COVID symptoms, testing, shielding impact on patient-reported outcomes and early vaccine responses in individuals with multiple myeloma

Patients with myeloma have been shielded and self-isolated since the start of the COVID-19 pandemic, due to the concern for and subsequent reports of higher risk of severe COVID-19 disease and mortality.[1] In addition, guidelines have encouraged attenuation of myeloma therapeutics or a switch to oral therapies, ostensibly to reduce hospital footfall, facilitate shielding and potentially to limit further treatment-related immune suppression.[2] Myeloma requires ongoing immune-suppressive chemotherapy, frequent medical visits and has previously demonstrated universally poor response to vaccinations.[3]

The protective titre of antibodies required to prevent re-infection is unclear, as is the ability to protect patients from SARS-CoV-2 virus variants of concern (VoC). Cycles of shielding and self-isolation can cause considerable physical and psychological distress for myeloma patients. High mortality rates with COVID-19 coupled with anticipated poor COVID-19 vaccine responses will increase isolation periods and be detrimental to their myeloma care.

In order to address these evidence gaps, we initiated a national web-based prospective study of adults with multiple myeloma (MM) from December 2020 using patient co-developed measures of COVID symptoms, testing, vaccination, SARS-CoV-2 immunity acquired by infection or vaccination and quality-of-life (QoL) impact with standardised generic and disease-specific patient-reported outcome measures. Using the existing RUDYstudy.org platform (LREC 14/SC/0126 & RUDY LREC 17/SC/0501),[4] informed online dynamic consent was obtained for all participants. Participants completed validated patient-reported questionnaires including the Hospital Anxiety and Depression (HADS) and Lubben Scales.[5] A group of four adults with myeloma co-developed a RUDY COVID-19 consensus questionnaire (Data S1). Participants entered information about their myeloma diagnosis, current disease status and chemotherapy treatment. A serum sample collected from each patient; was tested for antibodies against SARS-CoV-2 nucleocapsid (N) or spike (S) protein. SARS-CoV-2 N protein antibodies were measured by turbidimetry (Abbott Labs, Abbott Park, IL, USA), with samples that produced values of >1·4 considered to be positive. SARS-CoV-2 S protein antibodies were measured by turbidimetry (Abbott; IgG serology only), with a cut-off value of 50 considered to be a positive result. Both of these assays are FDA-approved for use in clinical diagnostic settings.

Between 5 February and 29 March 2021, when the UK was still in lockdown, 109 adults with myeloma completed the COVID-19 questionnaire with a returned blood sample. Patient characteristics are listed in Table I with 10% of recruited adults non-UK white. Although the majority of patients reported they were in remission, 20% of patients reported they had poorly controlled myeloma, either relapse or progressive disease. A minority of participants (6%) reported major symptoms of COVID-19 and only one patient reported a polymerase chain reaction (PCR)-positive result (Table SI). Almost all patients were either partially or fully shielded during both waves of the pandemic with fewer patients fully shielded in the second wave. The primary reason for shielding was due to current or recent immunosuppressive therapy (Table SII). Almost a third of respondents identified with making less healthy diet choices during the pandemic but few reported increases in alcohol, smoking or medical treatment for anxiety or depression. The reported impact of the pandemic on lifestyle and social activities varied considerably between participants (Figure S1). One in five respondents scored 'at risk of social isolation', with no differences by age but men significantly more likely to be at risk than women ($P = 0{\cdot}027$). Using HADS, 23·1% of patients reported symptoms of mild to moderate anxiety or mild to moderate depression during this period (Table II).

Out of the 107 patients suitable for serological analysis at the time of reporting, five were found to have positive levels of N protein antibodies, indicating that they had suffered a natural infection. Only one of these patients had a history of a PCR-positive result known at study entry, with the remaining patients having had asymptomatic infections. When looking at the timing of samples that were received from these patients, approximately 25% of them were taken from the patient >3 weeks post their first dose of vaccine (range 21–68 days). Approximatetly 50% of patients who received Astra-Zeneca/Oxford (AZ) vaccination and 44% of patients who received Pfizer (P) vaccination produced a successful response >3 weeks post first dose [sample $n = 14$ (AZ) vs 9 (P)]. All patients who had had a previous infection had a robust antibody response to the first dose of COVID-19 vaccine and 60% of patients had an optimal immune response to the first dose of COVID-19 vaccination. There were no differences noted in humoral response after the first dose of either AZ (Adenoviral vector) or P mRNA based vaccination (Table SIII).

Table I. Patient characteristics of first 109 study participants who took part in the PREPARE study.

		Total (n = 109)	Female (n = 42)	Male (n = 67)
Age		62·9 (9·9)	61·4 (10·2)	63·9 (9·6)
Ethnicity	UK white	97 (89·0%)	38 (90·4%)	59 (88·0%)
Myeloma status	Complete remission	38 (34·9%)	15 (35·7%)	23 (34·3%)
	Very good remission	10 (9·2%)	5 (11·9%)	5 (7·5%)
	Partial remission	9 (8·3%)	2 (4·8%)	7 (10·5%)
	Stable disease	10 (9·2%)	6 (14·3%)	4 (6·0%)
	Progressive disease/relapse	22 (20·2%)	9 (26·2%)	13 (19·4%)
	Don't know/missing	20 (17·4%)	5 (11·9%)	12 (17·9%)
Myeloma treatment status	Currently not on chemotherapy	25 (22·9%)	5 (11·9%)	20 (29·8%)
	Reported chemotherapy during lockdown	29 (26·6%)	15 (35·7%)	14 (20·9%)
	Reported chemotherapy within 4 months prior to lockdown	19 (17·4%)	10 (23·8%)	9 (13·4%)
	Missing	36 (33%)	12 (28·5%)	24 (35·8%)
Myeloma treatment includes	Proteasome inhibitors	21 (19·2%)	9 (19·0%)	12 (17·9%)
	Immunomodulatory treatment	37 (33·9%)	19 (45·2%)	18 (26·9%)
	CD38 ab-based therapy	13 (11·9%)	7 (16·7%)	6 (9·0%)
	Other (includes dexamethasone)	47 (43%)	27 (64·3%)	19 (28·4%)

Table II. Participant reported impact on mental and social well-being due to COVID 19 in the PREPARE trial.

		Total (n = 100)	Male (n = 65)	Female (n = 35)
Stress related	Less healthy diet	29	18 (27·7%)	11 (31·4%)
	More smoking	2	0	2 (5·7%)
	More alcohol	5	3 (4·6%)	2 (5·7%)
Prescribed anti-depressants/ani-anxiety since pandemic		2	2 (3·1%)	0
At risk of social isolation* (n = 99)		21 (21·2%)	18 (28·1%)	3 (8·6%)
		n = 59	n = 20	n = 39
Anxiety (from HADS)	Mild	5 (5·1%)	1 (5%)	2 (5·1%)
	Moderate/severe	4 (6·7%)	2 (10%)	2 (5·1%)
Depression (from HADS)	Mild	8 (7·3%)	3 (15%)	5 (12·8%)
	Moderate/severe	3 (5%)	1 (5%)	2 (5%)

HADS, Hospital Anxiety and Depression Scale.
*As measured by the Lubben scale.

This is the first prospective study to report on the history of COVID19 symptoms, testing, healthcare resource impact, and mental and social well-being in the shielded population during both waves of the COVID-19 pandemic from a community-based sample. The study was exclusively online and may have underrepresented older patients.

Terpos *et al.* report that 28·2% of myeloma patients generated neutralising antibody titres following a first dose of P COVID-19 vaccine and Bird *et al.* report a 56% antibody response to a first dose of vaccine.[6,7] These are early results following the first vaccine and both humoral antibody and T cell responses following require ongoing evaluation. Pimpinelli *et al.* report 78% optimal humoral responses in 44 myeloma patients two weeks following their second dose.[8]

Our data suggest myeloma patients have relatively poorer vaccine immune response in comparison with their age-matched peers following first vaccine dose,[9,10] which fuels concerns that such patients should continue to isolate despite lockdowns easing. Our study continues to recruit myeloma patients and we will report COVID-19 vaccine T cell and humoral responses following two doses in due course. Urgent measures should be taken to suitably modify healthcare provision and provide psychological support for these patients. Measures to improve COVID-19 immunity such as additional booster vaccination or passive antibody trials should be prioritised for this patient population.

Acknowledgements

Blood Cancer UK – Funding, Myeloma UK patient panel – Review of questionairre, RUDY patient panel – review of questionnaire and research methodology.

Conflicts of interest

All authors completed the ICMJE disclosure form. The following personal or financial relationships relevant to this manuscript existed during the conduct of the study. MD reports shares in Abingdon Health. SM reports honoraria from Takeda, Janssen, Sanofi and Celgene. MD also reports advisory board from Takeda, Celgene, Janssen, Sanofi, Oncopeptide, Karyopharm and Amgen. DS reports honoraria for Abbvie, Jannsen and Takeda. GC reports honoraria from Celgene, Janssen, Takeda, Amgen, Roche, Sanofi, Onopeptides, Karyopharm and IQVIA. GC also reports research grants from Celgene, Takeda and IQVIA. NG reports horarraria from Janssen and Amgen and research grant from Kyowa Kirin. KMJ reports honoraria, research grant and advisory board from Amgen, Janssen, Kyowa Kirin Hakin and UCB. KMJ is also the president of the Bone Research Society, Co-Chair of the Capture the Fracture Steering Committee in the International Osteoporosis Foundation. KR reports honoraria and research grants from Janssen, Celgene, Takeda and Amgen. He also reports advisory board from Celgene, Takeda, Janssen, Amgen, Abbvie, Sanofi, Oncopeptides, Karyopharm, GSK, Adaptive biotech, Pfizer and speakers bureau from Celgene, Takeda and Adaptive Biotech.

Author contributions and guarantor information

All listed authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and drafting the work or revising it critically for important intellectual content; they gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KR is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Ethics approval

The study is based on the existing RUDYstudy.org platform (LREC 14/SC/0126 & RUDY LREC 17/SC/0501), an established online rare-disease platform with online dynamic consent and patient-reported outcome assessments. IRAS no: 213780, RUDY study Minor amendment 3, HRA approval 28 January 2021.

Karthik Ramasamy[1,2]
Ross Sadler[1]
Sally Jeans[3]
Sherin Varghese[1]
Alison Turner[2]
Jemma Larham[1]
Nathanael Gray[2]
Joe Barrett[2]
Stella Bowcock[4]
Gordon Cook[5]
Chara Kyriakou[6]
Dean Smith[7]
Mark Drayson[8]
Supratik Basu[9,10]
Sally Moore[1,11]
Sarah McDonald[12]
Sarah Gooding[2]
Muhammad K. Javaid[2]

[1]Oxford University Hospitals NHS Trust, [2]Oxford University, [3]RUDY Study Participant Forum Member, Oxford, [4]King's College Hospital NHS Trust, London, [5]Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, [6]University College London Hospitals NHS Trust, London, [7]Nottingham University Hospitals NHS Trust, Nottingham, [8]University of Birmingham, Birmingham, [9]University of Wolverhampton, [10]Royal Wolverhampton NHS Trust, Wolverhampton, [11]Bath Royal United Hospitals, Bath and [12]Myeloma UK, Edinburgh, UK.
E-mail: karthik.ramasamy@ndcls.ox.ac.uk

Keywords: myeloma, COVID-19, vaccination, wellbeing, shielding

First published online 2 August 2021
doi: 10.1111/bjh.17764

Supporting Information

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

Table SI. Characteristics of study participants who reported COVID symptoms and/or reported having PCR testing performed.

Table SII. Level of shielding and reasoning reported by participants in the PREPARE trial.

Table SIII. Vaccination status for 109 study participants in the PREPARE trial and their antibody response.

Fig SI. Participant-reported impact[1] on mental and social well-being due to COVID in the PREPARE trial.

Data SI. RUDY COVID-19 questionnaire.

References

1. Cook G, John Ashcroft A, Pratt G, Popat R, Ramasamy K, Kaiser M, et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. *Br J Haematol*. 2020;**190**(2):e83–6.
2. Sharpley FA, Larham J, Haines A, Djebbari F, Tseu B, Leary H, et al. Myeloma clinical outcomes following the first wave of COVID-19: results from the Thames Valley Cancer Alliance (UK). *Br J Haematol*. 2021;**192**(6):e136–9.
3. Chicca IJ, Heaney JLJ, Iqbal G, Dunn JA, Bowcock S, Pratt G, et al. Antibacterial antibodies in multiple myeloma patients at disease presentation, in response to therapy and in remission: implications for patient management. *Blood Cancer J*. 2020;**10**(11):114.

4. Javaid MK, Forestier-Zhang L, Watts L, Turner A, Ponte C, Teare H, et al. The RUDY study platform – a novel approach to patient driven research in rare musculoskeletal diseases. *Orphanet J Rare Dis*. 2016; **11**(1):150.
5. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;**67**(6):361–70.
6. Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, et al. Low neutralizing antibody responses against Sars-Cov-2 in elderly myeloma patients after the first bnt162b2 vaccine dose. *Blood*. 2021;blood.2021011904. https://doi.org/10.1182/blood.2021011904.
7. Bird S, Panopoulou A, Shea RL, Tsui M, Saso R, Sud A, et al. Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma. *Lancet Haematol*. 2021;S2352-3026(21)00110-1. https://doi.org/10.1016/S2352-3026(21)00110-1.
8. Pimpinelli F, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. *J Hematol Oncol*. 2021;**14**(1):81.
9. Madhumita S, Ellen F, Cyril G, Vincent N, Sarah B, Isobel B, et al. Spike-antibody responses following first and second doses of ChAdOx1 and BNT162b2 vaccines by age, gender, and clinical factors - a prospective community cohort study (Virus Watch). *medRxiv*. 2021;21257102. https://doi.org/10.1101/2021.05.12.21257102
10. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2021;**396**(10267):1979–93.