recurrences of herpes-zoster, autoimmunity flares, epilepsy, and orthostatic tachycardia. Of note, most of these adverse events are considered mild to moderate in severity, indicating that COVID-19 vaccines are actually safe [7–14].

In this review, we discuss the potential molecular mechanisms leading to the aforementioned rare adverse events and we also associate them with the various vaccine components and vectors. An emphasis is put on mRNA-1273 and BNT16b2 RNA vaccines, as well as Ad26.CoV2.S and AZD1222/ChAdOx1 nCoV-19 non-replicating viral vector based vaccines, as these four COVID-19 vaccines are the most widely used (at least, in Europe). A search of the literature was conducted using PubMed and Google Scholar databases. The search, which refers to December 2019 to December 2021 time period, was based on keywords such as "COVID-19 vaccines," "Adverse events," "Adverse effects," "Adverse drug reactions," "Side effects," and "Mechanisms." Based on the glossary of WHO that defines that "adverse event" is "any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it," we used the term adverse event throughout the manuscript [15].

COVID-19 vaccine platforms

RNA vaccines

For the first time ever, mRNA vaccines have gained approval for human use. These vaccines utilize an mRNA that encodes the spike (S) protein of SARS-CoV-2, encapsulated in lipid nanoparticles (LNPs) [16, 17]. The mRNA-1273 consists of a nucleoside-modified mRNA that encodes a perfusion-stabilized form, known as SARS-CoV-2P antigen, which elicits a vigorous immune response [17–19]. The LNPs consist of four negative charged lipids, in a fixed ratio of mRNA and lipid. Once the LNP encapsulated mRNA enters the cell, the LNP surface obtains is positively charged, facilitating mRNA's release in the cytosol [17, 18, 20]. The BNT16b2 vaccine also consists of a single stranded mRNA, embedded in a lipid nanoparticle. This mRNA encodes a perfusion stabilized, membrane anchored, SARS-CoV-2 full length spike protein, which carries two point mutations within the central helix [18, 19].

Non-replicating viral vector vaccines

These vaccines exploit the ability of an adenovirus to infect and produce viral mRNA, using the mechanisms of the host's cells [16]. The Ad26.CoV2.S vaccine, in more detail, is using a recombinant non-replicating adenovirus serotype 26 (Ad26) vector, encoding a full length SARS-CoV-2 spike protein [3, 18], whereas the AZD1222 vaccine, also known as ChAdOx1 nCoV-19, is a non-replicating simian adenovirus(ChAdOx1) vector, encoding the SARS-CoV-2 S-glycoprotein, along with a tissue plasminogen activator (tPA) leader sequence [19, 21].

Other vaccine platforms

Apart from the mRNA and the non-replicating viral vector DNA vaccines, other vaccine platforms that have been approved for emergency use against SARS-CoV-2 include protein subunit vaccines, inactivated vaccines, and a circular strand of DNA-based vaccine [1]. These latter types of vaccine platforms have not been widely used in Europe; thus, we do not extensively refer to them in the review. However, in order to be completely accurate, we find it important to mention their existence as well.

Adverse events of COVID-19 vaccines

Allergic reactions and anaphylaxis

COVID-19 vaccines, especially the mRNA platforms, have been associated with allergic reactions and anaphylaxis. The anaphylactic reports had a prevalence of 11.1 cases per million for the BNT16b2 vaccine and 2.5 cases per million for the mRNA-1273 vaccine [22]. It is worth noting that, among these reactions, some refer to delayed local reactions (painful edematous plaques) in the injection site, with a median onset of 8 days after mRNA-1273 vaccination [23, 24]. These skin reactions diminish soon after the onset and thus are not considered severe adverse events [23, 24]. As far as adenoviral vector vaccines are concerned, there are no reports of allergic reactions released by the Center for Disease Control and Prevention (CDC) so far.

The approved mRNA vaccines contain polyethylene glycol (PEG), a family of hydrophilic polymers of ethylene oxide, as well as a phospholipid known as distearoylphosphatidylcholine (DSPC). Moderna's vaccine also contains trometamol as an excipient, whereas AstraZeneca's and Johnson & Johnson's vaccine contains polysorbate 80, a nonionic surfactant and emulsifier often used in foods and cosmetics. AstraZeneca's vaccine also contains ethylenediaminetetraacetic acid (EDTA) [25, 26].

PEG is widely used in everyday products, such as cosmetics, food, and pharmaceutical products. The molecular weight (MW) of PEG can vary from 300 to over 10.000 g/mol, and thus can elicit hypersensitivity reactions [27]. More specifically, low molecular weight (LMW) PEG can cause contact dermatitis or rash on repeated exposure, whereas high molecular weight PEG (HMW), such as the one found in laxatives, can trigger systemic reactions [27, 28]. PEG 2000 in Pfizer's and Moderna's vaccine may cause a hypersensitivity reaction to previously sensitized patients [29, 30]. Female subjects might be more susceptible to allergies, due to potential previous sensitization from cosmetic products and/or due to mRNA vaccine's mRNA mediated stimulation of TLR7 receptor, whose expression is enhanced by estrogens, thus mounting a stronger immune response [31–33].

The proposed mechanisms for vaccine induced related allergies are being described below. IgE-mediated reactions, via mast cell activation and degranulation, may occur when allergen specific IgE antibodies bind to FcεRI receptors on mast cells and basophiles [25, 31, 34, 35] (Fig. 1). On the other hand, non-IgE-mediated reactions, the so called complement activation-related pseudoallergy (CARPA), result in mast cell degranulation that occurs via complement activation and generation of inflammatory stimulators, such as

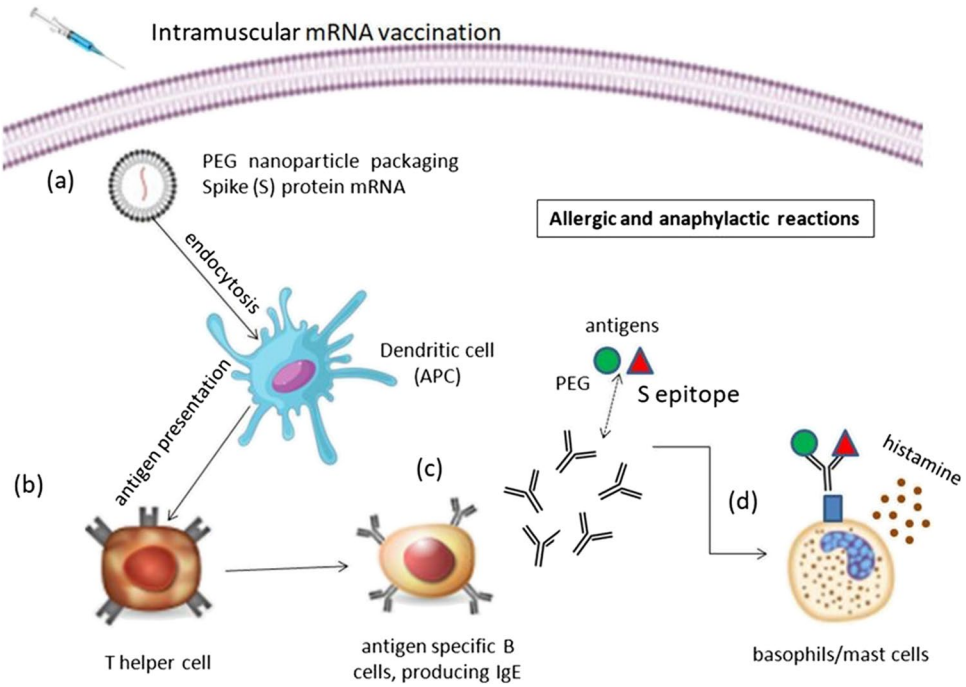

Fig. 1 Proposed mechanism of allergic and anaphylactic reactions, following mRNA vaccination. **a** PEG nanoparticle packaging S protein mRNA enters an APC cell, such as dendritic cells, via endocytosis. The mRNA is then translated to S protein, in the ribosomes. **b** The APC presents free floating PEG or S protein epitopes, as antigens, to T helper cells. The latter secrete cytokines and thus lead to B cell activation. **c** B cells produce IgE antibodies against PEG or S protein epitopes. **d** Antigen specific IgE antibodies bind to FcεRI receptor. The engagement of the aforementioned receptor leads to histamine release from basophils and/or mast cells, thus leading to allergic/anaphylactic reactions

C1q, C3a, C4, anaphylatoxins, C5a, and complement factor B. The latter mechanism is the most plausible, considering the fact that PEG is present in mRNA vaccines and plays a role in hypersensitivity reactions [25, 31, 34–36]. Another possible scenario suggests LNP-mediated activation of the Mas-related G protein-coupled receptor X2 which in turn activates mast cells [31, 34, 35, 37]. Allergy may also be the result of a cell mediated hypersensitivity reaction caused by overstimulation of T cells and macrophages [34, 35]. Previous formation of antibodies against LNPs / PEG (IgM,IgG,IgE) can lead to hypersensitivity reactions, after re-exposure [31, 38]. LNP formulation can, up to a point, protect against naked RNA's proinflammatory properties since they get disrupted intracellularly, releasing their payload after phagocytosis [31, 39]. It is also important to mention that, according to a new study, amino acid residues (437–508 sequence of the spike protein) may cause anaphylaxis [40]. In addition, genetic and environmental factors can lead to mast cell hyperactivation [31]. For instance, estrogen activates Th2 responses, while testosterone diminishes them [33, 40]. Stress and drugs also, such as non-steroidal anti-inflammatory drugs and opioids, can affect mast cell degranulation [41, 42]. Other genetic factors such as mastocytosis, idiopathic mast cell activation syndrome, hereditary alpha tryptasemia, and rare mutations in KARS, a dual localized lysyl-tRNA synthetase, are also to be taken into account [31, 35, 43, 44].

AstraZeneca and Janssen (Johnson & Johnson) vaccines contain a stabilizer and emulsifier, which is an analog of PEG, called polysorbate 80. Polysorbate 80 has been associated with hypersensitivity reactions from viral vectored vaccines, due to cross-reactivity with PEG. Both of these excipients share a common allergenic epitope, the polyether domain. Immediate hypersensitivity reactions can occur after a previous sensitization from PEG [26, 29, 45].

Other excipients associated with hypersensitivity reactions are trometamol, a component in Moderna's vaccine, that regulates the pH of nucleic acid solutions [29, 45]. DSPC is another component present in mRNA vaccines that may have an allergenic potential, because it is a substrate for phospholipase A2, a proinflammatory mediator [26, 29]. Moreover, AstraZeneca's vaccine contains EDTA which may cause systemic allergic reactions [26, 29, 35, 46]. Lastly, chlorhexidine, used for sterilization of the injection site, may also cause an allergic reaction [45].

Thrombosis and thrombocytopenia

COVID-19 adenoviral vector vaccines, Ad26.CoV2.S and AZD1222 (ChAdOx1 nCoV-19), have been associated with thrombosis and thrombocytopenia [5, 6, 47–51]. Cases of thrombosis and thrombocytopenia have also been reported following COVID-19 mRNA vaccination, although no association was established thus far [52, 53]. Following, we present the different molecular mechanisms through which thrombotic phenomena may arise after adenoviral vector vaccination.

The most accepted mechanism of induction of thrombotic phenomena is the vaccine-induced immune thrombotic thrombocytopenia (VITT) syndrome [47–49] (Fig. 2). This syndrome resembles heparin-induced thrombocytopenia (HIT), in which IgG specific antibodies against platelet factor 4(PF4)(anionic) and heparin(cationic)form complexes, causing platelet activation through the FcγRIIA receptor [54]. In VITT, since patients have not received heparin, anti PF4-antibody (IgG) production may be elicited by the vaccine induced immune response and/or even by the vaccine itself. Supporting the above is the fact that adenoviruses are known to directly interact with PF4 and cause platelet aggregation [55, 56]. It is important to mention that no confirmative evidence exist so far, regarding enhanced risks of VITT syndrome in patients with prior history of HIT [57, 58].

The adenoviral double stranded DNA is negatively charged and interacts with PF4, forming DNA-PF4 complexes. These complexes amplify TLR9 and interferon-α (IFNα) production, thus contibuting to immunothrombosis [59, 60]. Of note, RNA vaccines utilize TLR7 as a pattern recognition receptor, whereas viral vector vaccines can exert their effects through TLR9 to promote cellular and humoral immunity against the spike protein [61]. It is important to mention that, not only DNA but also RNA can be transported to plateletes via endocytosis, and form complexes with PF4, leading to the induction of PF4/heparin antibodies in mice [55, 62, 63]. Moreover, a hypothesis suggests that the DNA-PF4 interplay may be a component of antiviral innate immunity system that, in rare cases, may lead to autoimmunity and thrombosis [59]. Interestingly, a DNA/PF4 interaction in the injection site has been documented, hastening antigen presenting cell (APCs) uptake and memory B cell activation, leading to anti-PF4 antibody production or T-cell dependent persistant autoantibody responses [59, 64]. VITT may also be an atypical form of COVID-19 infection, as both feature platelet activation, thrombosis, and thrombocytopenia with the presence of anti PF4 antibodies [64]. Another hypothesis suggests that, in order for thrombosis to be triggered, three requirements need to be met. The first one refers to adenoviral leakage from the injection site,capable of leading to adenoviremia and high production of spike protein. The second and third requirements, respectively, refer to the presense of specific and cross reactive antibodies, as well as high titer of glycosilated antibodies (glycosilation of anti SARS-COV-2 IgG is a pro thrombotic stimulus for platelets) [65].

Self DNA released by neutrophil extracellular traps (NETS) at injury sites is citrullinated and thus leads to electric charge rebalancing by eliminating DNA–protein

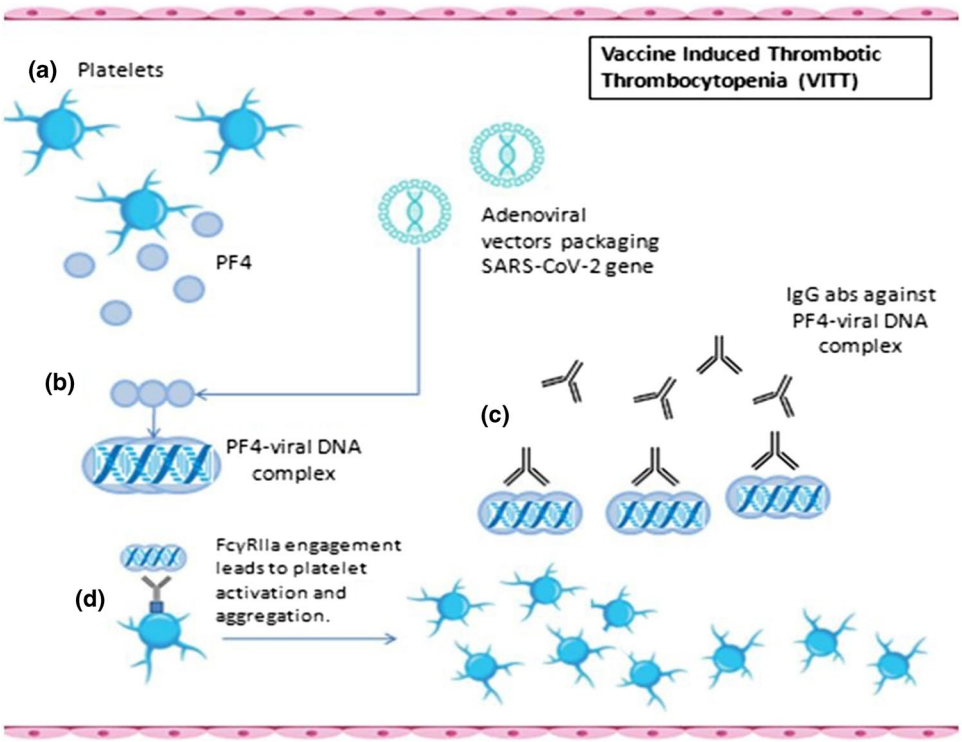

Fig. 2 Proposed mechanism for VITT syndrome, following vaccination with viral vector DNA vaccines. **a** and **b** Platelets secrete PF4 (anionic), which potentially forms complexes with viral vector DNA (cationic). **c** IgG antibodies against PF4-viral DNA complexes are produced. **d** The IgG antibodies bind to FcγRIIa receptor, whose engagement leads to platelet activation and aggregation

interactions [59, 66]. This process, called NETosis, is a physiologial process that traps pathogens. Excessive formation of NETS contributes to inflammation. Immune complexes, composed of PF4/heparin antibodies, can activate NETosis, after stimulation of platelets, and further contribute to hypercoagulation [67–69].

Platelets express CAR (coxsackie/adenovirus receptor); thus, it can be hypothesized that vaccine adenoviruses can "infect" megakaryocytes [70, 71]. Adenoviruses may also bind to circulating platelets, in a von Willebrand Factor or P-selectin dependent manner, causing their activation and an increase in prothrombotic phenomena [70, 72, 73]. Supporting this mechanism is the fact that high adenoviral load in the blood can lead to thrombocytopenia [63, 74]. Moreover, once COVID-19 spike protein is expressed, platelets might become antibody targets and/or enhance thromboxane A2 production [63]. Mast cells also express CAR. The mast cell activation syndrome (MCAS), a genetic disorder, can cause chronic and abberant mast cell activation, inflammation, and heparin release, characterized by a potential anti PF4/heparin antibodies production [75]. Anti PF4 – antibodies can directly bind to neutrophils, monocytes, or endothilial cells, promoting subsequent thrombotic events [70].

Cell entry of adenovirus type 26 (Ad26) does not depend on CAR receptor. CD46 molecule was first proposed to be the primary cellular receptor for the virus, but this scenario has recently been excluded. According to new data, sialic acid has been demonstrated to be the primary cell receptor. Human platelets differ in their content of sialic acid and it seems that adenovirus-platelet interactions, after Ad26.CoV2.S vaccination, may result in platelet aggregation [63, 76]. Furthermore, binding of Ad26 vector to CD46 upregulates the complement pathways and leads to thrombosis [62, 77].

EDTA contained in AstraZeneca's vaccine may increase local vascular permeability in the injection site, causing a serum sickness-like illness, activating anti-PL4 antibodies [70, 75, 78]. The spike protein DNA payload may also affect the charge of EDTA and promote DNA/PF4 interaction [59]. Moreover, chimpanzee adenoviral vectors are cultured using an immortilized kidney cell line (REx-HEK293) and, although the product is purified, some vaccine preparations may contain DNA and protein contaminants that may interact with platelets [75].

Splicing events have been demonstrated, following the transcription of the viral DNA vector to RNA (a process which is absent from the direct mRNA transcripion), leading to shorter spike protein variants which bind to angiotensin-converting enzyme 2 (ACE2) receptors, causing thrombosis [70, 79]. The neo-synthesized spike protein can also directly activate platelets and thus lead to prothrombotic events. This spike protein can either be a product of viral vector or mRNA vaccines [18, 63, 75, 80]. Note that molecular mimicry between spike protein and PF4 may be possible, although it has not yet been confirmed [63].

Platelet microparticles (PMPs) may play a role in prothrombotic events, due to their smaller size and better diffusion in unreachable sites, compared to platelets. Additionaly, phosphatidyloserine and membrane proteins, participating

in the binding of coagulation factors, are both concentrated in the PMPs [72]. Another factor that may aggravate the situation is the DNA and histone release that takes place during inflammation which might stimulate coagulation and thrombosis [72].

An association between periodontal pathogen infection and natural circulating anti-PF4/heparin antibodies has been described. The periodontal pathogens involved serve as primary immunogens [81]. Anti-phospholipid autoantibodies and/or other autoantibodies may be ivolved in thrombosis and thrombocytopenia, after vaccination [72]. Post-vaccination anti vector-antibodies may play a role in the observed VITT as well, but this hypothesis requires further investigation [63]. FcγRIIA receptor gene polymorphism is also associated with the development of thrombosis [72, 82]. Other genetic factors need to be taken into account, such as single nucleotide polymorphisms (SNPs) in the T cell death associated gene 8 and a SNP on the HLA class II alpha chain gene (*HLA-DRA*), since they are associated with the formation of anti-PF4/Heparin antibodies in non heparin treated patients [72, 83]. Platelet endothelial cell adhesion molecule 1 gene (*PECAM-1*) is expressed in platelets and neutrophils andits polymorphism has being associated with HIT. Human platelet antigen genotype (HPA-1a/b) has also been associated with HIT. Lastly, *CXADR* (encoding for coxsackie and adenovirus receptor) enhances the affinity of adenoviruses for platelets [84].

The adenoviral vector vaccines contain a tPA leader sequence, which has been previously associated with thrombosis, although such incidents are unlikely due to low percentage of cases [62, 85]. Both RNA and viral vector DNA vaccines can cause thrombosis and thrombocytopenia, after interaction of the spike protein with heparin sulfate proteoglycans, C-type lectin receptors, and/or CD147, on the host cell surface. These molecules can regulate the complement pathway [62, 86]. Furthermore, heparin sulfate proteoglycans, shed from damaged endothelial cells, contribute to PF4 immunogenicity [87]. SARS-CoV-2 is also known to target dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), a C-type lectin receptor, in order to enter the host's cell, in low ACE2 expressed tissues. DC-SIGN has been linked to thombocytopenia; thus, the vaccine's spike protein may cause such a blood disorder via a DC-SIGN dependent manner [62, 88].

Myocarditis

Myocarditis has been associated with COVID-19 mRNA vaccines. The risk rate seems to be about threefold to fourfold higher for mRNA-1273, compared to the BNT16b2 [89, 90]. The discrepancy, regarding the frequencies of myocarditis occurrence for the two vaccines, could probably be explained by the different time span between the two doses, the differences in composition (LNPs) and in purity of the materials, as well as in the production protocols [90, 91]. Despite the higher rate of myocarditis for the mRNA-1273, CDC considers the complication as rare in all cases of mRNA COVID-19 vaccination [92, 93]. COVID-19 infection is a potential trigger of myocarditis, as it affects the vascular system, resulting in myocardial injury in 12–20% of hospitalized patients [92, 93]. Since a variety of reports is linking the mRNA vaccines to myocarditis adverse events, several mechanisms have been proposed [94–96].

SARS-CoV-2 spike protein binds to ACE2 receptors, which are abundant in cardiovascular tissues [97]. Naïve T cells can be primed by viral antigens or other proteins released by damaged cardiomyocytes, leading to inflammation [98]. Moreover, a past COVID-19 infection can predispose a higher incidence of myocarditis after vaccination, with previously primed T cells attacking both the vaccine's spike protein and the cardiac antigens [95, 96]. Molecular mimicry between the spike protein and self antigens is another possible mechanism. The spike glycoprotein has been shown to cross-react with proteins with similar sequence, such as α myosin, and so it is possible that inflammatory reactions may occur in predisposed patients [92, 99]. Also, heart reactive autoantibodies have been linked to higher rates of myocarditis, although it has yet to be determined if they are pathogenic or simply a result of myocardial injury [100]. These autoantibodies are present mostly in first degree relatives of patients with cardiomyopathy, a fact that indicates an important role for the individual's genetic background. Moreover, in some patients, a deregulation of proinflammatory cytokines and an elevated number of NK cells, in conjunction with the autoantibodies, may result to heart injury, after COVID-19 vaccination [92].

RNA molecules are immunogenic and, in some individuals with genetic predisposition, the modified RNA of the vaccine may be recognized as an antigen [101]. As a result, a proinflammatory cascade can be activated playing a potential role in myocarditis [92, 101]. Of note, male's predominance in myocarditis incidents may be due to testosterone's anti-inflammatory properties and, also, due to the activation of Th1 responses. Estrogens inhibit pro inflammatory T-cells, decreasing cell mediated immune responses [92, 102]. Moreover, myocarditis may be associated with ingredients of the vaccine. Cases of myocarditis, due to vaccine adjuvants, have been described in the past, although mRNA COVID-19 vaccines do not contain the same components as the vaccines used thus far (non mRNA vaccines) [94]. Minor differences in the manufacturing practices, during biologic vaccine's production, as well as the inherent instability of the mRNA, should be taken into account, as they may play a role in immunogenicity and myocarditis [103].

Neurological adverse events

After the initiation of the mass vaccination program against COVID-19, reports concerning neurological adverse events of the vaccines started to emerge. Among these neurological adverse events, the most common observed were Guillain–Barre syndrome, transverse myelitis and Bell's Palsy, although no association with COVID-19 vaccines has been confirmed yet [9, 104–108].

Guillain–Barre syndrome has been linked with viral vector vaccines. Molecular mimicry, anti-gaglioside antibodies, and compliment activation play a role in the pathogenesis of the disease, which may result from viral infections, such as in cases of infections with adenoviruses [106]. It has been also postulated that the vaccine's components, as well as contaminating proteins, can induce anti-gaglioside antibodies leading to inflammation [64, 104] (Fig. 3).

Transverse myelitis is an demyeliting disease, linked to COVID-19 vaccines. It has been suggested that post-vaccination demyelination might be a trigger for the disease's expression, in people already predisposed towards it [104, 109]. Transverse myelitis can also appear as a result of viral infection, suggesting that viral antigens, present in the vaccine, or even the adenovirus itself can induce relevant immune responses. The most likely mechnanism is molecular mimicry and bystander activation of the immune system, leading to autoimmunity [9]. In cases where mRNA vaccines had being used, the possible mechanisms differ from those mentioned above. In more detail, SARS-CoV-2 spike protein antibody, directly reacts with the myelin. Additionally, interaction of the spike protein with ACE2 receptors, present in neurons, results in demyelination processes [99, 107].

Bell's Palsy appears to be a rare adverse event of mRNA vaccines. A potential mechanism is the activation of type I interferons, by the vaccine's mRNA and/or lipids, leading to lymphocyte activation and inflammation. Furthermore, IFNα seems to have the ability to breakdown myelin antigens, thus leading to neuropathy [108, 110]. The autoimmune responses may also result from molecular mimicry or bystander activtion of T cells [108, 111]. Another underlying mechanism refers to anaphylaxis reactions, caused by the vaccine components and thus facilitating the appearance of Bells's Palsy [112].

Some other reports discuss the possibility of a link between the vaccines and epilepsy and/or encephalopathy [8, 104, 113]. More specifically, a case of new-onset refractory status epilepticus (NORSE) has been described, after ChAdOx1 nCoV-19 vaccination. The vaccine induced high fever which provoked seizures. An alternative hypothesis focuses on the ACE2-mediated accessibility of the viral vector into the brain, which can trigger a pro inflammatory cytokine cascade, neuronal hyper excitation, and seizures [8, 104]. As far as encephalopathy is concerned, a cytokine storm associated encephalopathy syndrome, following mRNA vaccination, has been proposed. Spike protein is considered the trigger of the syndrome [77, 113].

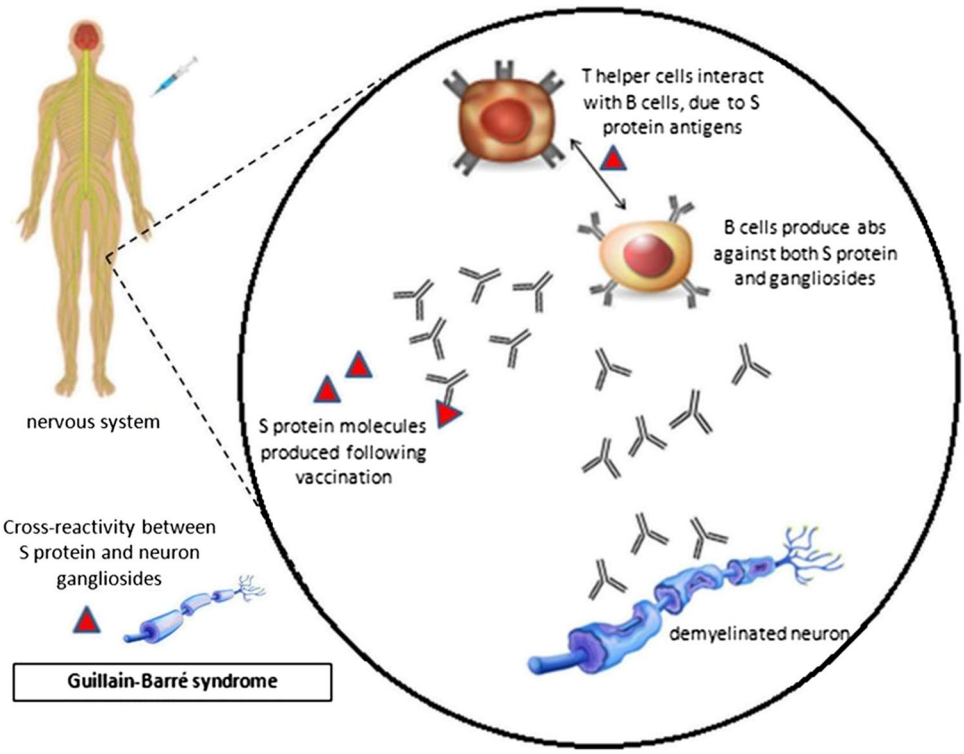

Fig. 3 Proposed mechanism for Guillain–Barre syndrome, following COVID-19 vaccination. The immune cells produce antibodies against S protein. In terms of molecular mimicry, as S protein cross-reacts with gangliosides, the antibodies also damage the neurons, thus leading to their demyelination

Other adverse events

Autoimmunity may be triggered by COVID-19 vaccines. Although these cases are all considered extremely rare, an infection-induced autoreactive mechanism can occasionally lead to autoimmune disease pathogenesis, especially in patients with predisposition (such as subjects carrying gene polymorphisms that affect IL-4 expression) [101, 105, 114]. The mRNA vaccines, as well as the viral vector ones, can potentially induce autoimmune disease flares or new onset disease, through the activation of TLR7/8 and TLR9 receptors respectively, thus resulting in type I interferon production and nuclear factor NF-kB expression [11, 105, 115, 116] (Fig. 4). The triggering of autoimmune phenomena, following COVID-19 vaccination, may occur due to the expansion of potentially pathogenic B cells, such as the transcription factor T-bet expressing B cells, which rely on TLR7 and TLR9 for their differentiation. The characterization of these cells, especially in people with autoimmune history, could enable a better management of patients with minimized adverse events and maximized therapeutic benefits of immunization against SARS-CoV-2 [117, 118]. Additionally, mRNA can stimulate dendritic cells' maturation and activate T cells, B cells, and bystander autoreactive lymphocytes, thus reactivating autoimmune responses. It is important to mention though that mRNA can potentially inhibit antigen expression [105, 119]. Autoimmunity may also be stimulated by molecular mimicry between the spike protein and self-epitopes, resulting in a robust activation of autoreactive T cells and B cells [105]. The cytokines secreted by macrophages should be taken into account as well, as they recruit additional T cells aggravating the situation [120]. Despite all these mechanisms that trigger disease flares or even new onsets, the majority of people can be vaccinated without any risk of autoimmunity, as these phenomena are considered rare and mild to moderate in severity [11, 105].

Antibody dependent enhancement (ADE) has been suggested as a probable phenomenon that exacerbates COVID-19, through anti SARS-CoV-2 antibodies produced by the vaccine [121]. The two main mechanisms, leading to ADE, are an enhanced antibody-mediated virus uptake into FcγIIa receptor and/or a formation of immune complexes that have inflammatory properties and lead to increased inflammation. ADE occurs when non neutralizing antibodies bind to viral antigens, without eliminating them [121]. To date, there is no evidence confirming ADE's association with COVID-19 vaccination.

Tachycardia following COVID-19 vaccination is another well documented adverse event [10, 122]. In more detail, cross reacting antibodies are proposed to target the nervous system, leading to postural orthostatic tachycardia (POTS). POTS may, alternatively, result from an autoantibody mediated mechanism, in which autoantibodies target α1 adrenergic receptors [123]. The targeting of α1 receptors provokes impaired vasoconstriction, increased sympathetic nervous system activity, and also activation of baroreceptors [10, 123]. Other mechanisms leading to POTS pertain to

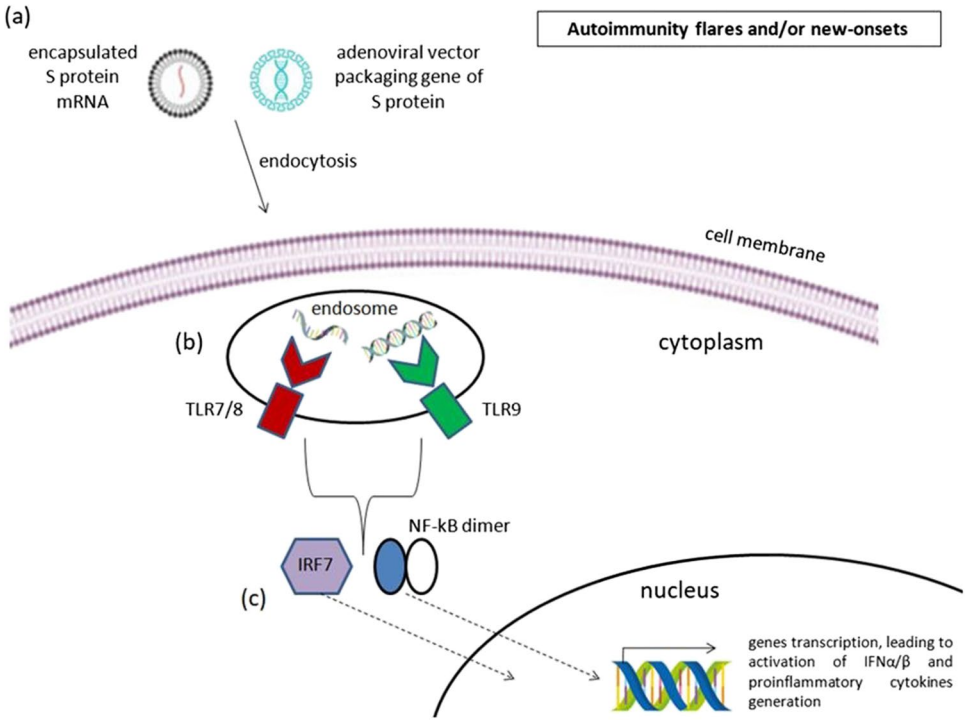

Fig. 4 Potential mechanisms leading to autoimmunity flares and/or new-onsets of disease. **a** Following COVID-19 vaccination, the mRNA or the viral vector DNA enters a cell via endocytosis. **b** In endosomes, the ssRNA or the double-stranded DNAs (dsDNA) are sensed by TLR7/8 or TLR9 respectively. TLRs engagement triggers a series of signal transduction pathways, resulting in the formation of interferon regulatory factor 7 (IRF7) and NF-kB. **c** After being formed, both IRF7 and NF-kB translocate to the nucleus. In the nucleus, genes transcription leads to interferon type I activation and proinflammatory cytokines generation

autoantibodies targeting vascular and/or cardiac adrenergic receptors, anti SARS-CoV-2 antibodies that display cross-reactivity with receptors in the ganglia, and ACE2 receptor's dysfunction [10, 124]. The spike protein produced by mRNA vaccines can stimulate autoimmune responses, leading to POTS, as well [10].

Recurrences of herpes zoster is another reported adverse event of COVID-19 vaccines [7, 14, 125]. In general, its incidence increases with age and factors such as stress, trauma, and immunosuppression, can lead to viral reactivation and inflammation of ganglia, associated with vesicular eruptions of the skin [14, 125].

To conclude, we provide a table summarizing all the issues discussed above. More specifically, all the potential mechanisms described, regarding COVID-19 vaccine adverse events, are presented in Table 1.

Discussion

COVID-19 vaccines offer an opportunity to end the current global pandemic, with the approved vaccines eliciting sufficient immune response while being safe. Despite the different platforms used, all vaccines encode SARS-CoV-2 spike protein that is being recognized by the immune system forming anti-SARS-CoV- 2 IgG antibodies [18].

The rapid research and manufacturing process, in order to immediately confront the pandemic, raised concerns, especially regarding the safety profiles of the mRNA and viral vector vaccines. The literature so far suggests that the mRNA vaccines might be more likely to cause an adverse event in comparison to the viral vector ones [126, 127]. Pain in the injection site is considered the most common local reaction, while fatigue and headache as the most common systemic [126, 127]. The pool rates of the aforementioned reactions were 89.4% and 83.3% respectively, for the mRNA vaccines, and 55.9% and 66.3% respectively, for the viral vector vaccines [126, 127]. Moreover, serious gastrointestinal complications and infections were more common among viral vector vaccines, while the occurrences of serious vessel disorders and medically attended events were more frequent in mRNA vaccines [126, 127]. That said, it is imperative to stress out that all approved COVID-19 vaccines have an acceptable safety profile [126, 127].

mRNAs technology, despite being new, has some advantages over other platforms. Some of the advantages of mRNA-based vaccines include the fast-track manufacturing process, the inability of mRNA to integrate to the host cell's genome, reduced contamination issues, biodegradability, and elicitation of robust humoral and cellular immunity, thus acting concomitantly as both an immunogen and an adjuvant [18, 20, 128–130]. However, mRNA products present stability issues which might be considered a major obstacle for worldwide distribution [129, 130]. Furthermore, data for the extent of the trapped mRNA inside the LNPs are not currently available [130].

In terms of the adenoviral vaccines, viral vectors have the potential of targeted gene delivery to the cells that results in efficient immune responses [18, 131]. These vaccines can also induce a high level of antibody production and T cell activation [130]. On the other hand, they contain a double stranded gene, encoding for spike protein and thus neither the integration of the viral DNA in the host's genome, nor the production of various spike protein fragments can be excluded as factors implicated in some of the reported side effects [18, 131].

In this review, the potential molecular mechanisms leading to the rare adverse events, following COVID-19 vaccination, have been discussed. It must be noted that most of these mechanisms are hypothetical and thus must be interpreted with caution. More specifically, mRNA vaccines can cause anaphylactic and allergic reactions with the main culprit being an LNP component called PEG. Previous PEG allergies reported reinforce such a hypothesis [29, 30]. Adenoviral vector vaccines have been associated with thrombosis and thrombocytopenia, through a newly characterized syndrome called VITT, in which anti PF4-antigen antibodies lead to a proinflammatory cascade and platelet activation [47–49]. Several factors play a role in the initiation of these phenomena, with the adenovirus itself, or other vaccine components, such as spike protein and DNA, being associated with thrombosis [55, 56, 59, 60, 79]. Myocarditis has also been linked to mRNA vaccines, with both RNA reactogenicity and spike protein binding to ACE2 receptors in the cardiovascular system being the possible culprits [92, 101]. Other important adverse events are of neurological nature. There, a mechanism of molecular mimicry and bystander activation of T cells facilitating an autoimmune response can lead to neuronal dysfunction [9]. Autoimmune responses from the vaccine may also lead to flares of pre-existing autoimmunity diseases or even initiate new onsets in predisposed patients [11].

Moreover, biological sex is a factor that seems to correlate with all these responses [32]. PEG allergies, autoimmune phenomena, and thrombosis are more frequent in females. The mRNA vaccines utilize a TLR7 recognition receptor, while viral vector vaccines recruit a TLR9, which activates interferon I responses, a molecule acting as mediator in many autoimmune diseases [32, 33]. Additionally, PEG is a component widely used in cosmetic industry; thus, female individuals are more likely to exhibit past exposure and sensitization to this component [31]. The danger is increased for women receiving oral contraceptives since they already display an increased thrombosis risk [132]. Myocarditis is more frequently reported in young adults, as testosterone enhances Th1 responses and leads to inflammation, while

Table 1 The potential mechanisms underlying the adverse events of interest

COVID-19 vaccines	Adverse events	Vaccine components	Possible mechanism
BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)	Anaphylaxis	PEG, DSPC, trometamol (mRNA-1273 only)	• IgE mediated reactions [25, 31, 34, 35] • Non IgE mediated reactions [25, 31, 34–36] • Direct activation of the Mas-related G-Protein- coupled receptor X2,by the LNPs [31, 34, 35, 37] • Overstimulation of T cells and macrophages [34, 35] • Previous formation of antibodies against LNPs / PEG (IgM,IgG,IgE) [31, 38] • Naked RNA [31, 39] • Amino acid residues (437–508 sequence of the spike protein) [40] • Estrogen activates Th2 responses, while testosterone diminishes them [33, 40] • Stress, drugs, genetic factors [31, 35, 40, 42–44]
Ad26.CoV2.S (Janssen/Johnson & Johnson)AND AZD1222 (Oxford/Astrazeneca)	Anaphylaxis	Polysorbate 80, EDTA(AZD1222 only)	• Cross-reactivity with PEG [26, 29, 45] • EDTA may cause systemic allergic reactions (in AZD1222 vaccine only) [26, 29, 35, 46]
BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)	Myocarditis	mRNA, spike protein, impurities	• Spike binds to ACE2 receptor in cardiomyocytes [97] • Past COVID 19 infection contribute to previous primed antigens [95, 96] • Molecular mimicry [92, 99] • Heart reactive autoantibodies and deregulation of cytokines [92, 100] • RNA antigenic properties [101] • Sex hormone differences [92, 102] • Vaccine components and manufacturing practice [103]
Ad26.CoV2.S (Janssen/Johnson & Johnson)AND AZD1222 (Oxford/Astrazeneca))	Guillen Barre syndrome	Adenovirus, spike protein, impurities	• Molecular mimicry [106] • Anti-gaglioside antibodies [106] • Complement activation [106] • Vaccine components [64, 104]
*Ad26.CoV2.S (Janssen/Johnson & Johnson)AND AZD1222 (Oxford/Astrazeneca)*AND *BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)*	Transverse myelitis	Adenovirus, spike protein, mRNA	• Adenovirus infection demyelination [104, 109] • Molecular mimicry [9] • Bystander activation of T-cells [9] • Anti-spike antibody directly interacts with myelin (in cases of mRNA vaccines) [99, 107] • Interaction of spike protein with ACE2 in neurons [99, 107]
BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)	Bell's palsy	mRNA, LNPs, spike protein, impurities	• Activation of INFI by mRNA or lipids [108, 110] • Molecular mimicry and bystander activation [108, 111] • Anaphylaxis from vaccine components [112]
Ad26.CoV2.S (Janssen/Johnson & Johnson)AND AZD1222 (Oxford/Astrazeneca)	NORSE	Adenovirus	• High fever leading to seizures [8, 104] • Entry of viral vector into the brain, via ACE2 receptors, triggers seizures [8, 104]
BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)	Encephalopathy	mRNA, spike protein	• Cytokine storm associated encephalopathy syndrome, caused by spike protein [77, 113]
*Ad26.CoV2.S (Janssen/Johnson & Johnson)AND AZD1222 (Oxford/Astrazeneca)*AND *BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)*	Autoimmunity	Adenovirus, mRNA, TLR ligands, spike protein	• Activation of TLR7/8 and TLR9 receptors, resulting in type I interferon production [11, 105, 115, 116] • mRNA stimulates immune system [105, 119] • Molecular mimicry [105] • Cytokines secreted by macrophages [120]

Table 1 (continued)

COVID-19 vaccines	Adverse events	Vaccine components	Possible mechanism
BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)	Tachycardia	mRNA, spike protein	• Cross reacting antibodies target the nervous system [123] • Autoantibodies target α1 adrenergic receptors [123] • Autoantibodies targeting vascular and/or cardiac adrenergic receptors [10, 124] • Anti SARS-CoV-2 antibodies that display cross-reactivity with receptors in the ganglia [10, 124] • ACE2 receptor's dysfunction [10, 124] • mRNA spike protein can stimulate autoimmune responses [10]
*Ad26.CoV2.S (Janssen/Johnson & Johnson)AND AZD1222 (Oxford/Astrazeneca)*AND *BNT16b2 (Pfizer/Biontech)AND mRNA-1273 (Moderna)*	Herpeszoster	Adenovirus, mRNA	• Age, stress, trauma and immunosuppression, lead to reactivation and inflammation of ganglia [14, 125]
Ad26.CoV2.S *(Janssen/Johnson & Johnson)AND* ***AZD1222*** *(Oxford/Astrazeneca)*	Thrombosis and thrombocytopenia	Adenovirus, spike protein, EDTA, tPA, CAR receptor, sialic acid receptor, TLR ligands, impurities	• Vaccine-induced immune thrombotic thrombocytopenia (VITT) [47–49] • Adenoviral double stranded DNA interacts with PF4 [55, 56] • DNA-PF4 interplay may be a component of antiviral innate immunity system [59] • DNA/PF4 interaction in the injection site [59, 64] • VITT may be an atypical form of COVID-19 infection [64] • Adenoviral leakage from the injection site,the presense of specific and cross reactive antibodies, as well as high titer of glycosilated antibodies [65] • NETosis [67, 68] • Platelets express CAR (coxsackie/adenovirus receptor) [70, 71] • Adenoviruses bind to circulating platelets [70, 72, 73] • High adenoviral load in blood [63, 74] • Platelets might become antibody targets and/or enhance thromboxane A2 production [63] • Mast cells also express CAR [75] • Anti PF4 – antibodies can bind to neutrophils, monocytes or endothilial cells [70] • Platelets differ in their content of sialic acid,the cell entry of adenovirus type 26 [63, 76] • Binding of AD26 vector to CD46 up regulates the complement pathways [62, 77] • EDTA contained in Oxford/AstraZeneca's vaccine may increase local vascular permeability [70, 75, 78] • Number of spike protein DNA copies could charge agents, such as EDTA [59] • Vaccine preparations may contain contaminants [75] • Splicing events create shorter spike protein variants [70, 79] • Spike protein can directly activate platelets [18, 63, 75] • Platelet microparticles (PMPs) [72] • DNA and histone release in inflammation [72] • Periodontal pathogen infection [81] • Anti-phospholipid autoantibodies and/or other autoantibodies [72] • Genetic factors [72, 82–84] • Tissue plasminogen activator (tPA) leader sequence [62, 85] • Interaction of the spike protein with heparin sulfate proteoglycans, C-type lectin receptors and/or CD147 [62, 86–88]

estrogen inhibits them [92, 102]. It is important to note that many females diagnosed with myocarditis are post-menopausal [133].

All biological products have adverse effects, calling for heightened pharmacovigilance reflexes [134]. The pharmaceutical industry should focus on improving the current COVID-19 vaccines, as well as future versions, in order to bring about maximization of the therapeutic benefits, while keeping side-effects at bay. The fact that SARS-CoV-2 displays a high mutation rate, thus leading to the emergence of new variants of concern (such as delta and omicron) [135, 136], highlights the necessity of constantly developing new vaccines, in order to successfully confront the new dominant variant. To this end, a third "booster" shot is now required for being protected against the omicron variant, which is currently considered the dominant one [136, 137]. Fortunately, the fast-tracking development of COVID-19 vaccines has led to the in time immunization of people around the world [138]. However, despite the fast and massive vaccine production, poorer countries — up to now — do not seem to easily have access to the vaccines [138]. Moreover, it is important to mention that such an immediate worldwide vaccination approach (that refers to new vaccine technologies) has given rise to concerns regarding the effectiveness and the safety of the vaccines; thus, several individuals have been hesitant to be vaccinated against SARS-CoV-2 [138]. As it stands, the landscape has changed considerably since the first COVID-19 wave, where the virus had taken the world by storm causing a pandemic [135]. Considerable portions of the worldwide population have nowadays either been vaccinated and/or infected with the virus. This has led to accumulation of the relevant clinical knowledge on the course of the disease, as well as the development of appropriate therapeutic protocols [136, 137]. Furthermore, world-wide mobilization has led to the development of an array of different vaccines to choose from [1]. Given the above, it would be prudent to suggest that fast-tracking vaccine products can now be approached in less urgent terms, in order to allow adequate time for proper evaluation of the efficacy and safety of the emerging vaccines [138].

Pharmaceutical industries should also take into consideration a wide variety of confounding factors such as genetic predisposition, sex differences, and environmental triggers of the different populations, when designing and developing a vaccine. Novel components can be evaluated for the composition of future vaccines. Theoretically, proven ingredients which are absent from COVID-19 vaccines, but present in other non COVID-19 vaccines (such as latex, egg, or yeast proteins and antibiotics) could be considered for the composition of the final product, at least in non-allergic subjects [139]. The genetic background of the patient population should be taken into account, paying attention to polymorphisms leading to susceptibility to different diseases [72, 83, 84]. LNPs, including those utilizing PEG with lower MW, are a future consideration, since these molecules are less immunogenic [27]. The recombinant adenoviruses as vectors are well used platforms and can be rendered safer by modifying their ability to bind to platelets, or even by using other recombinant viruses as vectors, against which no pre-existing immunity exist in humans, minimizing the likelihood for off-site effects [139]. Moreover, alternative splicing requires to be taken into consideration, as the introduction of an RNA virus component into a DNA virus may lead to the translation of a different product with unknown effects on the cell [79, 80]. Bioinformatics tools could probably contribute to the prediction of harmful splicing variants [79, 80]. Last but not least, TLRs are efficient immune response mediators used in COVID-19 vaccines; thus, their link with autoimmunity should be well considered, especially for the female population, as *TLR7* gene is located on X chromosome [32]. In order to avoid TLR binding, which is indissolubly linked to autoimmunity [140], emphasis should probably be put on protein vaccines (at least in females, which are more vulnerable to autoimmune diseases [32]). Fortunately, advances in the fields of precision medicine, genomics, immunology, and bioinformatics will extend our knowledge and resolve the issues mentioned above.

Declarations

Conflict of interest The authors declare no competing interests.

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