SARS-CoV-2 vaccination in 361 non-transplanted patients with aplastic anemia and/or paroxysmal nocturnal hemoglobinuria

SARS-CoV-2, first recognized in December 2019 in Wuhan, China, was responsible for the largest global pandemic in recent history. Patients with hematological disease, including aplastic anemia (AA) and/or paroxysmal nocturnal hemoglobinuria (PNH) were considered potentially vulnerable, being advised to take precautions such as home isolation to reduce infection risk.[1] There are also often concerns about vaccination in this patient group, due to case reports of vaccination e.g., flu vaccination causing AA *de novo*, or disease relapse.[2-4]

In addition, vaccination of patients with PNH, a highly hemolytic and thrombotic condition usually treated with complement inhibition, may cause potential issues of overwhelming hemolysis or thrombotic complications.[5]

SARS-CoV-2 posed a potential life-threatening health risk to patients with AA and/or PNH, thus consensus advice was to proceed with vaccination in this cohort.[6]

The Severe Aplastic Anemia Working Party and Infectious Diseases Working Party of European Society for Blood and Marrow Transplantation (EBMT) undertook an observational study of SARS-CoV-2 vaccination outcome to guide clinical practice which we report here, with the largest cohort of patients to date with aplastic anemia and/or PNH receiving SARS-Cov-2 vaccination. Disease-related outcome, vaccine complications including overall survival, comparison between those on immunosuppression and those not on immunosuppression and PNH-related complications were considered.

All EBMT centers were invited to participate in this prospective observational study. Non-transplanted adult patients with AA and/or PNH invited to receive a SARS-CoV-2 vaccine were included. Patients consented to share their data with EBMT.

Data was collected from January 2021 to September 2022 and included disease status, vaccinations received, vaccination side effects, blood parameters 3, 6 and 12 months post-vaccination with disease status at these time points, and SARS-CoV-2 infection occurrence.

Four hundred and fifty-seven patients were included from 20 centers; 361 patients received at least one vaccination and were included for detailed analysis. See Table 1 for baseline characteristics.

One hundred and thirty-nine patients were on active immunosuppression at first vaccination, and 120 patients on complement inhibitors with the majority on C5 inhibition (90.8%) (see Table 1).

Treatment received within 1 year of first vaccination included PNH treatment only (99/361), AA treatment only (149/361), PNH and AA treatment concurrently (30/361) and no treatment for either disorder (83/361).

Three hundred and forty-seven patients had at least two vaccinations, with a mean of 45.51 days between vaccine one and vaccine two. Side effects within 5 days post vaccination were experienced by 117 of 361 patients (32.4%), most commonly pyrexia, myalgia, headache and/or fatigue or a combination of the four symptoms (101/117). Two patients had pancytopenia, which recovered and was not considered AA relapse with disease status stable at 6 and 12 months with partial remission (1/2) and complete re-

Table 1. Baseline characteristics.

Baseline characteristic	Patients within study N=361
Median age at vaccination in years (IQR)	55.2 (38.1-69.2)
Sex: female, N (%)	206 (57)
PNH only (no AA), N (%)	52 (14)
AA disease status at time of vaccination, N (%)	N=309
Complete remission	102 (33)
Partial remission	158 (51.1)
Relapsed/refractory/progression	19 (6.1)
Stable disease	22 (7.1)
Not applicable	8 (2.6)
Treatment status at time of vaccination, N (%)	N=361
AA on IST	117 (32.4)
AA on non-IST treatment	27 (7.4)
No treatment for AA or PNH	97 (26.8)
PNH and AA on treatment for both*	24 (6.6)
C5 inhibitor	21 (87.5)
Factor B inhibitor	2 (8.3)
Anticoagulation	1 (4.2)
PNH on complement inhibitor	96 (26.5)
C5 inhibitor	88 (91.7)
C3 inhibitor	3 (3.1)
Factor B inhibitor	5 (5.2)
Number of vaccines administered, N (%)	
1	14 (3.9)
2	110 (30.5)
3	225 (62.3)
>3	12 (3.3)
Mean time in days between vaccines (IQR)	76 (30-186)

*Twenty-two patients were on immunosuppressive therapy (IST) treatment for aplastic anemia (AA) and complement inhibition. IQR: interquartile range; PNH: paroxysmal nocturnal hemoglobinuria.

mission (1/2). For patients with PNH, PNH-related side effects were experienced by 19 (14.7%), including four complement inhibitor-treated patients experiencing a breakthrough hemolysis event. One patient on complement inhibition and calcineurin inhibitor immunosuppression who received ChAdOx1-S vaccine experienced a pulmonary embolism 16 days post vaccination. Platelet count at vaccination was 161x10^9/L, 146x10^9/L at presentation of thrombosis, and 100x10^9/L 3 days post thrombosis. D dimer were not taken at the time of thrombosis. This was considered vaccine-induced pulmonary embolism and no further SARS-CoV-2 vaccinations were undertaken.
Disease relapse: nine patients experienced AA relapse with six patients undergoing a concomitant reduction in immunosuppression, one with unknown circumstances, and one due to myelodysplastic syndrome transformation. One relapse considered possibly vaccine-related with platelet count reduction from 72x10^9/L to 12x10^9/L 1 week post vaccination. This patient responded to oxymethalone dose increase within 4 weeks, although this could be considered vaccine induced thrombocytopenia.
Twelve-month overall survival was 98% (95% confidence interval [CI]: 97-100), with no difference in outcome of those on active immunosuppression compared to patients not on active immunosuppression with 12-month survival of 99% in patients not on immunosuppression and 98% in patients taking immunosuppression at first vaccination; *P*=0.5.
There were six deaths within 1 year after the first vaccination, none related to SARS-CoV-2 vaccination or infection (3 due to aplastic anemia relapse, progression or refractory disease, 1 due to bacterial infection, 1 due to diffuse large B-cell lymphoma and 1 due to brain hemorrhage).
Blood counts remained stable up to 1 year post vaccination with minimal change (see Table 2).
Cumulative incidence of SARS-CoV-2 12 months post vaccination was 16% (95% CI: 12-20) (53/361), with 76.9% of patients (40/53) experiencing symptoms which were generally mild. No patients required oxygen or had pulmonary findings on chest X-ray (39/40, 1 missing data point) and no patients died from Covid-19.
We report the largest vaccine study to date in non-transplant patients with AA and/or PNH. The consensus guideline for patients with AA and/or PNH recommended to proceed with vaccination, due to significant concerns about disease-related complications associated with potential SARS-CoV-2 infection.6
There are case reports of *de novo* AA in patients testing positive for SARS-CoV-2,[7] and of SARS-CoV-2 causing reduction in blood counts or new transfusion requirements in patients with known AA, although insufficient to cause relapse. PNH related complications post infection were also reported with hemolysis.[1,8,9]
Case reports of patients developing *de novo* or relapsing AA caused by different vaccines e.g., flu vaccine, hepatitis vaccines, has led to caution in vaccinating this cohort of patients. Case reports are also available following SARS-CoV-2 vaccination, irrespective of vaccine used, with patients presenting with *de novo* AA several weeks after vaccination.[10,11]
We did not identify any newly diagnosed patients with AA within this study, as patients included were those already diagnosed. Country-wide vaccine observational data are required to assess this without reporting bias, such as Sweden's CoVacSafe-SE study, although registry level 'big' data have advantages and disadvantages.[12]
Röth *et al.* report four patients who had AA relapse at median 77 days post vaccination, with mainly platelet counts affected. All four patients were on calcineurin inhibitors, and all needed treatment for relapsed AA.[13] Within our cohort, nine patients relapsed within 12 months post-vaccination, the majority associated with immunosuppression withdrawal and thus cannot be attributed to vaccination.
Our cohort had 38.5% of patients on active immunosuppression at time of vaccination, with no outcome difference compared to patients not on immunosuppression. Rajput *et al.* report similar outcomes, with 30% (15/50) of patients on immunosuppression at vaccination, and 94% of patients

Table 2. Blood results at 3, 6 and 12 months post vaccination.

	Baseline, N=361		3 Months, N=361		6 Months, N=361		12 Months, N=361	
	Median (IQR)	Missing N (%)	Median (IQR)	Missing N (%)	Median (IQR)	Missing N (%)	Median (IQR)	Missing N (%)
Hb, g/L	116.5 (98-129.8)	3 (0.8)	114 (96-128)	38 (10)	115.5 (97-130)	25 (6.9)	119 (101-132)	56 (15.5)
WBC, x10^9/L	4 (2.9-5.2)	8 (2.2)	4 (3-5)	42 (11.6)	3.9 (3-5.1)	30 (8.3)	4.1 (3.2-5)	60 (16.6)
Neutrophils, x10^9/L	2 (1.4-2.9)	5 (1.4)	2 (1.4-2.7)	44 (12.2)	2 (1.4-2.9)	30 (8.3)	2 (1.5-2.8)	61 (16.9)
Platelets, x10^9/L	123 (74-171)	4 (1.1)	122.5 (73.8-169.2)	41 (11.4)	122 (79-172)	27 (7.5)	128 (86-174.8)	55 (15.2)

IQR: interquartile range; Hb: hemoglobin; WBC: white blood count.

having no disease status change post vaccination. Six percent (3/50) patients relapsed post vaccination, although similar to our cohort, two of the three patients had discontinued AA treatment 2 and 30 days prior to vaccination, raising the question of whether this was vaccine-related relapse or due to withdrawal of immunosuppresion.[14] Potential considerations would be to suspend immunosuppression withdrawal during a vaccination program.

PNH-related complications in those on complement inhibitors in our cohort were moderate, similar reports conclude up to a 14% breakthrough hemolysis risk in patients undergoing vaccination.[8,15] This is manageable, but requires physician vigilance and patient education. Advising patients with PNH to receive vaccines within the first half of complement inhibitor treatment schedule is preferable to reduce risks of breakthrough hemolysis e.g., within 1 week post eculizumab, within 4 weeks post ravulizumab.

There was a high proportion of patients in this cohort experiencing SARS-CoV-2 infection following vaccination, the majority of whom were symptomatic. Reassuringly, there were no deaths from COVID-19 in this large 361 patient cohort, supporting vaccination for patients with AA and/or PNH.

There were some study limitations: analyzing vaccine response in patients with AA and/or PNH was not done, as not all participants had access to antibody testing. However, several groups have undertaken vaccine response studies in this patient cohort, demonstrating similar antibody response to healthy volunteers after the second SARS-CoV-2 vaccine irrespective of immunosuppression use.[8,14] In the current prospective study, some data points were missing, and a cohort of non-vaccinated patients would have been useful for comparison.

In conclusion, we report the largest study to date assessing non-transplant patients with AA and/or PNH receiving vaccination for SARS-CoV-2 infection. Vaccination was well tolerated, with low complication rates and low relapse risk of AA. There was no difference in outcome of those on active immunosuppression compared to patients who were not on active immunosuppression and no deaths from SARS-CoV-2 infection were observed post vaccination.

This cohort would suggest clinicians and patients should be reassured regarding vaccination for SARS-CoV-2 in patients with AA and/or PNH.

Authors

Morag Griffin,[1] Dirk-Jan Eikema,[2] Inge Verheggen,[3] Alexander Kulagin,[4] Jennifer M-L. Tjon,[5] Bruno Fattizzo,[6] Wendy Ingram,[7] Uzma Zaidi,[8] Lana Desnica,[9] Sabrina Giammarco,[10] Joanna Drozd-Sokolowska,[11] Blanca Xicoy,[12] Andrea Patriarca,[13] Michael Loschi,[14] Anna Szmigielska-Kaplon,[15] Fabian Beier,[16] Alessandro Cignetti,[17] Beatrice Drexler,[18] Eleni Gavriilaki,[19] Francesco Lanza,[20] Corentin Orvain,[21] Antonio Maria Risitano,[22] Rafael de la Camara[23] and Régis Peffault de Latour[24]

[1]Department of Hematology, St James University Hospitals, Leeds, UK; [2]EBMT Statistical Unit, Leiden, the Netherlands; [3]EBMT Leiden Study Unit, Leiden, the Netherlands; [4]RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation; [5]Department of Hematology, Leiden University Medical Center, Leiden, the Netherlands; [6]SC Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [7]Department of Hematology, University Hospital of Wales, Cardiff, UK; [8]National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan; [9]Department of Hematology, University Hospital Center Zagreb, Zagreb, Croatia; [10]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [11]Department of Hematology, Medical University of Warsaw, Warsaw, Poland; [12]Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol; Josep Carreras Leukemia Research Institute, Barcelona, Spain; [13]Azienda Ospedaliero-Universitaria Maggiore della Carità and Translational Medicine Department, University of Eastern Piedmont, Novara, Italy; [14]Department of Hematology, Nice University Hospital, Cote d'Azur University, Nice, France; [15]Department of Hematology, Copernicus Hospital, Lodz, Poland; [16]Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University, Aachen, Germany; [17]University Division of Hematology, A.O. Ordine Mauriziano, Torino, Italy; [18]Department of Hematology, University Hospital Basel, Basel, Switzerland; [19]Department of Hematology, George Papanicolaou General Hospital, Thessaloniki, Greece; [20]Metropolitan Transplant Network, Hospital Santa Maria delle Croci, Ravenna, Italy; [21]Centre Hospitalier Universitaire d'Angers, Angers, France; [22]Department of Hematology, AORN Moscati, Avellino, Italy; [23]Department of Hematology, Hospital de la Princesa, Madrid, Spain and [24]Clinical Investigations Center, Hôpital Saint-Louis, Paris, France

Correspondence:
M GRIFFIN - m.griffin@nhs.net

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Disclosures

MG is on the advisory board and/or has received speaker fees from Alexion AstraZeneca rare disease, Sobi, Biocryst, Novartis and Amgen; consults for Regeneron and Biocryst. BF consults for and has received speaker bureau fees from Alexion AstraZeneca rare disease, Amgen, Annexon, Novartis, Janssen and Sobi. WI is on the advisory board of

Celgene, Novartis, Gilead, Alexion and Sobi; has received honoraria from Takeda and Medac. JS has received honoraria and/or speakers fees from AstraZeneca, Swixx, AbbVie, Janssen, Sanofi and Servie; consults for AstraZeneca and Roche. AR has received honoraria/speakers fees from Alexion, Pfizer, Apellis, Sobi and Novartis; is on the advisory board of Alexion, Roche, Sobi, Achillion, Apellis and Novartis; has received research funding from Alnylam: RdL has received lecture and research grants from Alexion, AstraZeneca, Novartis and Pfizer. All other authors have no conflicts of interest to disclose.

Contributions

MG, AR, RD, RC devised the study, collected data, reviewed the data, wrote and edited the manuscript. DE analyzed the data, reviewed and edited the manuscript. IV collated the data, reviewed and edited the manuscript. All other authors collected the data, reviewed and edited the manuscript

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Data-sharing statement

Datasets are maintained in the EBMT electronic database; data requests will be considered on request from the corresponding author and the Severe Aplastic Anaemia Working Party of EBMT.

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