DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Eric Matthew Jurgens[1], Thomas Joseph Ketas[2], Zhen Zhao[3], Michael Joseph Satlin[1,3], Catherine Butkus Small[1], Ashley Sukhu[3], Erik Francomano[2], Per Johan Klasse[2], Arcania Garcia[1], Emeline Nguyenduy[1], Erica Bhavsar[1], Silvia Formenti[4], Richard Furman[1], John Philip Moore[2], John Paul Leonard[1], Peter Martin[1]

[1]*Department of Medicine, Weill Cornell Medicine-New York Presbyterian Hospital-Weill Cornell Medical College, New York, New York, USA*

[2]*Department of Microbiology and Immunology, Weill Cornell Medicine-New York Presbyterian Hospital-Weill Cornell Medical College, New York, New York, USA*

[3]*Department of Pathology and Laboratory Medicine, Weill Cornell Medicine-New York Presbyterian Hospital-Weill Cornell Medical College, New York, New York, USA*

[4]*Department of Radiation Oncology, Weill Cornell Medicine-New York Presbyterian Hospital-Weill Cornell Medical College, New York, New York, USA*

Correspondence

Peter Martin, Department of Medicine, Weill Cornell Medicine-New York Presbyterian Hospital-Weill Cornell Medical College, 525 East 68th Street, Box 403, New York, NY 10021, USA.

Email: pem9019@med.cornell.edu

ORCID

Eric Matthew Jurgens https://orcid.org/0000-0001-8280-2581

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SUPPORTING INFORMATION

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SARS-CoV-2 vaccination in patients with autoimmune cytopenias: The experience of a reference center

To the Editor:

Both SARS-CoV-2 infection and vaccination have raised concern in immune mediated diseases, including autoimmune cytopenias (AIC, ie, autoimmune hemolytic anemia, AIHA; immune thrombocytopenia, ITP; autoimmune neutropenia, AIN; aplastic anemia, AA; and their combination, termed Evans syndrome, ES). Autoimmune cytopenias are highly heterogeneous conditions with variable severity and a clinical course. They are marked by several relapses often triggered by immune-activating events (infections, traumas, surgery) including vaccines.[1,2] Some reports of ITP and AIHA exacerbations after SARS-CoV-2 vaccines (mRNA vaccines Pfizer-Biontech and Moderna, and Adenovirus based vaccine AstraZeneca) have been described,[3–16] but evidence-based indications for their management are lacking.

Here we prospectively studied a large series of 108 patients with AIC (56 AIHA, 41 warm type, wAIHA and 15 cold, cAIHA, 38 ITP, 7 AIN, and 7 AA) prospectively followed at a reference hematologic center in Milan, Italy, who underwent SARS-CoV-2 vaccination from March, 24 until the end of June 2021. The study was conducted in accordance with Helsinki Declaration and each participant had given a written informed consent for data collection. Patients (median age 62 years, range 25–89 years, female/male ratio 1.7) were monitored with whole blood counts (and LDH levels in AIHA) the week before and the week after each vaccination dose. Importantly, ongoing AIC therapy (38% of cases, including steroids, cyclosporine, eltrombopag, and complement inhibitor sutimlimab) were kept stable within the 2 weeks before the first dose.

Table 1 summarizes hematologic trends and side effects observed after each dose in patients with ITP, AIHA, AIN, and AA. Seven patients had ES, of whom four ITP plus AIHA and one ITP plus neutropenia. Patients mainly received Pfizer-BioNtech vaccine ($N = 90$), followed by Moderna ($N = 16$), and Astra-Zeneca ($N = 2$). Hematological parameters showed a wide distribution both at baseline and after vaccines. To better investigate intra-patient variation we calculated the delta% change of Hb and LDH for AIHA and of PLT in ITP patients, after the first and the second vaccine dose (supporting information Figure S1).

Regarding AIHA, four elderly patients experienced a clinically significant Hb reduction requiring treatment adjustment. In detail, patient number one was a 79-year-old female with warm type AIHA (wAIHA) who experienced an Hb decrease from 10.4 to 9.1 g/dL (LDH 1.2 to

TABLE 1 Hematologic values trends after the two doses of anti-SarsCoV-2 vaccine in patients with immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA), autoimmune neutropenia (AIN), and aplastic anemia (AA)

AIHA, *N* = 56[a]; 47 Pfizer, 8 Moderna, 1 AstraZeneca	**Baseline**	**After first dose**	**After second dose**
Hb g/dL, median (range)	12.8 (8.4;17.6)	12.8 (7.2;17.8)	12.7 (7.4;17.2)
Delta% change, median (range)	-	0 (−35;19)	0 (−41;20)
LDH U/L, median (range)	227 (129;800)	224 (129;840)	221 (144;574)
Delta% change, median (range)	-	−0.4 (−43;66)	−4 (−46;97)
Adverse events, *N*(%)	-	7 (12.5)	8 (14)
Fever, *N*(%)	-	3 (5)	3 (5)
Pain, *N*(%)	-	3 (5)	4 (7)
Other, *N*(%)	-	1 (2), vomit	1 (2), arthralgia
ITP, *N* = 38; 30 Pfizer, 7 Moderna, 1 AstraZeneca	**Baseline**	**After first dose**	**After second dose**
PLT $\times 10^9$/L, median (range)	118 (5–512)	116 (7–554)	127 (4;500)
Delta% change, median (range)	-	4.4 (−80; 158)	4.7 (−90;388)
Adverse events, *N*(%)	-	7 (18)	15 (39)
Fever, *N*(%)	-	1 (3)	3 (8)
Pain, *N*(%)	-	5 (13)	9 (24)
Other, *N*(%)	-	1 (3), headache	3 (8), headache, 2 arthralgia
AIN, *N* = 7; 7 Pfizer	**Baseline**	**After first dose**	**After second dose**
ANC $\times 10^9$/L, median (range)	0.4 (0.27;1.3)	0.7 (0.19;1.02)	0.4 (0.25;0.9)
Delta% change, median (range)	-	−20 (−29; −12)	−20 (−28; −7)
Adverse events, *N*(%)	-	1 (14)	1 (14)
Fever, *N*(%)	-	0	1 (14)
Pain, *N*(%)	-	0	0
Other, *N*(%)	-	0	0
AA, *N* = 7; 6 Pfizer, 1 Moderna	**Baseline**	**After first dose**	**After second dose**
PLT $\times 10^9$/L, median (range)	69 (11;153)	75 (10;132)	76 (5;138)
Hb g/dL, median (range)	12 (7.7;13.6)	12.2 (7.6;14.1)	12.2 (7.3;12.3)
ANC $\times 10^9$/L, median (range)	1.58 (0.8;2.4)	1.3 (0.9;3.4)	1.6 (0.9;3.2)
Adverse events, *N*(%)	-	1 (14)	2 (28)
Fever, *N*(%)	-	0	1 (14)
Pain, *N*(%)	-	1 (14)	1 (14)
Other, *N*(%)	-	0	0

[a]41 warm type, wAIHA, 30 with direct anti-globulin test (DAT) positive for IgG, and 11 for IgG + C, and 15 cold, cAIHA with DAT positive for C.

1.7 × ULN) after the first dose of Pfizer vaccine; she required a slight increase of steroid dose (to 5 mg day prednisone) and remained stable after the second dose. Patient number two was a 73-year-old male with wAIHA, off-therapy; he had a frank relapse 1 week after the first dose of Moderna vaccine (Hb 13.9 to 9.1 g/dL, LDH 1.1 to 1.6 × ULN), requiring prednisone 0.5 mg/kg day with prompt response. The patient refused to receive the second dose. Patient number three was a 77-year-old male suffering from cold type AIHA (cAIHA), who had an Hb drop from 9.3 to 7.2 g/dL 1 week after after the first dose of Moderna vaccine, requiring steroids, rituximab, and recombinant erythropoietin. The second dose was administered without adverse events. Patient number four was a 73-year-old man suffering from multi-relapsing wAIHA on low-dose steroids, who experienced a severe relapse (Hb 14 to 7.4 g/dL, LDH 1.1 to 2.3 × ULN) 5 days after the second dose of Pfizer vaccine. He required high dose intravenous steroids and hemolysis improved in about 1 week.

Concerning ITP, 4 patients experienced a clinically significant platelets (PLT) reduction. Patient number five and number six were two elderly male subjects (81-year-old and 78-year-old) on low-dose eltrombopag who experienced a severe relapse (PLT 21 and 29 × 10^9/L, 80% and 90% decrease from pre-vaccine, respectively) with mucosal bleeding, 9 days after the first and 7 days after the second dose of Pfizer vaccine, respectively. Patient number six had a concomitant reactivation of his chronic bronchitis. Both were rescued by

increasing eltrombopag dose and with the addition of prednisone 1 mg/kg day. Patient number five deferred the second dose due to hip fracture requiring surgery. Patient number 7 was a 63-year-old man on low-dose steroids plus eltrombopag and rivaroxaban for a previous pulmonary embolism. He experienced a PLT drop to 40×10^9/L (40% reduction) 10 days after the first dose of Pfizer vaccine and required eltrombopag and steroid increase. The second dose was administered without adverse events. Patient number eight was a 70-year-old woman on steroid therapy for persistent ITP. Her PLT decreased to 20×10^9/L (70% reduction) after the second dose of Pfizer vaccine and the patient was rescued with intravenous immunoglobulin and steroids increase.

Patients with AIN and AA had no significant changes in their hematologic values (one AIN had a neutrophil decrease by 30% but was consistent with previous oscillations) and required no treatment changes. Finally, the following non-hematologic adverse events were observed (all grade I): fever (11%), pain at the injection site (21%), arthralgia (3%), headache (2%), and vomiting (1%), without significant differences between the first and the second dose.

Our data show that SARS-CoV-2 vaccination may be associated with a clinically significant decrease of hematologic values in 7.4% of AIHA and ITP cases that were rapidly rescued by treatment adaptation. Mild decrease was observed in about 10% of AIHA and 20% of ITP, requiring no treatment change. Notably, AIC recrudescences were not predictable, since they occurred in both patients on active treatment and off therapy, independently from AIHA type, after either the first or the second dose, and regardless vaccine type. Regarding available literature, three AIHA patients developing/reactivating AIHA after SARS-CoV-2 vaccine have been reported so far: one cAIHA exacerbation after the first and second dose of Pfizer vaccine[16] and two severe wAIHAs developing after the first and the second dose of Pfizer vaccine. All cases have been successfully managed with steroids and transfusion support.[14,15] More data are available for ITP, including 21 patients (15 Pfizer, four Moderna, two Johnson&Johnson) from nine case reports/series.[3–11] Most patients rapidly improved with steroids or adjustment of ongoing treatment, including TPO-RA that may reduce the need of immunosuppression. The latter may abate the immune response to vaccines,[17] although further studies are needed to assess vaccination efficacy under immunosuppressive treatment. Additionally, two large epidemiological studies in Scotland and USA[12,13] estimated an incidence of ITP of 0.8 million doses with Pfizer BioNTech, and of 1.71 million doses of AstraZeneca. This incidence was inferior to that expected for primary ITP in the general population (3.3 cases per 100 000 adults per year).[12,13]

In conclusion, our study along with the evidence above, underlines that post-vaccine AIC flares are manageable and that the benefits of vaccination greatly outweigh the risks. The hematologic monitoring adopted in our survey (1 week before, 1 week after the first and the second dose) appears appropriate to promptly intercept and manage AIC reactivations. We also avoided modifications of the ongoing AIC treatment in the 2–3 weeks preceding vaccine to prevent AIC exacerbations unrelated to vaccination. One of the main concerns is whether to administer the second dose after an AIC flare following the first one. Apart from patients' refusal, the second dose should be carefully weighed, and may be feasible upon close monitoring of blood counts and therapy adjustment. All these measures will ensure a safe vaccination campaign in this patient population.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

B.F., J.A.G., N.C., and W.B. designed the study, collected data and wrote the paper.

DATA AVAILABILITY STATEMENT

Further data will be available upon request to the corresponding author.

Bruno Fattizzo[1,2], Juri A. Giannotta[1], Nicola Cecchi[1,2], Wilma Barcellini[1]

[1]*Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

[2]*Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy*

Correspondence

Bruno Fattizzo, Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, via F. Sforza 35, 20122, Milan, Italy.

Email: bruno.fattizzo@unimi.it

ORCID

Bruno Fattizzo https://orcid.org/0000-0003-0857-8379

Wilma Barcellini https://orcid.org/0000-0003-1428-9944

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The International Hemoglobinopathy Research Network (INHERENT): An international initiative to study the role of genetic modifiers in hemoglobinopathies

To the Editor:

Hemoglobinopathies, including sickle cell disease (SCD) and thalassemia syndromes, represent the commonest monogenic diseases in the world. Although their pathogenesis is established, the diverse clinical manifestations and the varying degree of severity are less understood and are thought to be governed, in part, by genetic modifiers. Previous studies have demonstrated the role of genetic modifiers in different hemoglobinopathy phenotypes, with co-inheritance of α-thalassemia and higher levels of fetal hemoglobin (HbF) being the best characterized disease modifiers. Several genome-wide analyses have identified three major quantitative trait loci modulating HbF levels: a promoter variant on *HBG2* (XmnI-rs7482144), the *HBS1L-MYB* intergenic region and *BCL11A*, which together explain up to 50% of the genetic variation affecting HbF.[1,2] More recently, studies have identified genetic modifiers associated with laboratory and clinical markers of disease complications.[3,4] However, few of these modifiers have reached a level of clinical utility.

Importantly, most association studies in SCD have been restricted to patients that have not received disease-modifying therapies. Given that the influence of genetic disease modifiers may change with treatment, identification of genetic modifiers requires high-quality clinical, laboratory and treatment data to allow accurate genotype/phenotype correlation. Furthermore, with the emergence of novel targeted therapies for hemoglobinopathies, such as gene therapy, genetic modifiers can facilitate patient stratification and, also, influence the response to these treatments.

Currently, the ITHANET portal[5] manually curates around 800 disease-modifying variants in over 420 genomic locations. However, most of these variants have not been validated with confirmatory or large-scale studies, and across diverse ethnic populations. In addition, data from different studies are not frequently reproducible and their possible effect size remains unknown.[6] Most importantly, with most studies having a sample size of less than 2000 patients, it is not possible to identify genetic modifiers with high confidence. As a result, the translation of these results into clinical practice has been limited. There are currently very few established polygenic risk scores related to disease complications, severity, or response to treatment, that can be used as an evidence base to stratify disease and offer patient specific treatment regimens in hemoglobinopathy patients.[7]

A validated standard for data collection and phenotypic definitions is crucial for the accurate comparison and pooling of data. The recently developed Sickle Cell Disease Ontology[8] represents a positive step towards disease-specific standardization that can facilitate integration of datasets in the field. In parallel, other ongoing initiatives, such as patient registries by RADeep and SPARCO, are working on standardization of clinical data collection for hemoglobinopathies using well-established international standards, such as the Human Phenotype Ontology.[9] Despite these efforts, a common understanding and discussion among different initiatives is necessary to allow integration of data for large-scale clinical and genomic studies. Furthermore, there is a limited amount of high-throughput or genome-wide data available for further research, despite several genetic studies in the field. A large, international disease-specific data repository, compliant with the FAIR data principles,[10] would revolutionize research in the field of hemoglobinopathies towards evidence-based approaches that utilize data science and artificial intelligence.