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

by Morag Griffin, Dirk-Jan Eikema, Inge Verheggen, Alexander Kulagin, Jennifer M-L Tjon, Bruno Fattizzo, Wendy Ingram, Uzma Zaidi, Lana Desnica, Sabrina Giammarco, Joanna Drozd-Sokolowska, Blanca Xicoy, Andrea Patriarca, Michael Loschi, Anna Szmigielska-Kaplon, Fabian Beier, Alessandro Cignetti, Beatrice Drexler, Eleni Gavrilaki, Francesco Lanza, Corentin Orvain, Antonio Maria Risitano, Rafael de la Camara, and Régis Peffault de Latour

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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 Szmielierska-Kaplon,15 Fabian Beier,16 Alessandro Cignetti,17 Beatrice Drexler,18 Eleni Gavrilaki,19 Francesco Lanza,20 Corentin Orvain,21, Antonio Maria Risitano,22 Rafael de la Camara,23 and Régis Peffault de Latour24

Affiliations
1: St James University Hospitals, Leeds, UK
2: EBMT Statistical Unit, Leiden, Netherlands
3: EBMT Leiden Study Unit, Leiden, Netherlands
4: RM Gorbacheva Research Institute, Pavlov University, St. Petersburg, Russian Federation
5: Department of Hematology, Leiden University Medical Center, Leiden, Netherlands
6: SC Ematologia, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy
7: University Hospital of Wales, Cardiff, United Kingdom
8: National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan
9: 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: 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: 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: University Hospital Basel, Basel, Switzerland
19: 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: AORN Moscati, Avellino, Italy
23: Hospital de la Princesa, Madrid, Spain
24: Clinical Investigations Center, Hôpital Saint-Louis, Paris, France
Author contributions:
MG, AR, RD, RC devised the study, collected data, reviewed the data, wrote and edited the manuscript
DE analysed 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

Running title: SARS-CoV-2 vaccination in patients with AA/PNH

Corresponding author
Dr Morag Griffin; St James University Hospital, Leeds, UK; m.griffin@nhs.net

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Datasets are maintained in the European Blood and bone marrow transplant 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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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 (SAAWP) and Infectious Diseases Working Party (IDWP) 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 timepoints, and SARS-CoV-2 infection occurrence.

457 patients were included from 20 centers. 361 patients received at least one vaccination and were included for detailed analysis. See table I for baseline characteristics.

139 patients were on active immunosuppression at 1st vaccination, and 120 patients on complement inhibitors with the majority on C5 inhibition (90.8%) (See table I). Treatment received within a 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).

347 patients had at least 2 vaccinations, with a mean of 45.51 days between vaccine one and vaccine two. Side effects within 5 days post vaccination were experienced by 117/361 patients (32.4%), most commonly pyrexia, myalgia, headache and/or fatigue or a combination of the 4 symptoms (101/117). 2 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 remission (1/2). For patients with PNH, PNH related side effects were experienced by 19 (14.7%), including 4 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: 9 patients experienced AA relapse with 6 patients undergoing a concomitant reduction in immunosuppression, one with unknown circumstances, and one due to MDS transformation. 1 relapse considered possibly vaccine related with platelet count reduction from 72 x10^9/l to 12 x10^9/l 1 week post vaccination. This patient responded to oxymethalone dose increase within 4 weeks, although this could be considered vaccine induced thrombocytopenia.

12-month overall survival was 98% (95% 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 6 deaths within 1 year after 1st vaccination, none related to SARS-CoV-2 vaccination or infection (3 due to aplastic anaemia 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 a year post vaccination with minimal change (see table II).

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.

There are case reports of de-novo AA in patients testing positive for SARS-CoV-2, 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 haemolysis. 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.

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. Röth et al report 4 patients who had AA relapse at median 77 days post vaccination, with mainly platelet counts affected. All 4 patients were on calcineurin inhibitors, and all needed treatment for relapsed AA. Within our cohort, 9 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 having no disease status change post-vaccination. 6% (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 immunosuppression. 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. 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; Analysing 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. 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.
References


### Table I: Baseline characteristics

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

IST: Immunosuppressive therapy

*22 were on IST treatment for AA and complement inhibition
**Table 2. Blood results at 3, 6 and 12 months post vaccination**

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

Hb = Hemoglobin, WBC = white blood count