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Determinants of durable humoral and T cell immunity in myeloma patients following COVID-19 vaccination

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Abstract

Objective: To describe determinants of persisting humoral and cellular immune response to the second COVID-19 vaccination among patients with myeloma.

Methods: This is a prospective, observational study utilising the RUDYstudy.org platform. Participants reported their second and third COVID-19 vaccination dates. Myeloma patients had an Anti-S antibody level sample taken at least 21 days after their second vaccination and a repeat sample before their third vaccination.

Results: 60 patients provided samples at least 3 weeks (median 57.5 days) after their second vaccination and before their third vaccination (median 176.0 days after

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second vaccine dose). Low Anti-S antibody levels (<50 IU/mL) doubled during this interval ($p = .023$) and, in the 47 participants with T-spot data, there was a 25% increase negative T-spot tests ($p = .008$). Low anti–S antibody levels prior to the third vaccination were predicted by lower Anti-S antibody level and negative T-spot status after the second vaccine. Independent determinants of a negative T-spot included increasing age, previous COVID infection, high CD4 count and lower percentage change in Anti-S antibody levels.

Conclusions: Negative T-spot results predict low Anti-S antibody levels (<50 IU/mL) following a second COVID-19 vaccination and a number of biomarkers predict T cell responses in myeloma patients.

KEYWORDS
COVID-19 vaccination, myeloma, predictors

Novelty statements

What is the new aspect of your work?

Longitudinal sampling to assess humoral and T cell response in a cohort of myeloma patients following COVID-19 vaccination heralds a new approach to assessing immunity and the factors that influence this, in this vulnerable patient population.

What is the central finding of your work?

The central finding is that successful antibody response, in myeloma patients, to the second COVID-19 vaccination, is predicted by a negative T spot result and there are measurable biomarkers that predict T-cell response.

What is (or could be) the specific clinical relevance of your work?

The clinical relevance of these findings is that they contribute to the understanding of vaccine response in myeloma patients, paving the way for further studies to identify which patients may require additional vaccinations to confer adequate protection or alternative COVID-19 treatments.

1 | INTRODUCTION

Myeloma treatment requires immune-suppressive chemotherapy and has previously demonstrated universally poor vaccine-induced seroconversion rates resulting in high risk of poor outcomes following COVID-19 infection.[1] Analysis of the pre-COVID vaccine era revealed an overall mortality rate of 33% in hospitalised myeloma patients.[2] Understanding drivers of poor response to vaccination and potential salvage strategies is key to managing both COVID-19 risk and myeloma optimally.

To address these evidence gaps, in December 2020 we initiated the PREPARE study, a national, web-based, prospective study of adults with multiple myeloma (MM) that investigated SARS-CoV-2 immunity acquired by infection or vaccination.[1] Initial data showed that 50% of patients who received Astra-Zeneca/Oxford and 44% who received Pfizer/BioNTech vaccination had a successful immune response ≥3 weeks after their first dose ($n = 107$).[3] Following two doses of COVID-19 vaccination ($n = 214$), 92.7% of patients were found to elicit Anti-S protein antibodies.[3] Those with a positive Anti-N antibody (natural infection) had a significantly higher anti-S protein response ($p = .002$).[3]

In other studies, it has been reported that up to 50% of myeloma patients elicit a T-cell response which correlates with Anti-S antibody response, as observed in our patient population.[4] Equally approximately 70% of myeloma patients may have detectable levels neutralisation antibody response.[5]

Here we describe changes in humoral and T cell response between vaccine doses, and identify their patient, COVID-19 and myeloma-related determinants.

2 | METHODS

The Prepare project within the RUDY study (LREC 14/SC/0126 & RUDY LREC 17/SC/0501) focuses on the immune response after

TABLE 1 Relationship between the categorical predictors and the two outcome variables (S-protein and T-spot levels, respectively) before the third vaccine dose.

	Anti-S antibody outcome ($n = 60$)			T-spot outcome ($n = 47$)		
Predictors	**<50 IU/mL**	**≥50 IU/mL**	***p*-value**	**Negative**	**Positive**	***p*-value**
Sex[a]						
Female	5 (8.3%)	23 (38.3%)	0.379	10 (21.3%)	12 (25.5%)	0.248
Male	9 (15.0%)	23 (38.3%)		16 (34.0%)	9 (19.1%)	
Ethnicity[a]						
White-UK	13 (21.7%)	40 (66.7%)	1.000	20 (42.6%)	21 (44.7%)	0.027
Others	1 (1.6%)	6 (10.0%)		6 (12.8%)	0 (0.0%)	
N-protein levels after second vaccine dose[a]						
Negative (≤1.4 IU/mL)	14 (23.3%)	43 (71.7%)	1.000	26 (55.3%)	19 (40.4%)	0.194
Positive (>1.4 IU/mL)	0 (0.0%)	3 (5.0%)		0 (0.0%)	2 (4.3%)	
S-protein levels after second vaccine dose[a]						
<50 IU/mL	4 (6.7%)	2 (3.3%)	0.023	5 (10.6%)	0 (0.0%)	0.056
≥50 IU/mL	10 (16.7%)	44 (73.3%)		21 (44.7%)	21 (44.7%)	
T-spot levels after second vaccine dose[b]						
Negative	11 (18.3%)	16 (26.7%)	0.014	16 (34.0%)	4 (8.5%)	0.008
Positive	3 (5.0%)	27 (45.0%)		9 (19.1%)	16 (34.0%)	
Unknown	0 (0.0%)	3 (5.0%)		1 (2.1%)	1 (2.1%)	
Type of vaccine[b]						
Oxford/AstraZeneca	5 (8.3%)	18 (30.1%)	0.933	10 (21.3%)	10 (21.3%)	0.168
Pfizer/BioNTech	5 (8.3%)	14 (23.3%)		10 (21.3%)	3 (6.4%)	
Unknown	4 (6.7%)	14 (23.3%)		6 (12.8%)	8 (17.0%)	
Myeloma treatment at second vaccine date[b]						
CD38 antibody	2 (3.3%)	9 (15.0%)	0.664	4 (8.5%)	4 (8.5%)	0.065
No therapy	3 (5.0%)	12 (20.0%)		3 (6.4%)	9 (19.1%)	
Other	5 (8.3%)	9 (15.0%)		9 (19.1%)	3 (6.4%)	
Unknown	4 (6.7%)	16 (26.7%)		10 (21.3%)	5 (10.6%)	
Myeloma disease status at second vaccine date[b]						
CR/VGPR	2 (3.3%)	19 (31.7%)	0.288	10 (21.3%)	9 (19.1%)	0.674
PR/stable	5 (8.3%)	9 (15.0%)		5 (10.6%)	5 (10.6%)	
Progressive/relapse	1 (1.6%)	3 (5.0%)		1 (2.1%)	2 (4.3%)	
Unknown	6 (10.0%)	15 (25.0%)		10 (21.3%)	5 (10.6%)	

Note: Highlighted *p*-values correspond to the significant variables.
[a]Fisher's exact test.
[b]Chi-square test.

COVID-19 vaccination.[1–3] South Central Berkshire B Research Ethics Committee approved the study.

2.1 | Data description

Participants self-reported their second and third COVID-19 vaccine type and dates via the online Rudy platform. Sample boxes were then posted, containing serum, EDTA and heparin blood tubes 21 days after the second vaccine and before their third vaccine. Returned samples were analysed for Anti-S antibody levels and other variables, as described below.

2.2 | Description of data variables

Sample collection and analysis described in Ramasamy et al.[3]

The primary outcome was to measure the S-protein concentration ≥50 IU/mL (anti-S-antibody) and (negative) T spot result in the second sample prior to the third vaccine dose and determining factors that predict response. There were 18 predictors namely: age, ethnicity, myeloma disease status at time of second vaccine date, myeloma treatment at second vaccine date, vaccine name, percentage change in Anti-S antibody levels after the second vaccine and laboratory findings after the second vaccine dose: serological evidence of COVID-19

TABLE 2 Estimated crude and adjusted odds ratios of significant predictors of S-protein concentration <50 IU/mL and negative T-spot level before third vaccine dose.

Predictors	Crude OR (95% CI)	Adjusted OR (95%)	*p*-value (LR test)
Anti-S antibody<50 IU/mL outcome[a]			
T spot (ref: positive)			
Negative	18.615 (2.150, 161.192)	16.921 (1.413, 202.641)	.006
Negative T-spot outcome[b]			
Pre third vaccine dose N-antibody	0.260 (0.019, 3.619)	0.024 (0.000, 3.214)	.020
Post second vaccine dose CD4 (continuous)	0.059 (0.002, 1.811)	0.0003 (0.000, 0.686)	.007
Age (continuous)	1.087 (1.000, 1.181)	1.162 (1.010, 1.338)	.009
% Change between			
Anti-S antibody (continuous)	0.789 (0.427, 1.458)	0.482 (0.223, 1.040)	.025

Note: The sample size of the training set for the anti-S protein prediction = 47 & for the T cell positivity prediction = 38.
[a]Significant predictor of best fitted binary logistic regression model to predict S-protein concentration <50 IU/mL before the third vaccine dose with 80.0% accuracy, Nagelkerke pseudo R^2 = .520, and AUC = 0.875 (0.630, 1.000). Other covariates in the adjusted model included Post second vaccine dose Anti-S antibody (continuous), NK cells per μL (continuous), and Ethnicity.
[b]Significant predictors of best fitted binary logistic regression model to predict negative T-spot levels; with 55.5% accuracy, Nagelkerke pseudo R^2 = .511, and AUC = 0.650 (0.172, 1.000). *p*-value (LR test) is estimated based on Likelihood Ratio (LR) test. Best model was obtained using stepwise regression (forward and backward elimination) method. Other covariates in the adjusted model included post second vaccine dose: IgG, CD8, FLC, nk.

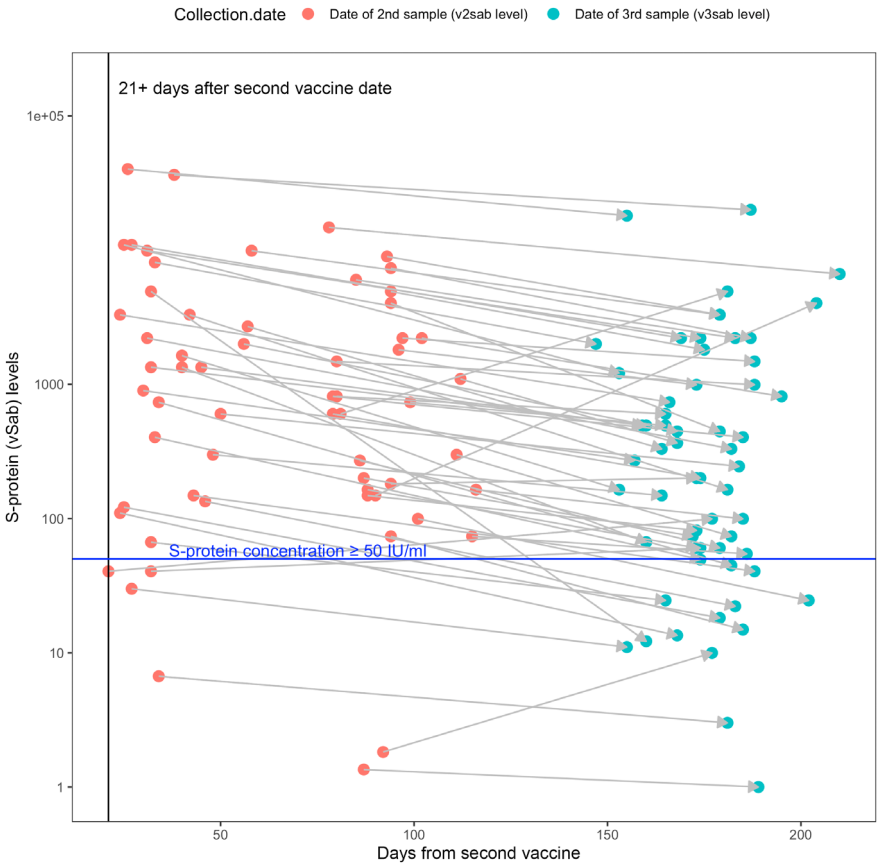

FIGURE 1 Change in S protein levels after the second COVID-19 vaccination. A slope graph visualising the S-protein levels from 21 days after second vaccine date until the pre third vaccine vaccine collection dates (n = 60). Median time from the second vaccine date till post second vaccine sample collection date was 57.5 days, and the median time from the second vaccine dose till the pre third vaccine sample collection date was 176.0 days.

infection as defined by a N-protein level >1.4 IU/mL, general immune profile: IgG, IgA, IgM, FLC, Lymphocyte count, CD4, CD8, B lymphocyte and Natural killer cells, Anti-S antibody and T spot.

2.3 | Statistical analysis

Descriptive statistics (Tables 1 and 2) and tests of association (Table 1) were performed, and the change in S-protein concentration

TABLE 3 Baseline characteristics of myeloma patients who met the study's inclusion criteria for the analysis of the COVID-19 Anti-S antibody concentration and T-spot levels after second vaccination.

Characteristics	Anti-S antibody group[a] ($n = 60$)	T-spot data[b] ($n = 47$)
Sex		
Female	28(46.7%)	22(46.8%)
Male	32(53.3%)	25(53.2%)
Ethnicity		
White-UK	53(88.3%)	41(87.2%)
Others	7(11.7%)	6(12.8%)
Type of vaccine		
Oxford/AstraZeneca	23(38.3%)	20(42.6%)
Pfizer/BioNTech	19(31.7%)	13(27.7%)
Unknown	18(30.0%)	14(29.8%)
Myeloma disease status at second vaccine date		
CR/VGPR	21(35.0%)	19(40.4%)
PR/stable	14(23.3%)	10(21.3%)
Progressive/relapse	4(6.7%)	3(6.4%)
Unknown	21(35.0%)	15(31.9%)
Myeloma treatment at second vaccine date		
CD38 antibody	11(18.3%)	8(17.0%)
No therapy	15(25.0%)	12(25.5%)
Other	14(23.3%)	12(25.5%)
Unknown	20(33.3%)	15(31.9%)
Anti-N antibody levels after second vaccine dose		
Negative (≤1.4 IU/mL)	57(95.0%)	45(95.7%)
Positive (>1.4 IU/mL)	3(5.0%)	2(4.3%)
Anti-N antibody levels before third vaccine dose		
Negative (≤1.4 IU/mL)	57(95.0%)	45(95.7%)
Positive (>1.4 IU/mL)	3(5.0%)	2(4.3%)
Anti-S antibody levels after second vaccine dose		
<50 IU/mL	6(10.0%)	5(10.6%)
≥50 IU/mL	54(90.0%)	42(89.4%)
Anti-S antibody levels before third vaccine dose		
<50 IU/mL	14(23.3%)	8(17.0%)
≥50 IU/mL	46(76.7%)	39(83.0%)
T-spot levels after second vaccine dose		
Negative	27(45.0%)	20(42.6%)
Positive	30(50.0%)	25(53.2%)
Unknown	3(5.0%)	2(4.3%)
T-spot levels before third vaccine dose		
Negative	26(55.3%)	26(43.3%)
Positive	21(35.0%)	21(44.7%)
Unknown	13(21.7%)	0 (0%)

Abbreviations: CR/VGPR, complete remission/very good partial remission; PR/stable, partial remission/stable.

[a]Restricted data to 60 Myeloma patients who have recorded S-protein results at least 21 days from second vaccine dose, and another sample before third vaccine dose.

[b]Excluded data of 13 Myeloma patients from the patient cohort (defined by [a]), but had unknown status for T-spot levels after the second vaccine.

levels from 21 days after second vaccine date for each sample were visualised using an informative slope graph (Figure 1). A multivariate binary logistic regression (Table 2) used an 80%–20% split rule to obtain training (80%) and validation (20%) datasets for the purpose of cross-validating or assessing the fitted logistic regression models.

Among six different variable-selection techniques adopted, the classical stepwise-regression selection method resulted in the best fitted logistic regression model (with minimal Akaike Information Criterion value). The percentage accuracy measure, the Nagelkerke pseudo r-squared value and area under the ROC curve (AUC) were estimated to assess model fit. Finally, the crude and adjusted odds ratios (OR) with 95% confidence intervals were used with significance determined at p-value, $p < .05$.

3 | RESULTS

Sixty adults with myeloma provided blood samples at least 3 weeks (median 57.5 days) after second vaccine and before the third vaccine (median 176.0 days after the second vaccine) (Table 3). There was no evidence of incidental COVID-19 infection between the two sample periods as measured by Anti-N antibody titres. The proportion of patients with low Anti-S antibody levels (<50 IU/mL) doubled between the two sample points ($n = 6$ vs. $n = 14$ respectively, $p = .023$) (Table 1). In comparison, there was a smaller increase in negative T-spot results ($n = 20$ vs. $n = 25$, $p = .008$) (Table 1). The median values for Anti-S and Anti-N antibodies and the general immune profile are shown in Table 4.

The results of the adjusted and unadjusted multivariate logistic regression of Anti-S antibody and T-spot results before the third vaccine dose are summarised in Table 2. Loss of humoral immune response was predicted by Anti-S antibody level (adjusted OR = 1.006, 95% CI = 1.000–1.0013; $p = .006$) and negative T-spot status (adjusted OR = 0.068, 95% CI = 0.007–0.688; $p = .008$) after the second vaccine. Independent determinants of a negative T-spot included increasing age, no evidence of previous COVID infection, lower CD4 count and smaller percentage change in Anti-S antibody levels after the second vaccine (Table 2).

4 | DISCUSSION

Our results indicate that immune response to the COVID-19 vaccine wanes over time. The proportion of patients with low Anti-S antibody levels (<50 IU/mL) doubled between the two sample points. We have highlighted several clinically applicable biomarkers that could identify patients who are more likely to lose humoral and cellular immunity against COVID-19 following vaccination.

Predictors of immune response following vaccination can help clinicians to identify patients who may require alternative treatments for better protection, such as monoclonal antibodies or newer

TABLE 4 Median values of numerical characteristics of Myeloma patients who met the study's inclusion criteria for the analysis of the COVID-19 S-protein concentration and T-spot levels after second vaccination.

Continuous characteristics Median (Q1, Q3)	Anti-S antibody group ($n = 60$)	T-spot group ($n = 47$)
Age	65.50 (59.75, 73.25)	66.00 (60.50, 73.00)
Anti-N antibody (>1.4 IU/mL) Post second vaccine dose	2.26 (1.92, 3.82)	3.82 (3.04, 4.59)
Anti-N antibody (>1.4 IU/mL) Pre third vaccine dose	1.98 (1.87, 2.65)	2.65 (2.32, 2.99)
Anti-S antibody (IU/mL) Post second vaccine dose	1174.20 (216.20, 3779.90)	1341.55 (314.00, 4779.68)
Anti-S antibody (IU/mL) Pre third vaccine dose	469.00 (165.75, 1971.25)	504.00 (131.50, 2061.00)
Change in Anti-S antibody (%)	−0.65 (−0.79, −0.47)	−0.64 (−0.78, −0.43)
General immune profile after second vaccine dose		
IgG (per g/L)	7.06 (3.46, 10.84)	8.09 (3.75, 11.75)
IgA (per g/L)	0.51 (0.18, 1.15)	0.48 (0.18, 1.28)
IgM (per g/L)	0.23 (0.11, 0.39)	0.26 (0.11, 0.42)
FLC (per mg/L)	1.29 (0.93, 3.30)	1.23 (0.96, 3.44)
LC (per uL)	0.32 (0.28, 0.51)	0.97 (0.78, 1.53)
CD4 cells (per μL)	0.28 (0.19, 0.50)	0.32 (0.24, 0.45)
CD8 cells (per μL)	0.11 (0.03, 0.20)	0.28 (0.18, 0.50)
Bly cells (per μL)	0.16 (0.08, 0.27)	0.10 (0.03, 0.20)
nk cells ($\times 10^{-3}$ per μL)		0.16 (0.08, 0.26)

Note: The summary statistics of the numerical data are computed based on the median with the first quartile (Q1) and third quartile (Q3) values due to the high variability and skewness in the observed data.
Abbreviations: Bly, B lymphocytes; LC, lymphocyte count; nk, NK cells.

COVID vaccination strategies and studies[6] or advise patients to shield more effectively. Poor serological responses in myeloma patients receiving BCMA and CD38 targeted monoclonal antibody therapies has been reported[7] although this finding was not observed in this study. Another study exploring serological responses of 157 MM patients following two doses of BNT162b2 mRNA COVID-19 did not identify any predictors of poor humoral response with only 33.9% of haemato-oncology patients maintaining a good vaccine response.[8]

A similar decline in the durability of N protein antibody titres following a second vaccine dose (median of 111 days, range 37–252 days) has been observed in 82 patients with haematological malignancies (29 myeloma patients) following two doses of COVID-19 vaccine.[9] Patients without a detectable T cell response following the second dose remained negative and an initial response ($n = 12$) was maintained in 42% ($n = 5$). Patients with Oxford/AstraZeneca vaccination had higher neutralisation antibody responses to all SARS-Cov2 strains in comparison to Pfizer/ BionTECH vaccination. We did not observe these results although the assays are not directly comparable.

5 | LIMITATIONS

This study has several limitations. First, we have investigated the response to the Pfizer/BioNTech and Oxford/AstraZeneca vaccines only. The durability after other vaccines may be different and may differ with subsequent re-vaccination. Second, although patients generated an encouraging antibody response, uncertainty remains regarding the antibody threshold for disease protection.[9] Therefore, results should be interpreted with caution. Third, only a proportion of participants (60 of 224) satisfied the study's main inclusion criteria and therefore it is possible that a larger sample size may yield more nuanced results. Finally, due to limited number of patients in our study showing evidence of natural infection, the question of vaccine durability following natural infection and according to COVID-19 variant is unexplored.

6 | CONCLUSION

Our study has identified negative T spot status as a determinant of serological durability to the COVID-19 vaccine in patients with multiple myeloma. No apparent association with remission status or type of anti-myeloma therapy was observed. With ongoing waves of COVID-19, these predictors enable identification of patients who may require additional vaccine doses and alternative COVID-19 treatments.

AUTHOR CONTRIBUTIONS

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; final approval of the version to be published; and agreement 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. Karthik Ramasamy 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. *Concept and design*: Muhammad K. Javaid, Karthik Ramasamy, Ross Sadler, Sarah Gooding, Sally Moore, Sally Jeans, Sarah McDonald and Shelagh McKinley. *Acquisition, analysis, or interpretation of data*: All authors. *Drafting of the manuscript*: Clement Twumasi, Sally Moore, Sherin Varghese, Gaurav Agarwal, Karthik Ramasamy, Ross Sadler and Muhammad K. Javaid. *Critical revision of the manuscript for important intellectual content*: All authors. *Statistical analysis*: Clement Twumasi, Muhammad K. Javaid. *Obtained funding*: Karthik Ramasamy and Muhammad K. Javaid. *Administrative, technical, or material support*: Vicky Gamble, Joe Barrett, Oluremi Carty, Sherin Varghese, Alison Turner and Nathanael Gray. *Supervision*: Muhammad K. Javaid and Karthik Ramasamy.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Patients have consented to anonymised data sharing for research and publication purposes.

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