Development of antibody response to SARS-CoV-2 following asymptomatic infection in patients with plasma cell disorders on immunomodulatory therapy

Patients with multiple myeloma and related plasma cell disorders (PCD) are considered extremely vulnerable to SARS-CoV-2 infection due to disease-related impaired humoral and cellular immunity as well as receipt of immunosuppressive therapy.[1] Overall mortality from COVID-19 disease in 650 PCD patients across 10 countries was 33%.[2] Poor outcomes from COVID-19 disease have resulted in recommendations for modifications to systemic anti-cancer therapy (SACT) to reduce the risk of infection whilst balancing the potential complications of untreated PCD.[3]

With the rollout of the COVID-19 vaccines, there is urgent need to understand seroconversion in immunocompromised patients for ongoing patient management and recommendation. Previous influenza vaccine experience in PCD has demonstrated a poor response, up to 40% after the first dose with doubling after a booster dose.[4] A Cochrane review revealed a significant but limited reduction in mortality of patients with solid and haematological malignancies, including PCD,[5] therefore recommendations remain for influenza vaccinations in PCD patients.[4] Limited information is available about humoral responses to SARS-CoV-2 infection, or the influence of SACT.

We introduced SARS-CoV-2 antibody screening with the Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics, Basel, Switzerland), a semi-quantitative assay of IgG and IgM against the nucleocapsid (N) antigen[6] as routine care in July 2020 for patients having blood tests at our institution. We report findings after six months of antibody screening which includes two high-incidence periods of SARS-CoV-2 in London, UK, one from March–May 2020, and an ongoing second wave from October 2020,[7] exacerbated by the variant identified in Kent, UK.[8] Here we describe positive antibody findings, and relationship with symptomatic infection, PCD characteristics and associated SACT. Table I gives diagnostic and clinical information in 243 patients who had at least one antibody test, of whom 106 had longitudinal samples.

Twenty-six (10·7%) patients had positive antibody results, 12 of whom had documented nose and throat polymerase chain reaction (PCR)-swab-positive COVID-19 disease. In a separate but overlapping cohort, 41 patients have had PCR-confirmed COVID-19 disease (Table I). Their clinical outcomes are summarised in Fig 1B. In a subset of 20 patients who have recovered and undergone testing, 12 (60%) seroconverted at median time to antibody testing from PCR positivity of 60 (range 5–256) days for all tested patients. Eight seronegative patients were tested at median 30·5 (range 5–176) days. Seven patients who died did not have antibody testing prior to death, and 14 have not been tested (Figure S1).

In screening the asymptomatic cohort, 14 (6·3%) had an unexpected positive antibody result. Their clinical course, with relevant exposure details, are summarised (Fig 1A). Two patients described symptoms suggestive of COVID-19 disease two weeks or more prior to a positive antibody test, while the rest described no COVID-19-attributable symptoms. All possible contacts or exposures are indicated (Fig 1A). Seven (50%) were on SACT (including ixazomib, pomalidomide, lenalidomide and dexamethasone) throughout the period from their possible exposure to positive antibody test, none had their long-term oral immunomodulatory treatment interrupted.

Failure to mount an antibody response was not correlated with more lines of therapy, or with age, body mass index, ethnicity, time since PCD diagnosis, International Staging System (ISS) stage, genetic risk, autologous stem cell transplantation (ASCT), anti-CD38 therapy, disease status [partial response (PR) or active disease vs complete response (CR)/very good PR (VGPR)], immuneparesis (IgG < 6·5g/l), timing of antibody test, or time to viral clearance.

To explore antibody strengths between patients, positive results were semi-quantified as follows: borderline (<1·5), weak (<10), strong ($\geq$ 10) and very strong positive ($\geq$ 100) based on signal and a cut-off optical density of 1 (Figure S2). Antibody strength did not correlate with symptomatic [(χ^2 df 3, $n = 25$) 1·886, $P = 0{\cdot}60$] or PCR-confirmed diagnosis vs incidental [(χ^2 df 3, $n = 25$) 3·973, $P = 0{\cdot}26$]. At least two longitudinal positive antibody tests (median 45 days, range 21–119, apart) were documented in 10 patients. Strength of response fell between first and second test (mean difference −11·99, $t(9) = 1{\cdot}661$, $P = 0{\cdot}13$) (Figure S3).

Total seroprevalence rates over six months of 10·7% (26/243), and in asymptomatic patients, 6·3% (14/223), are lower but not dissimilar to that reported in London over a similar time period[9,10] reflecting the shielding behaviours of our patients, but also challenges in protecting them during high SARS-CoV-2 incidence in the community. In those with

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Table I. Patient characteristics.

Characteristic		All patients with antibody results $n = 243$	Patients with PCR-positive COVID-19 disease $n = 41$	Positive antibody test post PCR-positive COVID-19 disease $n = 12$	Screening-positive antibody test only $n = 14$
Male sex	(%)	140 (57·6)	22 (53·7)	7 (58·3)	5 (35·7)
Median age	[Range]	65 [31–84]	62 [31–88]	58·5 [32–79]	63·5 [35–79]
BMI	[Range]	29·4 [15·4–53·5]	25·1 [20·9–36·1]	25 [21–33]	27·9 [25·3–35·6]
Caucasian	(%)	129 (53·1)	19 (46·3)	8 (66·7)	5 (35·7)
African/Caribbean	(%)	38 (15·6)	9 (22·0)	1 (8·3)	3 (21·4)
Asian	(%)	23 (9·5)	6 (14·6)	1 (8·3)	4 (28·6)
Other	(%)	22 (9·1)	6 (14·6)	2 (16·7)	1 (7·1)
Undisclosed	(%)	31 (12·8)	1 (2·4)	0 (0·0)	1 (7·1)
ISS Staging					
Stage 1	(%)	79 (32·5)	12 (29·3)	5 (41·7)	6 (42·9)
Stage 2	(%)	42 (17·3)	10 (24·3)	4 (33·3)	2 (14·3)
Stage 3	(%)	41 (16·9)	6 (14·6)	1 (8·3)	1 (7·1)
Not performed	(%)	81 (33·3)	13 (31·7)	2 (16·7)	5 (35·7)
cytogenetic risk at diagnosis and most recent relapse	(%)	86 (35·3)	19 (46·3)	6 (50·0)	6 (42·9)
Adverse risk	(%)	82 (33·7)	13 (31·7)	5 (41·7)	5 (35·7)
Not performed	(%)	75 (30·9)	9 (22·0)	1 (8·3)	3 (21·4)
IgG	(%)	144 (59·3)	30 (73·2)	8 (66·7)	6 (42·9)
IgA	(%)	52 (21·4)	4 (9·8)	2 (16·7)	2 (14·3)
LC	(%)	35 (14·4)	4 (9·8)	2 (16·7)	3 (21·4)
Other	(%)	12 (4·9)	3 (7·3)	0 (0·0)	3 (21·4)
MGUS	(%)	4 (1·6)	0 (0·0)	0 (0·0)	0 (0·0)
SMM	(%)	15 (6·2)	1 (2·4)	0 (0·0)	0 (0·0)
MM	(%)	212 (87·2)	37 (90·2)	12 (100·0)	11 (78·6)
Other (i.e. plasmacytoma, AL amyloid, POEMS with or without associated MM)	(%)	12 (4·9)	3 (7·3)	0 (0·0)	3 (21·4)
Median time since MM diagnosis in months	[Range]	45 [1–331]	41 [1–175]	15 [6–175]	32 [6–233]
Median prior lines of therapy	[Range]	2 [0–8]	1 [0–5]	3·5 [1–6]	1 [0–3]
On active treatment	(%)	139 (57·2)	28 (68·3)	7 (58·3)	7 (50·0)
Prior treatment with PI	(%)	207 (85·2)	36 (87·8)	11 (91·7)	10 (71·4)
Prior treatment with anti-CD38 mAb	(%)	70 (28·8)	11 (26·8)	4 (33·3)	3 (21·4)
Prior treatment with IMiDs	(%)	171 (70·4)	28 (68·3)	11 (91·7)	9 (64·3)
Has received an ASCT	(%)	151 (62·1)	27 (65·9)	9 (75·0)	6 (42·9)
Disease status at time of antibody test					
PD	(%)	35 (14·4)	6 (14·6)	0 (0·0)	2 (14·3)
SD/PR	(%)	81 (33·3)	19 (46·3)	6 (50·0)	3 (21·4)
VGPR/CR	(%)	96 (39·5)	14 (34·1)	6 (50·0)	8 (57·1)
Not yet performed	(%)	31 (12·8)	2 (4·9)	0 (0·0)	1 (7·1)
Other comorbidities					
COPD	(%)	4 (1·6)	3 (7·3)	0 (0·0)	1 (7·1)
Diabetes	(%)	23 (9·5)	4 (9·8)	0 (0·0)	4 (28·6)
HTN	(%)	65 (26·7)	4 (9·8)	0 (0·0)	6 (42·9)
IHD	(%)	9 (3·7)	2 (4·9)	0 (0·0)	1 (7·1)
CKD	(%)	23 (9·5)	6 (14·6)	0 (0·0)	0 (0·0)
Immuneparesis	(%)	70 (28·8)	13 (31·7)	3 (25·0)	6 (42·9)
Receiving IVIG	(%)	4 (1·7)	0 (0·0)	0 (0·0)	2 (14·3)

BMI Body Mass Index; ISS International Staging System; ISS Stage 1, B2-microglobulin <3·5 mg/l and albumin >35 g/l; ISS stage 3, B2-microglobulin >5·5 mg/l; ISS Stage 2, patients not fulfilling criteria for stage 1 or 3; adverse risk, cytogenetics defined as per International Myeloma Working Group (IMWG) criteria t(4;14), t(14;16), t(14;20), del17p and 1q gain. MM, multiple myeloma; SMM, smouldering myeloma; MGUS, monoclonal gammopathy of undetermined significance; ASCT, autologous stem cell transplant; PI, proteosome inhibitor; mAb, monoclonal antibody; IMiD, immunomodulatory drug; PD, progressive disease; SD, stable disease; PR, partial response; VGPR, very good partial response; CR, complete response. Disease response assessed as per IMWG criteria. COPD, chronic obstructive pulmonary disease; HTN, hypertension; IHD, ischaemic heart disease; CKD, chronic kidney disease; IVIG, intravenous immunoglobulins. Immuneparesis is defined as IgG levels <6·5 g/l.

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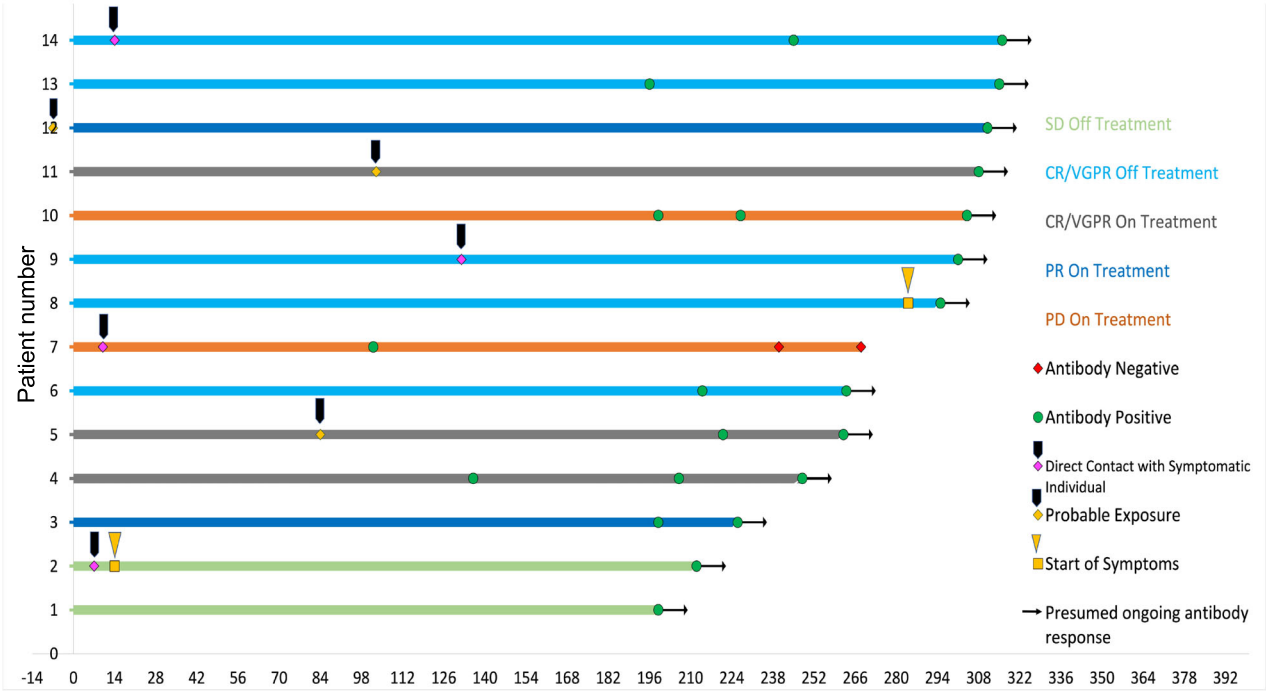
(A) Time course of patients with SARS-CoV-2 positive antibody test on screening only

Abbreviations: Current disease response as defined by IMWG Criteria: PD, Progressive disease, SD, Stable disease, PR, Partial response, VGPR, Very good partial response, CR, Complete response.
Direct contact - defined as direct contact with a symptomatic individual or one who has tested PCR-positive for COVID-19 infection.
Probable exposure – defined as an activity including using public transport, visiting a restaurant or having household members attend school or work-place settings.
Longitudinal strength of antibody response is depicted in Supplementary Figure 3 in patients who had more than one antibody test.
Numbered patients correspond with numbered patients in Supplementary Figure 3.



Time (Days) after advice to shield was issued on 23rd March 2020 by the UK government

(B) Clinical outcomes of patients diagnosed with COVID-19 disease by nose and throat PCR swab

Abbreviations: CPAP, Continuous Positive Airway Pressure, PCR, Polymerase chain reaction
COVID-19 disease supportive therapies described as the highest level of therapy received.

		All patients diagnosed with COVID-19 disease N=41	Positive antibody test post PCR-positive COVID-19 disease n=12	Negative antibody test post PCR-positive COVID-19 disease n=8
Required hospital admission	(%)	19 (46·3)	3 (25·0)	4 (50·0)
Received oxygen therapy only	(%)	10 (24·4)	2 (16·7)	0 (0)
Received nasal high flow oxygen therapy or CPAP therapy	(%)	6 (14·6)	0 (0)	1 (12·5)
Received intubation	(%)	2 (4·9)	0 (0)	0 (0)
Died	(%)	7 (17·1)	0 (0)	0 (0)
Median time (days) to PCR negative test	[Range]	24.5 [8-77]	26 [8-42]	23 [14-46]
Median time (days) to COVID-19 antibody testing	[Range]	60 [5-256]	86·5 [22-256]	30·5 [5-176]

Fig 1. Clinical outcomes and characteristics of all patients who had a positive SARS-CoV-2 antibody test in our cohort. [Colour figure can be viewed at wileyonlinelibrary.com]

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PCR-confirmed disease, seroconversion rates of 60% were lower than reported in the general population (95%),[11,12] another PCD cohort (96%),[13] a chronic lymphocytic leukaemia (CLL) cohort (67%)[14] and an acute leukaemia cohort (88%),[15] although differences in assays may account for some of this variation. Positive antibody test post PCR-confirmed infection occurred at a median of 86·5 days compared to 30·5 days for those who tested negative, suggesting a delayed response compared to the general population of 14–28 days.[12]

Our study and analyses are limited by small number of seropositive patients and those undergoing antibody testing post PCR-diagnosed COVID-19 disease. Although our analyses failed to reach statistical significance, we suspect failure or delay to mount an antibody response to be more likely with uncontrolled PCD, a heavily pre-treated PCD population and concurrent SACT. Antibody testing post PCR positivity was not uniform due to limited availability of testing early in the pandemic. Timings of antibody samples are based on patient attendances for blood tests and therefore heterogenous.

In summary we report that some PCD patients are able to mount and maintain a humoral response to SARS-CoV-2 infection through routine screening of a predominant outpatient population, although seroconversion rates are lower than reported for other populations. Notably, seroconversion can occur following asymptomatic infection, and despite receipt of immunomodulatory therapy. No seropositive patients have had SARS-CoV-2 re-infection in our cohort, although longer follow-up in a larger population of seropositive PCD patients will be required to understand the protection conferred.

This evidence supports advice for COVID-19 vaccination to be offered to all PCD patients although the delayed humoral response calls for close antibody monitoring of all vaccinated patients, and consideration of timely booster doses. Attention should also be paid to PCD patients undergoing a range of therapies including ASCT, to inform an optimised vaccination protocol for these patients.

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Conflict of interest

KLY has received honoraria from Janssen, Takeda, Sanofi, GSK and Amgen. KLY receives research funding from Sanofi, Celgene, Takeda, Janssen and Autolus. NR has received Janssen consultancy, travel support for meetings and Speakers Bureau outside the submitted work.

Author contributions

WYC, ES, SJC, CSYL and LA collected the data. WYC, ES and KLY analysed the data. WYC and KLY wrote the manuscript. WYC, ES, SJC, CSYL, LA, KX, BW, SM, XP, CK, JS, AW, RP, NR, LL, EN and KLY critically revised the final manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Consort diagram of Screening and COVID-19 PCR positive patients.

Fig S2. Patients with positive SARS-CoV-2 antibody test categorised by PCR-positive patients and unexpected antibody test positive patients.

Fig S3. Strength of response in positive antibody patients with longitudinal antibody test samples.

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