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COVID-19 Vaccination with Special Reference to Cardiovascular Side Effects

Review Article

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Abstract

Irrational use of health resources hinders regular patient care. In retrospect, the resulting rise in mortality may be attributed to COVID-19, and the subsequent decline - to Anti-Epidemic measures including vaccinations. Mass vaccination with new vaccines carries potential risks. It can be reasonably assumed that effects of the Spike Protein (SP), observed in COVID-19 patients, would occur to a certain degree also after inoculation of vaccines containing SP or inducing its synthesis by cells. SP can injure endothelial cells, downregulate the Angiotensin Converting Enzyme 2 (ACE2) and bind to ACE2 receptors on platelets. The endothelial and platelet alteration would result in Thrombosis and Thrombocytopenia. Adenoviral vectors in vaccines may also contribute to blood clotting derangements, trigger immune responses, bind to platelets and induce their aggregation. Vaccines may contain various substances of human and viral origin depending on the manufacturing standards. Endothelial cells bearing SP or other antigens may be attacked by the immune system. Among potential consequences are Vasculitis, Perivascular Encephalitis and Myocarditis. Moreover, it has been shown in vitro that SP enters cell nuclei and impairs DNA repair. Reports on side effects of renowned vaccines do not imply an association with higher risks but indicate that they are generally better studied and objectively characterized.

Keywords: COVID-19, vaccine, cardiovascular, blood clotting, vasculitis

It has been argued that COVID-19 as a cause of death is overestimated, the role of co-morbidities being undervalued [1]. "Died with COVID-19" is not the same thing as "died of COVID-19". In terms of years of life lost, the current pandemic will presumably score similarly to the 1957 and 1968 influenza pandemics in view of the advanced mean age of COVID-19 fatalities [2]. Excessive anti-epidemic measures and lockdowns are harmful for the economy as well as for public health. The irrational use of health resources interferes with the regular patient care. In retrospect, the increase in mortality from different causes will probably be ascribed to COVID-19, and subsequent mortality decrease - to "successful" anti-epidemic measures including vaccinations. The topic is inflated and mixed with politics [3]. The effectiveness of travel restrictions, quarantines, and contact tracing is questionable because SARS-CoV-2 is already spreading worldwide like influenza did in the past. Historical data suggest no change in the speed of flu spread despite the proliferation of travel and human contacts. Travel restrictions can curb the international spread only if immediate and total [4]. Numerous mild and asymptomatic cases are inevitably missed.

Compulsory vaccination with new vaccines entails known and unknown risks. Although SARS-CoV-2 vaccinations are usually presented as safe, concerns are backed by increasing numbers of reports on moderate-to-severe side effects [5]. Recent studies have suggested that some COVID-19 vaccines induce thrombotic thrombocytopenia. Cases of facial palsy, Guillain-Barre syndrome and transverse myelitis have been documented [5, 6, 7]. Statistics are of questionable reliability; adverse effects may be missed, ascribed to other causes or obfuscated to comply with actual or presumed unofficial directives - a known phenomenon e.g. in the former Soviet Union [8, 9, 10, 11]. For want of reliable data, the role of theoretic argumentation increases. An area of overlap between COVID-19 and the action of vaccines is related to the spike protein (SP). Theoretically, the downregulation by SP of angiotensin-converting enzyme 2 (ACE2) can lead to endothelial damage and hence to cardiovascular derangements [12, 13]. It can be reasonably assumed that effects of SP observed in COVID-19 would occur to some degree also after administration of vaccines containing SP or inducing synthesis of SP by cells. The SARS-CoV-2 virus uses ACE2 as a receptor, which may lead to the ACE2 degradation and angiotensin-II-mediated tissue injury [14]. SP binds to ACE2 receptors on platelets and is presented to the immune system potentially triggering autoimmunity [14]. The endothelial damage together with platelet activation provokes coagulopathy culminating in vaccine-induced Thrombotic Thrombocytopenia [15].

Blood clotting derangements may be caused not only by SP but also by adenoviral vectors in vaccines [16]. The vectors elicit cellular and humoral immune responses, bind to circulating platelets, induce their activation and aggregation. Adenoviral-

Table 1: Side Effects after COVID-19 Vaccination: Preferential Associations with Vaccine Types.

Vaccine Types	Side Effects	Supposed Mechanisms	Reference
All approved vaccines especially adenoviral vector-based	Headache, IMT, Guillain-Barre syndrome, cerebral venous sinus thrombosis, transverse myelitis	Immune reactions against SP, activation of platelets and endothelial cells, hemorrhages, vasospasm	[5]
Vector (n=8); mRNA (n=13)	IMT, central and peripheral neuropathies, myositis, arthritis	Immune reactions, autoimmunity	[6]
Vector	Cerebral venous sinus thrombosis, encephalitis, transverse myelitis, Guillain-Barre syndrome	Immune reactions, molecular mimicry	[7]
mRNA	Bell's palsy, reactivation of herpes zoster		
Vector	IMT	Autoimmunity with autoantibodies to PF4	[12]
Vector or unspecified	IMT	Autoantibodies to PF4, activation of platelets	[15]
Vector	Coagulopathy	Interplay of SP and adenoviral vector	[16]
Vector	IMT, cerebral venous sinus thrombosis, deep vein thrombosis	Cross-reactivity of SP antibodies with PF4	[17]
Vector	IMT, cerebral and splanchnic vein thrombosis, pulmonary embolism	Interactions between the vaccine, platelets and PF4	[18]
Vector	Cerebral venous sinus thrombosis, thrombocytopenia	May be associated with platelet-activating antibodies against PF4	[19]
Vector 79 cases in 99.3 million doses; mRNA 20 in 110.6 (p<0.001)	Encephalitis	Autoimmunity, inflammatory cytokines and, T cell response	[22]
mRNA	Myocarditis, pericarditis	Unclear; in genetic predisposed, SP-coding mRNA may act as antigen	[23]
mRNA	Myocarditis	Not specified	[24]
mRNA	Myocarditis, pericarditis	Not specified	[26]
mRNA	Anaphylaxis 2.5-11.1 cases per million doses	largely in individuals with a history of allergy	[29,30]

Annotations: Brand names and manufacturers of vaccines are not mentioned; of importance for potential side effects are the vaccine types. IMT - immune-mediated thrombocytopenia; SP - spike protein; PF4 - Platelet Factor-4.

vectored vaccines may cause autoimmunity with autoantibodies to the Platelet Factor-4 (PF4). The chain of events includes microvascular damage, platelet activation with PF4 release, adenoviral vector dispersal and DNA-PF4 engagement leading to PF4-directed autoimmunity and vaccine-associated immune-thrombosis, rarely diagnosed at the present time [12]. There is evidence of synergism between SP and adenoviral vectors [16]. The above mechanisms provide an explanation for the association of adenoviral vector-based COVID-19 vaccines with cerebral events such as venous sinus thrombosis, ischemic and hemorrhagic stroke as well as splanchnic vein thrombosis, pulmonary embolism and disseminated intravascular coagulation (Table-1) [5,7,16,17]. Among cases with post-vicinal thrombi-embolic events predominated younger women known to be more susceptible to certain autoimmune conditions [12,18,19]. Moreover, SP binds to T cell receptors thus enhancing immune reactions [20,21]. Endothelial cells bearing SP or other viral antigens would be attacked by the host immune system. In the brain it may result in vasculitis and perivascular encephalitis. Neurological side effects of SARS-CoV-2 vaccinations are usually mild; however, some cases were severe, required hospitalization and admission to intensive care units [5]. Cases of encephalitis after the use of adenoviral vector vaccines have been documented; subclinical cases must be more frequent considering headache as a typical post-vicinal symptom. Of note, encephalitis developed significantly (p,<0.001) more frequently after the use of adenoviral vector than after mRNA vaccines: 79 cases in 99.3 million doses vs. 20 cases in 110.6 [22].

Furthermore, significantly more cases of myo- and pericarditis than expected have been recorded after COVID-19 vaccinations (Table-1). The supposed mechanism is immune response with inflammatory reactions to SP or SP-coding nucleic acids [7, 23]. In a population-based cohort study (vaccinated by mRNA-based vaccine vs. control ~885,000 people in each cohort), the vaccination was associated with an elevated risk of myocarditis: the risk ratio 3.24, 95% confidence interval (CI) 1.55 to 12.44 [24]. In a group of individuals aged 12-39 years, who had recently received a second dose of mRNA-based COVID-19 vaccine, the rate ratio for myocarditis was 10.8 compared to the general population (95% CI 3.2 to 49.0) [25]. Symptoms of myocarditis usually start 2-4 days post-vaccination being more frequent after the second dose of mRNA vaccines. Chest pain was present in all patients; 67% of them had fever. Arrhythmias or heart failure were encountered in more severe cases [26]. In addition, myalgia was observed in 21% of athletes following the first dose of an mRNA-based vaccine, rising to 37% following the second dose [27]. Finally, SP has been shown in vitro to penetrate the cell nucleus and inhibit DNA repair [28] which needs to be further investigated. It might be speculated about long-term consequences: increased incidence of malignancies, impaired immune defense, genetic defects in the offspring, etc.

Discussion and Conclusion:

The benefit-harm ratio is not always clear. Children, young adults and many other people can mount their own immune response to SARS-CoV2 undergoing acceptably low risk. There is an opinion that it is unethical to impede the access to natural immunity [31]. A recent systematic review demonstrated that natural immunity in COVID-recovered individuals is at least equivalent to the protection by complete vaccination of COVID-naïve populations, with the possibility of enhanced durability of protection from natural immunity [32]; see also [33]. In future, the countries implementing strictest measures might find themselves with a weaker protection by natural immunity. The vaccine quality e.g. undeclared components are of importance for the risk of side effects. In addition to adenoviral vectors, vaccines may contain various substances of human and viral origin, protein and other contaminants [12,16]. Officially tested preparations are not necessarily always the same as those administered to the broad public. Political pressures for rapid approval of vaccines can result in distribution of preparations of unstable quality [34]. A winner of "the race for a vaccine against SARS-CoV-2" [35] may end up in a mass vaccination of citizens with suboptimal vaccines. There have been few reports from Russia about blood clotting-related, cardiovascular and other adverse events after injections of Gam-COVID-Vac and other vaccines [8,9,36]. The number of unreported/undetected cases is unknown. It remains unclear, which agency is responsible for the registration of adverse events after COVID-19 vaccinations [37]. The documentation reliability of side effects remains questionable, as it has been the case with some other medical statistics [8, 9, 10, 11]. This letter discusses predominantly adenovirus vector and mRNA vaccines. Sizable numbers of reports on side effects of the most renowned vaccines do not imply an association with higher risks but indicate that they are better studied and more objectively characterized than those coming from less open societies with traditions of scientific misconduct [11,38]. Theoretically, all the above considerations may pertain to some extent different vaccine types: inactivated, recombinant protein, DNA and others. There are perspectives to eliminate some side effects by development of synthetic mono-antigenic vaccines [35].

In conclusion, effects of SP, observed in COVID-19 patients, can to some extent appear also after administration of vaccines containing SP or inducing its synthesis by the host. In addition, adverse events after vaccinations may be caused by adenoviral vectors, other components and contaminants in vaccines, which may depend on the manufacturing quality. Blood clotting disorders are of particular importance [39]. A promising research direction would be experiments in animal models [40] and human volunteers using various vaccines, comparing with controls the levels of blood clotting (e.g. D-dimer) and other relevant markers. It would be interesting to carry out a survey among individuals who first experienced COVID-19 infection and later the vaccination, with the question, when the symptoms were more severe. In the author's case (65 years old; the infection diagnosed in May 2020, Gam-COVID-Vac vaccination in November 2021), the symptoms were clearly more pronounced after the vaccination, the leading manifestation being headache. Other similar cases are known. However, results of such survey will be probably biased because some people would write in the questionnaire what they perceive as officially or unofficially prescribed [41]. Apparently, some scientific writers conform to the same principle: the rarity of reports on the side effects of COVID-19 vaccinations may be caused by local policies discouraging such reporting [42]. In conclusion, healthcare providers should be vigilant for cardiovascular and other side events after COVID-19 vaccinations; further research especially of long-term risks is needed [43].

Abbreviations:

SP: spike protein;

ACE2: angiotensin converting enzyme 2;

PF4: platelet factor-4; CI: confidence interval;

mRNA: messenger ribonucleic acid.

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References:

1. Jargin SV. COVID-19: economic damage is a health risk. Am J Prev Med Public Health. 2020; 6(3): 62-64.
2. Petersen E, Koopmans M, Go U, Hamer DH, Petrosillo N, Castelli F, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect Dis. 2020; 20(9): e238-444.
3. Jargin SV. Chapter 5. COVID-19: Economic Damage – Cui Bono? Advances in Health and Disease. Vol. 24. Nova Science Publishers, Inc.; 2020.
4. MacKellar L. Pandemic influenza: a review. Laxenburg: IIASA; 2007.
5. Finsterer J. Neurological side effects of SARS-CoV-2 vaccinations. Acta Neurol Scand. 2022 Jan;145(1):5-9. doi: 10.1111/ane.13550.
6. Kaulen LD, Doubrovinskaia S, Mooshage C, Jordan B, Purrucker J, Haubner C, et al. Neurological autoimmune diseases following vaccinations against SARS-CoV-2: a case series. Eur J Neurol. 2021; doi: 10.1111/ene.15147.
7. Garg RK, Paliwal VK. Spectrum of neurological complications following COVID-19 vaccination. Neurol Sci. 2021; doi: 10.1007/s10072-021-05662-9.
8. Independent Medical Association. Complications and following Covid-19 vaccination (updated 13 Nov. 2021).
9. Independent Medical Association. Comprehensive expert assessment "Analysis of immunoprophylactic drugs for the prevention of SARS-CoV-2." Moscow, 15 April 2021.
10. Jargin SV. Cardiovascular mortality in Russia: a comment. Cardiovasc Diagn Ther. 2017; 7(6): E13-14.

11. Jargin SV. Misconduct in medical research and practice. Series: Ethical Issues in the 21st Century. Nova Science Publishers, Inc.; 2020. doi: 10.52305/GIEZ3244.
12. McGonagle D, De Marco G, Bridgewood C. Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection. J Autoimmun. 2021; 121: 102662.
13. Lei Y, Zhang J, Schiavon CR, He M, Chen L, Shen H, et al. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. Circ Res. 2021; 128(9): 1323-1326.
14. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol. 2020; 13(1): 120.
15. Favaloro EJ. Laboratory testing for suspected COVID-19 vaccine-induced (immune) thrombotic thrombocytopenia. Int J Lab Hematol. 2021; 43(4): 559-570.
16. Kircheis R. Coagulopathies after vaccination against SARS-CoV-2 may be derived from a combined effect of SARS-CoV-2 spike protein and adenovirus vector-triggered signaling pathways. Int J Mol Sci. 2021; 22(19): 10791.
17. Watts I, Smith D, Mounter S, Baker EH, Hitchings AW, Gill D. A case series of vaccine-induced thrombotic thrombocytopenia in a London teaching hospital. Br J Clin Pharmacol. 2021; doi: 10.1111/bcp.15116.
18. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021; 384: 2092-2101.
19. Centers for Disease Control and Prevention, Health Alert Network. Emergency preparedness and response: cases of cerebral venous sinus thrombosis with thrombocytopenia after receipt of the Johnson & Johnson COVID-19 vaccine. April13, 2021.
20. Scaglioni V, Soriano ER. Are superantigens the cause of cytokine storm and viral sepsis in severe COVID-19? Observations and hypothesis. Scand J Immunol. 2020; 92: e12944.
21. Cheng MH, Zhang S, Porritt RA, Noval Rivas M, Paschold L, Willscher E, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. Proc Natl Acad Sci U S A. 2020; 117: 25254-25262.
22. Zuhorn F, Graf T, Klingebiel R, Schäbitz WR, Rogalewski A. Postvaccinal encephalitis after ChAdOx1 nCov-19. Ann Neurol. 2021; 90: 506-511.
23. Istampoulouoglou I, Dimitriou G, Späni S, Christ A, Zimmermanns B, Koechlin S, et al. Myocarditis and pericarditis in association with COVID-19 mRNA-vaccination: cases from a regional pharmacovigilance centre. Glob Cardiol Sci Pract. 2021;2021: e202118.
24. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med. 2021; 385: 1078-1090.
25. Shimabukuro T. COVID-19 vaccine safety update. Advisory Committee on Immunization Practices (ACIP). 23 June 2021.
26. Dorfman AL, Murthy VL. Web Exclusive. Annals for hospitalists inpatient notes - myocarditis after vaccination for SARS-CoV-2. Ann Intern Med. 2021; 174: HO2-O3.
27. Hull JH, Schwellnus MP, Pyne DB, Shah A. COVID-19 vaccination in athletes: ready, set, go…. Lancet Respir Med. 2021; 9: 455-456.
28. Jiang H, Mei YF. SARS-CoV-2 spike impairs DNA damage repair and inhibits V(D)J recombination in vitro. Viruses. 2021; 13: 2056.
29. Vitiello A, Ferrara F. Brief review of the mRNA vaccines COVID-19. Inflammopharmacology. 2021; 29: 645-649. doi: 10.1007/s10787-021-00811-0
30. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA. 2021; 325: 1101-1102. doi: 10.1001/jama.2021.
31. Hart EM. Is it ethical to impede access to natural immunity? The case of SARSCoV2. Re.: Mahase E. Covid-19: UK starts social distancing after new model points to 260 000 potential deaths. BMJ. 2020; 368: m1089.
32. Shenai MB, Rahme R, Noorchashm H. Equivalency of Protection From Natural Immunity in COVID-19 Recovered Versus Fully Vaccinated Persons: A Systematic Review and Pooled Analysis. Cureus. 2021; 13: e19102. doi: 10.7759/cureus.19102
33. Block J. Vaccinating people who have had covid-19: why doesn't natural immunity count in the US? BMJ. 2021; 374: n2101. doi: 10.1136/bmj.n2101.
34. Greer SL, King EJ, Massard da Fonseca E, Peralta-Santos A. Coronavirus politics: the comparative politics and policy of COVID-19. Ann-Arbor: University of Michigan Press; 2021.
35. Pascolo S. Synthetic Messenger RNA-Based Vaccines: from Scorn to Hype. Viruses. 2021; 13: 270. doi: 10.3390/v13020270.
36. Denisenko AS, Riess ME, Kropachev IG, Nikitina NN. First cases of coagulation disorders as complications after the Gam-COVID-Vac (Sputnik V) vaccine. Vestnik NovSU Medical Sciences. 2021; 3(124): 61-64. doi: 10.34680/2076-8052.2021.3(124).61-64.
37. Independent Medical Association. (2021) Registration of post-vaccinal complications and death cases due to vaccination against COVID-19. Moscow, 06 November 2021.
38. Jargin SV. Manipulation of statistics in medical research. Dermatopathology: Practical & Conceptual 2009; 15(1): 21.
39. Lundstrom K, Barh D, Uhal BD, Takayama K, Aljabali AAA, Abd El-Aziz TM, et al. COVID-19 Vaccines and thrombosis-roadblock or dead-end street? Biomolecules. 2021; 11(7): 1020.
40. Vandeputte J, Van Damme P, Neyts J, Audonnet JC, Baay M, Neels P. Animal experiments show impact of vaccination on reduction of SARS-CoV-2 virus circulation: A model for vaccine development? Biologicals. 2021; 73: 1-7. doi: 10.1016/j.biologicals.2021.08.001.
41. Jargin SV. Re.: The crooked timber of humanity. BMJ Rapid Response 2013.

42. Joob B, Wiwanitkit V. Acute myocarditis after coronavirus disease 2019 vaccination. Anatol J Cardiol. 2021; 25: 841-842.

43. Cereda A, Conca C, Barbieri L, Ferrante G, Tumminello G, Lucreziotti S, et al. Acute myocarditis after the second dose of SARS-CoV-2 vaccine: Serendipity or atypical causal relationship? Anatol J Cardiol. 2021; 25: 522-523. doi: 10.5152/AnatolJCardiol.2021.99.

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