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COVID-19 vaccination antibody responses in patients with aplastic anaemia and paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia are part of a spectrum of rare and potentially life-threatening bone marrow failure disorders that are thought to result from an autoimmune attack targeting normal bone marrow haematopoietic stem cells. There is a concern that patients with these disorders might be less able to mount an effective immune response due to their underlying disease or treatment-related immunosuppression, and might be at risk of more severe SARS-CoV-2 infections. In the Leeds PNH service, we have seen suboptimal meningococcal vaccine responses in up to 42% of patients on anti-complement therapy (unpublished data).

In a post-implementation, real-world, prospective, observational study, we aimed to investigate antibody responses to SARS-CoV-2 vaccination in adult patients with aplastic anaemia and PNH. All patients under the care of the UK PNH National Service in Leeds were eligible for inclusion, except those with previous allogeneic bone marrow transplantation (detailed methods are in the appendix [p 1]). Healthy volunteers were recruited from among UK National Health Service and University of Leeds staff. Blood samples were obtained before vaccination and 4–6 weeks after the first and second vaccinations. Vaccinations were administered by local health-care providers as per the UK prioritisation schedule and there was no limitation on the type of SARS-CoV-2 vaccine received for inclusion in the study. Serum spike-specific composite IgA, IgG, and IgM antibodies were tested at the Leeds University (Leeds, UK) laboratory using an ELISA (The Binding Site Group, Birmingham, UK). Responses from all patients and healthy controls were compared. Post hoc, we also did subgroup analyses according to the variables: diagnosis (classic PNH, aplastic anaemia–PNH overlap, and aplastic anaemia), age, calcineurin inhibitor therapy, vaccine type, and, in patients with PNH on complement inhibitory treatment, history of a suboptimal meningococcal vaccination response. The study was approved by the independent Yorkshire and The Humber Leeds East Research Ethics Committee (16/YH/0290; Independent Research Application System identification number 105641) and conducted in agreement with Good Clinical Practice guidelines and according to the Declaration of Helsinki.

Between Jan 1 and Dec 1, 2021, 175 patients and 45 healthy volunteers were enrolled and their SARS-CoV-2 antibody responses were measured. Four patients were excluded from final analysis due to concurrent immunosuppression for other indications. In the analysable population, the median age was 52 years (IQR 40–67) and 118 (55%) of 216 were female and 98 (45%) were male; data on race and ethnicity were not collected (appendix p 5). After one vaccination, patients had a substantially reduced seroconversion rate of 63% (83 of 131 patients with data) compared with 95% (39 of 41) of healthy volunteers, which was similar across patient subgroups (63% [43 of 68] in those with classic PNH, 68% [28 of 41] in those with aplastic anaemia–PNH, and 55% [12 of 22] in those with aplastic anaemia; appendix p 6). Overall, patients showed a 2.4-fold lower antibody response than healthy volunteers (median optical density [OD] ratio 1·2 [IQR 0·8–2·0] vs 2·9 [1·8–4·1]; p<0·0001; figure). The absolute antibody levels were significantly lower in all patient subgroups.
than in healthy volunteers (classic PNH median OD ratio 1·2 [IQR 0·8–1·7]; aplastic anaemia–PNH 1·4 [0·8–2·4]; and aplastic anaemia: 1·2 [0·7–1·8]; p<0·0001). After second vaccination, seropositivity and magnitude of antibody responses improved, equivalent to healthy volunteers. Patient seroconversion rates were 99% (155 of 156) compared with 98% (40 of 41) healthy volunteers, with no difference in antibody levels (patient median OD ratio 3·3 [IQR 2·2–4·8] vs healthy volunteers 4·0 [3·5–4·8]; p=0·097). Healthy volunteers showed a 39% increase in antibody response between first and second vaccinations (p=0·0002) and substantial improvements were seen across all patient subgroups (classic PNH 175% increase, p<0·0001; aplastic anaemia–PNH 184% increase, p<0·0001; and aplastic anaemia 147% increase, p=0·0034; appendix p 7).

In univariate analysis, current calcineurin inhibitor therapy did not show a significant difference in antibody response (appendix p 8). Advancing age was found to be moderately inversely correlated (r=–0·61; p=0·0001) with antibody results in healthy volunteers after first vaccination and weakly correlated after second vaccination (r=–0·35; p=0·025; appendix pp 9–10). However, no significant correlation with increasing age was seen in any patient subgroups after either vaccination (appendix p 9). Increased antibody levels were seen after two vaccinations in patients who received BNT162b2 (Pfizer–BioNTech; median OD ratio 4·5 [IQR 3·1–6·5]) versus ChAdOx1-S (Oxford–AstraZeneca; 2·8 [1·8–4·1]; p=0·0001); a similar pattern was seen in the healthy volunteers (appendix p 11). A history of suboptimal response to meningococcal vaccination was not associated with a reduced antibody response after two SARS-CoV-2 vaccinations (appendix p 12).

We then did prespecified multivariate analyses to see if the patient group association seen in univariate models could be explained by potential confounding factors. Compared with healthy volunteers, being a patient was
significantly associated with reduced response to first vaccination even after controlling for other variables (odds ratio [OR] 9·10 [95% CI 1·49–55·43]; p=0·017). Being a woman versus being a man (2·64 [1·24–5·59]; p=0·012) and receiving ChAdOx1-S versus BNT162b2 (2·52 [1·10–5·80]; p=0·030) also had significant associations with non-response; other variables were not significantly associated with non-response (appendix p 13). No significant association was seen for any variable and non-response after second vaccination (data not shown).

Real-world post-implementation data are vital for understanding the effectiveness of vaccination programmes in rare diseases that are minimally represented in clinical trials. Kearns and colleagues have shown impaired humoral immune responses in patients with other haematological diseases and autoimmune disorders, and on immunosuppressants. Ours is the largest study to our knowledge providing outcome data in patients with PNH and aplastic anaemia.

The precise concentration of SARS-CoV-2 antibodies needed for complete protection is unknown. Before vaccines were available, we reported adverse clinical outcomes of COVID-19 in our patients and five patients known to the National PNH Service in Leeds died due to SARS-CoV-2 infection (unpublished data). No vaccinated patient enrolled in the present study has died within 28 days of a positive SARS-CoV-2 test, which supports that the antibody responses obtained are clinically significant. Breakthrough SARS-CoV-2 infections after second vaccination have occurred in 16 patients in the study as of March 18, 2022. 15 of 16 patients were on complement inhibitor therapy, and all patients had minor illness, except one who required admission to hospital but recovered without intensive care or ventilatory support.

The reason for the difference in response between patients and healthy volunteers after one vaccination but not two vaccinations is unclear. Although our healthy volunteer and patient cohorts were not perfectly age and sex matched, which restricts the direct comparability of the groups, the seroconversion rates seen are in line with other studies. Limitations of our data include the small sample size, as is the challenge of rare diseases, and, due to the inception of the study at the time of UK vaccination programme rollout, very few samples could be obtained before vaccination. Overall, when compared with studies in the general UK population, lower responses after first vaccine were noticed in our patient cohorts, in line with previous data from patients with other diseases treated with immunosuppressants.

Individuals receiving B-cell depleting therapies have shown reduced humoral responses to SARS-CoV-2 vaccination in other studies, and we know that patients with aplastic anaemia and PNH have substantially reduced absolute numbers of B cells. However, the responses seen after second vaccination were considerably better than those seen for other disorders, such as haematological malignancies. Another interesting question raised is whether complement inhibition itself might impair vaccine responses. Complement components can enhance antibody mediated viral neutralisation and have shown importance in determining responses to other vaccinations, although little is known of the role in SARS-CoV-2 viral mediated immunity, which merits further study.

Reassuringly, we found that current calcineurin inhibitor therapy did not affect responses. Calcineurin inhibitor therapy in studies of other diseases, including renal disorders, report variable effects on humoral response. A large number of patients in our study had previous anti-thymocyte globulin (ATG) therapy (appendix p 5), and were able to mount a good response to vaccination. However, none of the included patients had received ATG therapy within 12 months of vaccination, when the effect on immune responses is likely to be most profound. Interestingly, patients with a history of suboptimal response to meningococcal conjugate vaccination still mounted a response after two SARS-CoV-2 vaccinations (appendix p 12). This finding prompts the question as to whether the improved response observed is due to more efficacious novel mRNA and viral vector vaccine technologies or whether polysaccharide conjugate vaccines are poorly immunogenic in our patients.

Vaccination side-effects were comparable with published studies (appendix p 14). There were a small number of adverse events, including superficial femoral vein thrombosis (one [1%] of 171 patients), of vaccine-induced thrombotic thrombocytopenia (one [1%] patient), breakthrough haemolysis (four [3%] patients), and transient drops in haematological parameters (two [1%] patients) in the aplastic
anaemia cohort. Most patients on complement inhibitors were vaccinated without substantial symptomatic breakthrough haemolysis. There have been case reports of de-novo aplastic anaemia after vaccination, but SARS-CoV-2 infection itself seems to pose the greatest risk for this occurring. These events and reported side-effects could be simply temporally related rather than directly attributable to vaccination. Longer follow-up of larger cohorts is required to further characterise rare adverse events. However, benefits of vaccination continue to substantially outweigh any potential risk.

Our data highlight the importance of at least two vaccinations in patients with PNH or a history of aplastic anaemia to achieve a good SARS-CoV-2 antibody response, and we expect that they will benefit from booster programmes. Although we have found robust antibody levels after two vaccinations, further studies are needed to determine the longevity of response, degree of effective IgG responses, T-cell responses, and long-term infection outcomes.

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