Safety of COVID-19 mRNA vaccination in patients with history of acquired hemophilia A: a case series

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ABSTRACT

Coronavirus disease 2019 (COVID-19) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection called for a specific and massive vaccination campaign. Acquired hemophilia A (AHA) is a potential life-threatening coagulopathy. Hematological-targeted autoimmune conditions including immune thrombocytopenia, vaccine-induced thrombotic thrombocytopenia and AHA emerged during large-scale vaccination against SARS-CoV-2 and contributed to vaccination hesitation. The aim of the present study was to evaluate the putative recurrence of AHA after vaccination against SARS-CoV-2 with mRNA vaccines (BNT162b2 and mRNA-1273) in patients with relatively recent history of AHA. Thirteen patients (8 women and 5 men, mean age = 63.1±16.6 years) with AHA in the previous two-to-five years were enrolled in the study. Platelet count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and Factor VIII levels were evaluated 48 hours prior to each vaccine dose and 10 days post-vaccination. Clinical self-assessment and remote video visits were performed in the presence of even minor hemorrhagic signs. No major bleeding events were detected at any time-point, including evaluation at 30 days after the 3rd vaccine dose. No significant hemorrhagic changes were observed, in particular no thrombocytopenia and/or significant alterations in PTT and Factor VIII emerged across subjects. Patients with a previous history of AHA of various etiology do not seem to have an increased recurrence risk after a COVID-19 vaccination course of 3 doses with either mRNA vaccine. This finding supports this specific safety aspect in the face of the possible continuation of the vaccination campaign based on the trend of the COVID-19 pandemic.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a pandemic by the World Health Organization (WHO) on March the 11th, 2020.[1] Large-scale vaccination of at-risk groups and later of the general population is the most effective public health measure for the mitigation of the COVID-19 pandemic.[2]

Infection with SARS-CoV-2 has been strongly associated with immune-mediated reactions, including the development of autoimmune disorders.[3]

Emerging data also suggest a link between COVID-19 vaccination and the development of various hematological-targeted autoimmune conditions including immune thrombocytopenia (ITP).[4] Acquired hemophilia A (AHA) is a rare but potentially life-threatening autoimmune hemostatic disorder where autoantibodies against Factor VIII are present in the blood due to a failure in immune tolerance.[5]

AHA due to either SARS-CoV-2 infection or post-COVID-19 vaccination has been reported. In particular, the post-vaccine forms may range from asymptomatic to severe, requiring the treatment provided for AHA.[6-10] Fur-

thermore, relapses may characteristically occur in AHA and indeed, even after remission, whatever the cause, a prolonged follow-up is indicated to prevent the recurrence of serious clinical forms.[5]

In our Italian experience, vaccination hesitancy was not uncommon in various population groups and subjects with previous hematological and/or autoimmune and/or coagulative disorders were often referred to a specific consultation on this matter. In such a context, also the vaccine-induced thrombotic thrombocytopenia (VITT), an extremely rare condition that may develop after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of SARS-CoV-2 (ChAdOx1 nCov-19, AstraZeneca, Cambridge, UK)[11] has significantly contributed to the vaccination hesitancy.

Therefore, given the confusion generated above all by unscientific disclosure regarding general coagulation problems and vaccination risk, the aim of our study was to evaluate over time, after each dose of COVID-19 mRNA vaccines, patients previously affected by AHA of different origins regarding, in particular, the possible recurrence of the condition.

MATERIALS AND METHODS

Between June 2021 and January 2022, thirteen patients (8 females and 5 males, mean age = 63.1±16.6 years, range 34-81 years) with AHA in the previous two-to-four years and still in follow-up at our center were enrolled in the study. Each patient gave a specific further informed consent to participate in the study beyond that spontaneously provided for the vaccination course according to the Italian regulation for the vaccination campaign (2nd dose 21-28 days after the 1st and 3rd dose 4-5 months after the 2nd). The assessment schedule included platelet count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and Factor VIII levels in the 48 hours prior to each vaccine dose and 10 days post-vaccination. Each patient received homologue vaccine for the three doses (10 patients BNT162b2 and 3 mRNA-1273).

Clinical self-assessment was strongly recommended in presence of even minor hemorrhagic signs (International Society on Thrombosis and Haemostasias [ISTH] classification)[12] with immediate reporting to the center and consequent rapid clinical-laboratory evaluation. The patient was directly contacted and managed by the center in case of significant alterations in the laboratory tests. Fortnightly remote video visits were performed as a follow-up even in the absence of patient reports or alterations in blood chemistry tests. The last remote video visit of the study was performed 30 days after the 3rd dose of COVID-19 vaccine and considered as study closure in the absence of clinical bleeding or laboratory abnormalities.

Patient characteristics, including AHA history, are shown in Table 1. All patients had negative swab for SARS-CoV-2 throughout the study.

Table 1. Patient characteristics, including acquired hemophilia A (AHA) history.

	M/F	Age at diagnosis	PTT ratio at diagnosis	Hb at diagnosis (g/dl)	Factor VIII at diagnosis (% activity)	Inhibitor title at diagnosis (Bethesda Units)	Type of AHA (year of diagnosis)	Bleeding Site	Therapy	Relapse
1	F	59	3.5	6.6	0.9	25	R.A. (2017)	Cutaneous, Muscular	rVIIa, PDN, CY	0
2	F	67	3.5	7.7	0.3	35	LES (2019)	Cutaneous, Muscular	rVIIa, PDN, CY	0
3	F	31	2.4	6.3	0.4	20	post-pregnacy (2018)	Cutaneous, Muscular, Mocular	rVIIa, PDN, CY	0
4	M	74	2.5	6.2	0.6	35	Sepsis (2018)	Cutaneous,Muscular, Abdominal, Psoas	rVIIa, PDN, CY	1
5	M	84	2.4	11.4	1.6	20	Pemfigo (2019)	Cutaneous, Muscular	PDN	0
6	M	77	3.4	6.3	0.3	50	gastric cancer (2019)	Cutaneous, Muscular, Abdominal	rVIIa, PDN, CY	0
7	F	85	3.4	6.2	0.2	40	Sepsis (2020)	Cutaneous, Muscular, Joint	aPCC, PDN	0
8	F	75	3.2	6.2	0.1	40	Idiophatic (2017)	Cutaneous, Muscular, Abdominal, Psoas	aPCC, PDNCY	1
9	F	76	3.5	6.3	0.3	50	Idiophatic (2019)	Cutaneous, Muscular	rVIIa, PDN, CY	0
10	M	69	3.2	7.8	0.4	35	Idiophatic (2018)	Cutaneous, Muscular, Abdominal	rVIIa, PDN, CY	0
11	M	73	2.2	10.1	1.2	15	Idiophatic (2017)	Cutaneous	PDN	0
12	F	62	3.6	7.9	0.3	40	Idiophatic (2019)	Cutaneous, Muscular, Joint	aPCC, PDN, CY, Rituximab	0
13	F	60	2.2	9.1	2	10	Idiophatic (2019)	Cutaneous	PDN	0

M: male, F: female, PTT: partial thromboplastin time, H: hemoglobin, AHA: acquired hemophilia A, rVIIa: recombinant activated factor VII, aPCC: activated prothrombin complex, PDN: prednisone, CY: cyclofosfamide.

Hemoglobin level and platelet count were measured on a DXH 800 Beckman Coulter Counter (Brea, USA). Measurement of PT, PTT, fibrinogen (Clauss); and Factor VIII were performed on an ACL TOP 750 Analyzer and specific diagnostic kit according to manufacturer instructions (all by Instrumentation Laboratory Werfen, Barcelona, Spain). The possible presence of inhibitors, expressed in Bethesda Units, would have been evaluated in the presence of hemorrhagic alterations of the coagulation tests according to specific indications.[13]

Statistical analysis

Bleeding incidence, except eventually self-limiting bleeding at the injection site if less than 3 cm in diameter, was recorded and described in detail. Repeated measures analysis of variance (ANOVA) was used to assess putative differences in measurable variables across the study population at each time-point of the observation period. A p-value <0.05 was considered as statistically significant. All analyses were performed using the software SPSS v27 (IBM, Armonk, USA).

RESULTS AND DISCUSSION

No major bleeding events were detected during the study at any time-point, including evaluation at 30 days after the 3rd vaccine dose. Three patients showed local pain, which resolved after 48 hours (two after the 1st dose, one after the 2nd dose) while a fourth patient presented a local hematoma at the injection site, less than 3 cm in diameter, which developed four days after injection of the 2nd dose and resolved spontaneously in a few days without detectable thrombocytopenia and/or PTT and Factor VIII changes (patient number 7 in Table 2).

Table 2. Laboratory parameters in each patient throughout the study.

Patient and type of vaccine		Baseline	I dose +10 days	Pre-II dose	II dose +10 days	Pre-III dose +10 days	III dose
1 F 63y BNT162b2	INR	1.06	0.99	1.05	1.09	1.03	1.04
	PTT ratio	1.02	0.95	1.04	1	1.03	1.01
	VIII (%)	109	116	104	114	100	104
	Fibrinogen (mg/dl)	342	420*	351	402	360	395
	PLT (x10^3/µL)	303	316	299	305	296	293
	Hb (g/dl)	14.3	14.5	14.2	14.1	14.5	14.2
2 F 69y BNT162b2	INR	1.1	1.02	1.04	1.06	1.05	1
	PTT ratio	1.04	0.98	1.01	0.95	1.03	1
	VIII (%)	98	107	102	109	101	104
	Fibrinogen (mg/dl)	338	436*	367	438	350	399
	PLT (x10^3/µL)	234	218	229	216	228	210
	Hb (g/dl)	12.7	12.8	12.6	12.7	12.7	12.8
3 F 34y mRNA-1273	INR	0.99	0.98	1.03	1	0.98	1.04
	PTT ratio	1.01	0.94	1.1	1.02	1.06	0.96
	VIII (%)	121	130	117	120	112	116
	Fibrinogen (mg/dl)	295	368	324	370	316	348
	PLT (x10^3/µL)	267	258	276	280	257	260
	Hb (g/dl)	12.3	12.2	12.5	12.2	12.4	12.2
4 M 77y BNT162b2	INR	1.07	1	1.1	1	1.06	1.01
	PTT ratio	0.96	0.92	0.99	0.96	1.01	0.96
	VIII (%)	127	133	130	134	120	123
	Fibrinogen (mg/dl)	316	408*	352	390	328	356
	PLT (x10^3/µL)	219	208	232	220	229	218
	Hb (g/dl)	14.7	15	14.8	14.6	14.4	14.3
5 M 86y BNT162b2	INR	1.11	1.08	1.07	1.05	1.1	1.06
	PTT ratio	1.16	1.1	1.12	1.05	1.13	1.09
	VIII (%)	97	111	100	104	108	105
	Fibrinogen (mg/dl)	307	394*	328	352	326	344
	PLT (x10^3/µL)	249	230	233	228	226	230
	Hb (g/dl)	13.8	13.9	13.6	13.5	13.7	13.8
6 M 79y BNT162b2	INR	1.12	1.1	1.08	1.04	1.07	1.09
	PTT ratio	1.08	1.01	1.04	1.01	1.05	1.04
	VIII (%)	134	140	128	136	135	130
	Fibrinogen (mg/dl)	307	404*	338	374	346	350
	PLT (x10^3/µL)	224	209	216	211	208	205
	Hb (g/dl)	12.3	12.1	12.4	12.2	12.1	12.2

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No significant hemorrhagic alteration of the study parameters was observed, in particular no thrombocytopenia and/or significant changes in PTT and Factor VIII appeared across subjects (Table 2). Significant hyperfibrinogenemia ($p<0.05$) was found after the 1st dose but not after the 2nd or 3rd dose in the whole cohort (Table 3). No significant changes were observed in hemoglobin levels and platelet count (Table 2, Table 3). Furthermore, no thrombotic events occurred despite the transient increase in fibrinogen especially after the 1st dose of vaccine. In this setting, increased fibrinogen may be due to a temporary pro-inflammatory state induced by COVID-19 vaccine binding to pattern recognition receptors (PRR).[14]

Therefore, our data show that in patients with previous AHA of various origins (Table 1), immunization with mRNA vaccines is safe and does not induce clinical and/or laboratory relapses of AHA following 3 doses of vaccine.

This finding may be relevant, considering that the incidence of new post-vaccination AHA cases is already in its rarity difficult to understand whether induced by direct mechanism or by association of probability.[10]

Tab. 2. Continued from previous page.

Patient and type of vaccine		Baseline	I dose +10 days	Pre-II dose	II dose +10 days	Pre-III dose +10 days	III dose
7 F 88y BNT162b2	INR	1.16	1.2	1.14	1.13	1.15	1.17
	PTT ratio	1.13	1.1	1.07	1.09	1.06	1.04
	VIII (%)	106	102	111	114	115	118
	Fibrinogen (mg/dl)	348	436*	388	412	390	398
	PLT (x10^3/µL)	198	188	195	190	188	190
	Hb (g/dl)	13.8	13.7	13.8	13.6	13.5	13.3
8 F 79y BNT162b2	INR	1.06	0.99	1.06	1.01	1.05	1.01
	PTT ratio	1.02	0.93	0.97	0.94	0.99	1.06
	VIII (%)	116	122	120	123	121	113
	Fibrinogen (mg/dl)	295	364	340	348	332	329
	PLT (x10^3/µL)	277	260	268	279	260	268
	Hb (g/dl)	13.1	12.9	13.1	13	12.8	12.7
9 F 78y BNT162b2	INR	1.05	1.01	1.02	1.06	1.01	1.04
	PTT ratio	1.05	0.97	0.99	1.11	1.09	1.06
	VIII (%)	119	128	125	110	114	119
	Fibrinogen (mg/dl)	316	420*	402	390	364	348
	PLT (x10^3/µL)	211	220	233	220	218	210
	Hb (g/dl)	12.8	12.9	12.7	12.5	12.4	12.5
10 M 72y BNT162b2	INR	1.08	1.02	1.03	1.06	1.04	1.1
	PTT ratio	1.11	1.06	1.08	1.1	1.09	1.12
	VIII (%)	95	101	99	92	92	90
	Fibrinogen (mg/dl)	366	438	430	402	390	385
	PLT (x10^3/µL)	370	391	352	360	364	351
	Hb (g/dl)	15.8	16.2	16	15.8	16.1	15.9
11 M 77y BNT162b2	INR	1.03	1.01	1.06	1.03	1.08	0.99
	PTT ratio	0.96	0.91	0.94	0.93	0.96	0.92
	VIII (%)	129	137	130	135	131	132
	Fibrinogen (mg/dl)	337	427*	388	420	416	410
	PLT (x10^3/µL)	360	348	356	349	338	353
	Hb (g/dl)	16.1	16.3	15.8	15.9	15.9	16.2
12 F 64y mRNA-1273	INR	1.02	0.95	0.96	0.99	1.04	0.97
	PTT ratio	1.01	0.96	1.01	0.98	0.99	1.03
	VIII (%)	108	116	104	106	102	99
	Fibrinogen (mg/dl)	245	339*	301	278	280	265
	PLT (x10^3/µL)	199	190	188	184	190	189
	Hb (g/dl)	13.5	13.6	13.3	13.2	13.4	13.2
13 F 62y mRNA-1273	INR	1.06	1.01	1.06	1.02	1.08	1.01
	PTT ratio	1.1	1.02	1.06	1.1	1.09	1.11
	VIII (%)	95	99	96	93	93	91
	Fibrinogen (mg/dl)	307	412*	348	370	329	338
	PLT (x10^3/µL)	266	280	259	254	248	260
	Hb (g/dl)	12.9	12.8	12.5	12.9	12.6	12.8

*M, male; F, female; BNT162b2 and mRNA-1273, type of mRNA vaccine against SARS-CoV-2; INR, International Normalized Ratio; PTT, partial thromboplastin time; PLT, platelet count; Hb, Hemoglobin. II dose 21-28 days after I dose: III dose 4-5 months after II dose. Repeated measures analysis of variance (ANOVA): *p-value < 0.05.*

Table 3. Laboratory parameters in the whole cohort throughout the study.

	Baseline	I dose +10 days	Pre-II dose	II dose +10 days	Pre-III dose	III dose +10 days
INR	1.03±0.08	1.01±0.09	1.05±0.08	1.08±0.11	1.04±0.09	1.02±.011
PTT ratio	1.04±0.12	0.96±0.11	1.02±0.11	1.01±0.12	1.01±0.11	0.98±0.01
VIII (%)	103.2±18.4	111.6±21.2	102.2±19.3	109.9±20.1	99.8±18.6	106.8±20.1
Fibrinogen (mg/dl)	306.2±26.8	398.8±34.6*	334.3±25.1	369.8±28.3	328.1±21.2	350.6±23.4
PLT ($x10^3/\mu L$)	287±38	296±36	281±32	283±30	281±32	290±33
Hb (g/dl)	14.1±1.8	14.4±1.9	13.9±1.8	13.9±2.1	13.8±2.2	13.9±2.1

*INR, International Normalized Ratio; PTT, partial thromboplastin time; PLT, platelet count; Hb, Hemoglobin. II dose 21-28 days after I dose: III dose 4-5 months after II dose. Repeated measures analysis of variance (ANOVA): * p-value < 0.05.*

In fact, the specific evaluation of the cases found in the Swiss registry showed a possible mechanism linked to a subjective predisposition to the development of AHA and not to a direct mechanism induced by the vaccine in forming antibodies against factor VIII.[15]

Given the putative lethality of AHA,[16] any possible recurrence might contribute to the vaccination hesitancy due to fear of serious coagulation disorders as also emerged for VITT. In this context, our data suggest that already in the extreme rarity of new AHA cases possibly linked to anti-SARS-CoV-2 vaccination with mRNA vaccines,[10] even safety, in terms of no recurrence, in subjects with a previous pre-vaccination event is of relevant importance.

CONCLUSIONS

In conclusion, our data suggest that patients with a previous AHA of various etiology do not seem to have an increased risk of recurrence after a complete vaccination course (3 doses) with either mRNA BNT162b2 and mRNA-1273 vaccine. This finding supports specific safety in the face of the possible continuation of the vaccination campaign based on the trend of the COVID-19 pandemic.

REFERENCES

1. World Health Organization (WHO). 11 March 2020. Coronavirus disease (COVID-19) situation report – 51. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid- 19.pdf?sfvrsn=1ba62e57810.
2. Graham BS. Rapid COVID-19 vaccine development. Science 2020;368:945-6.
3. Ehrenfeld M, Tincani A, Andreoli L, et al. Covid-19 and autoimmunity. Autoimmun Rev 2020;19:102597.
4. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. Am J Hematol 2021;96:534-7.
5. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica 2020;105:1791-801.
6. Wang KY, Shah P, Roarke DT, Shakil SA. Severe acquired haemophilia associated with asymptomatic SARS- CoV-2 infection. BMJ Case Rep 2021;14:e242884.
7. Franchini M, Glingani C, De Donno G, et al. The first case of acquired hemophilia A associated with SARS- CoV-2 infection. Am J Hematol 2020;95:E197-8.
8. Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. J Thromb Haemost 2021;19:1515-8.
9. Farley S, Ousley R, Van Wagoner N, Bril F. Autoimmunity after Coronavirus Disease2019 (COVID-19) vaccine: a case of acquired hemophilia A. Thromb Haemost 2021;121:1674-6.
10. Cittone MG, Battegay R, Condoluci A, et al. The statistical risk of diagnosing coincidental acquired hemophilia A following anti-SARS-CoV-2 vaccination. J Thromb Haemost 2021;19:2360-2.
11. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021;384:2092-101.
12. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
13. Franchini M, Castaman G, Coppola A. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. Blood Transfus 2015;13:498-513.
14. Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases". Clin Immunol 2021;224:108665.
15. Hirsiger JR, Martinez M, Tsakiris DA, et al. Investigating potential mechanisms underlying FVIII inhibition in acquired hemophilia A associated with mRNA COVID-19 vaccines. J Thromb Haemost 2022;20:1015-8.
16. Puccetti L, Bacchiarri F, Calzoni P, et al. A fatal unsuspected case of acquired A hemophilia. Misleading role of therapy with acetylsalicylic acid? Int Emerg Med 2021;16:2339-40.