Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Post-adenoviral-based COVID-19 vaccines thrombosis: A proposed mechanism

There have been several reports of thrombosis and thrombocytopenia after vaccination with the ChAdOx1 nCoV-19 vaccine (Oxford–Astra-Zeneca) and Ad26.COV2.S vaccine (Johnson & Johnson/Janssen), a recombinant adenovirus serotype 26 vector encoding the SARS-CoV-2 spike glycoprotein.[1,2] These cases clinically manifest as disseminated intravascular coagulation-like phenomena. Recently anti-platelet factor 4 (PF4) autoantibodies detected by ELISAs were deemed as the number one culprit, but this finding has one main issue. The main issue is: Because these cases manifest as early as 5 days post-vaccination, there is typically not enough time for immunological tolerance to break and to generate high titer and class-switched, high-affinity IgG antibodies to trigger the proposed mechanism. However, it is possible that anti-PF4 is a byproduct of an initial mechanism that in turn can eventually lead to thrombocytopenia and amplify a viscous cycle. Interestingly, a proposed mechanism was FcγRIIa (CD32a)-dependent.[1] What is the initial mechanism? Bye et al.[3] recently demonstrated the role of aberrant glycosylation of anti-SARS-CoV-2 IgG as a pro-thrombotic stimulus for platelets. They showed that in COVID-19 patients, anti-SARS-CoV-2 IgG-spike glycoprotein immune complexes can, through FcγRIIa, which is the only FcγR present on the surface of platelets, activate platelets and lead to their adhesion to endothelial cells. The latter further triggered endothelial cells to produce von Willebrand factor (VWF). Additionally, VWF has been reported to be as high as five-fold in severe cases of COVID-19 compared to other cases.[4-6] More in-depth research is needed to substantiate such a ready-to-go mechanism; that being said, here I propose the following: a single vaccine dose contains 5×10^{10} adenoviral particles. If all is accidentally injected into the blood, for an approximate blood volume of 5000 ml, there will be an adenoviral load of 10^7/ml. Even lower levels or leaks from the injection site (over time) would culminate in still high-level adenoviremia. Although these adenoviruses are claimed to be replication-deficient, they are still able to travel to distant sites in the body and infect a range of permissive cells. Once infected, cells such as epithelial, endothelial, and fibroblasts, etc., that are not primarily antigen-presenting cells, may also secrete copious amounts of soluble spike glycoproteins leading to a relatively high level of SARS-CoV-2 spike "antigenemia." It is important to highlight that although chimpanzee adenovirus and human adenovirus 26 use different cellular receptors, that is, sialic acid-bearing glycans and Coxsackie-adenovirus receptor, respectively, both receptors are expressed on a large range of tissues.[7] Although a vaccine that uses a modified spike that may not be shed from cells, because adenoviremia can reach very high levels and infect a large number of cells, even focal expression of the spike is enough to trigger this mechanism. Nonetheless, this may not be possible in the case of mRNA-based vaccines as lipid nanoparticles cannot survive in the enzymatically hostile environment of plasma and are rapidly cleared by the reticuloendothelial system. In a person with a prior SARS-CoV-2 infection and/or with cross-reactive antibodies to common coronaviruses (CoVs), a large volume of the aforementioned immune complexes may form shortly after vaccination with adenovirus-based vaccines. Now using the Bye et al. study, in which IgG antibodies within these immune complexes are aberrantly glycosylated (for instance afucosylated), the above-mentioned mechanism can be triggered. The platelet adhesion to endothelial cells may also be one of the causes for severe thrombocytopenia observed in these cases. It was also previously shown that afucosylated antibodies were much more common among severe and critical COVID-19 cases.[8] Therefore, all three conditions—the amount of adenoviral vector leakage to the circulation, presence of specific and/or cross-reactive antibodies, and high enough titer of aberrantly glycosylated antibodies—need to be present to trigger such a mechanism. This may explain the rarity of the clinical observation. It is worth mentioning that the spike glycoprotein expressed in these vaccines is in fact the full spike antigen in its trimeric form. This means it contains highly cross-reactive domains (such as S2) that can be bound by antibodies against common CoVs. Very shortly after vaccination, anamnestic immune responses to common CoVs are activated and antibody titers can be found in very high titers.[9] Last, the apparent clinical response to intravenous immunoglobulin (IVIg) in these cases could very well be due to the competition between high-titer non-specific IgGs in the IVIg with the previously mentioned immune complexes through their Fc ends for CD32a on the surface of platelets. The latter would preclude their further adhesion to endothelial cells, which can lead to the reversal of thrombocytopenia.

The proposed mechanism here needs to be substantiated. Remedial actions would be to observe best practices in administering

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vaccines, possible reduction of the vaccine dose, and to avoid vaccinating those with underlying coagulopathies or thrombocytopenia.

KEYWORDS

adenovirus, COVID-19, thrombosis, vaccine

CONFLICT OF INTEREST

None declared.

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The failure rate does not equal the false-negative rate: A call for tailoring diagnostic strategy validation in low prevalence populations

Over the past decade, various new diagnostic strategies have been tested and validated for the diagnosis of pulmonary embolism (PE) in the emergency department or in primary care. The main goal of a new strategy is to safely decrease the need for further investigation, particularly imaging studies (usually computed tomographic pulmonary angiogram), and reducing overall resource consumption including time spent in the emergency department.[1]

The success of these recent strategies has resulted in excellent sensitivities with subsequent very high negative predictive values and low false-negative rates. Consequently, the further development of any new diagnostic strategies should not focus on improving the sensitivity or the overall discrimination, but rather on improving specificity without impairing sensitivity. To validate the safety of a strategy, a maximum acceptable failure rate is regularly redefined. From a former threshold between 2.7% and 4% based on pulmonary angiogram's performances, new recommendations suggested that the maximum threshold should be dependent on the prevalence of PE in the tested population.[2]

In 2017, the SSC of the ISTH recommended that the maximal acceptable failure rate should be 1.82% + 0.0053% × prevalence.[3] Therefore, in a low prevalence population, a new diagnostic strategy to rule out PE will be validated if the upper bound of the 95% confidence interval (CI) of the failure rate is below 1.82.

It is critical, however, to consider what we define as the "failure rate." The current definition is the number of missed PE (numerator) divided by the total number of patients in whom the strategy has been evaluated (denominator). This highlights a serious shortcoming: it is totally dependent on the tested population, which was addressed in the 2017 SSC recommendations.

Another serious shortcoming is that this definition omits an important variable: the number of patients in whom the strategy has actually changed the workup strategy (which can be partially capture by the net reclassification index). For example, imagine testing a strategy that will adjust the D-dimer threshold in a population of

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