Failure to mount a humoral response to COVID-19 vaccination identifies individuals with previously undiagnosed severe antibody deficiency state: preliminary data from the COVID-19 ENLIST study

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Introduction

Immunisation with mRNA or adenovirus-based COVID-19 vaccinations provides a potent immunogenic stimulus. In the vast majority of individuals, vaccination elicits cellular and humoral (antibody) immune responses to the spike protein mediating protection against severe disease against SARS-CoV-2 infection, including novel variants.[1] However, susceptibility to severe disease and failure to respond to COVID-19 vaccinations remain a particular concern in immunocompromised patient groups.[2] In a recent survey of vaccine responses in individuals with inherited and acquired forms of immunodeficiency, the magnitude of the humoral IgG vaccine response to COVID-19 vaccines appeared related to the magnitude and nature of the underlying immunodeficiency.[2] Here, I explore the novel concept that failure to elicit a humoral vaccine response can identify individuals with previously undiagnosed humoral immunodeficiency, in a pilot study of solid-organ transplant recipients (SOTRs).[3]

Material and methods

Serum was obtained from participants enrolled in the COVID-19 ENLIST vaccination sub-study (REC reference: 20/YH/0309). Samples were obtained following informed consent and at least 14-days following receipt of two doses of COVID-19 vaccination, as recently described.[3] Anti-SARS-CoV-2 spike S1 IgG serological responses were determined using a commercial assay (EUROIMMUN) as per kit instructions. Total IgG, IgA, and IgM levels were analysed using the Optilite® turbidimeter in consecutive stored sera with anti-SARS-CoV-2 spike IgG levels above ('responders', n=15) and below ('non-responders', n=18) the assay's limit of detection for a positive anti-spike IgG response. Comparisons are presented by vaccine response group and relative to the UK laboratory adult reference range (approximately normally distributed). Data were curated in Microsoft Excel with statistical analysis in GraphPad Prism v6.0. Severe hypogammaglobulinaemia was defined as a serum IgG <4 g/L, based on meta-analysis demonstrating a doubling in the risk of infections below this level.[4]

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Table 1. Percentage of solid organ transplant recipients with serum immunoglobulin class below the lower limit of normal

	UK reference range	Vaccine responders (n=15)	Vaccine non-responders (n=18)
IgG <6 g/L	5.0%	6.8%	22.2%
IgA <0.8 g/L	5.0%	0.0%	11.1%
IgM 0.5 g/L	5.0%	40.0%	44.4%

Results and discussion

The percentage of SOTRs with serum immunoglobulin class below the lower limit of normal is shown in Table 1. Individuals failing to mount a detectable anti-spike IgG response following COVID-19 vaccination display a substantially increased frequency of low IgG and low IgM levels, compared with the UK reference population (Fisher's exact test: $p=0.0093$ and $p<0.0001$, respectively). While there was no statistically significant difference in the odds of a low IgG (<6 g/L) between the SOTR vaccine responder/non-responder groups (Fisher's exact test: $p=0.340$), the lowest IgG in the vaccine non-responder group was 3.1 g/L is clinically relevant.

Conclusion

Antibody deficiency is a treatable cause of infection susceptibility;[5] however, recognition is reliant on laboratory diagnosis. Solid organ transplant recipients are at increased risk of hypogammaglobulinaemia due to factors including the use of anti-rejection immunosuppressive medications, but severe deficiency remains rare.[6] This preliminary data support the hypothesis that failure to produce a detectable anti-SARS-CoV-2 spike IgG response following at least two COVID-19 vaccine doses is associated with a reduction in the serum levels of IgG. Remarkably, this pilot study identified an individual with an IgG level of 3.1 g/L, consistent with severe IgG deficiency and directs clinical assessment with potential consideration of immunoglobulin replacement therapy. ■

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