Serological response to the BNT162b2 mRNA or ChAdOx1 nCoV-19 COVID-19 vaccine after first and second doses in patients with plasma cell disorders: influence of host and disease factors

We read with interest Avivi *et al.*[1] evaluating humoral response to two doses of BNT162b2 mRNA vaccine in multiple myeloma (MM) at manufacturer's dosing interval. Suboptimal response to one[2–4] and both doses[5] of coronavirus disease 2019 (COVID-19) vaccines in MM have also been reported elsewhere. Administration of COVID-19 vaccines is important to protect this vulnerable cohort. Recognised humoral and cellular immune dysfunction in plasma cell disorders (PCDs), which is multi-factorial and related to the disease itself, age, comorbidities and immunosuppressive therapies, may reduce vaccination protection. The UK experience differs as a substantial proportion of the population received ChAdOx1 nCoV-19, and intervals were extended to 12 weeks in December 2020.[6] With emergence of the Delta variant, from May 2021, identified immunosuppressed individuals had their second doses brought forward to 8 weeks. We report findings in PCD receiving both doses of COVID-19 vaccines within the UK vaccination programme, and the influence of dosing interval.

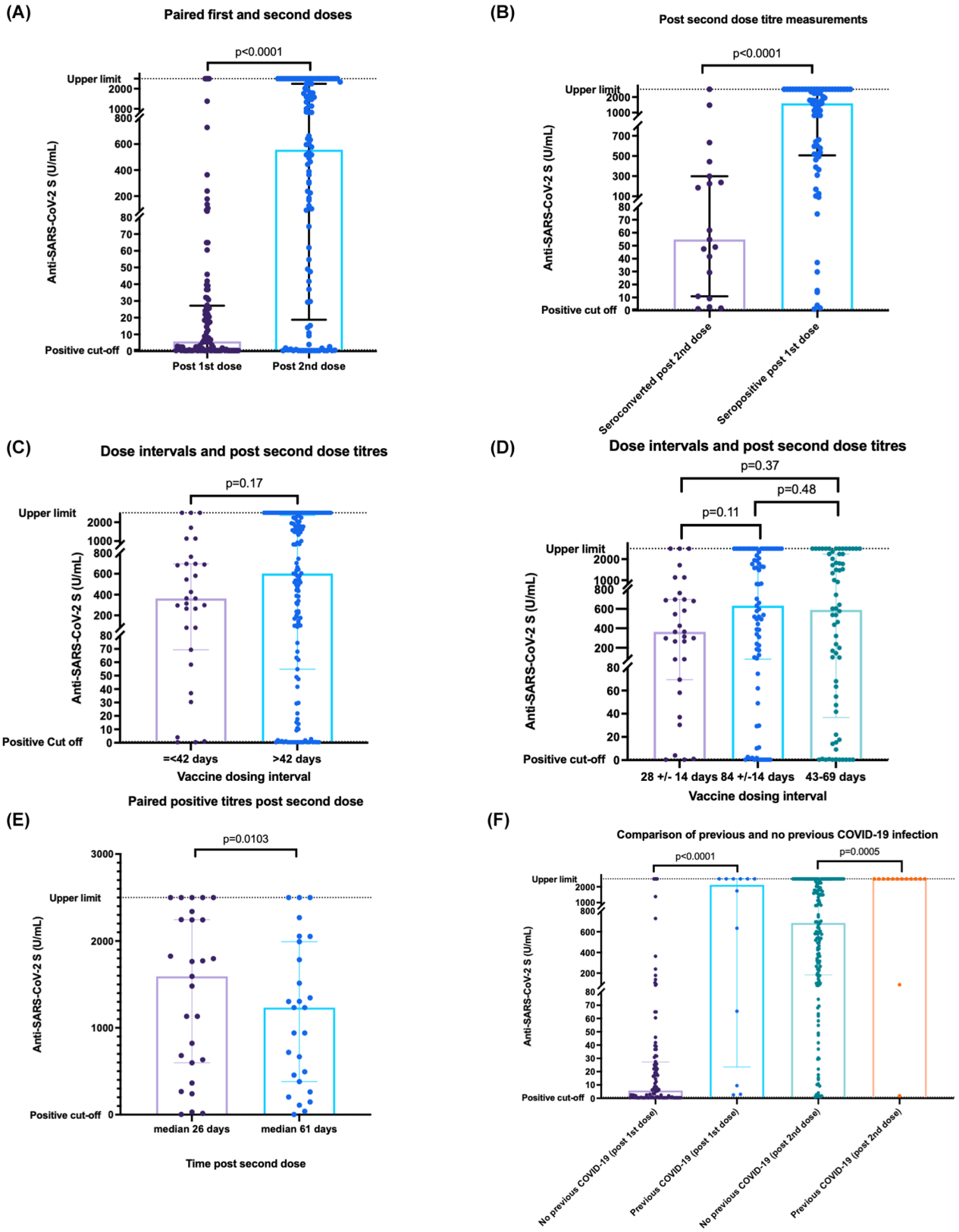
A clinical audit was conducted at University College London Hospitals between December 2020 and July 2021 of anti-spike protein antibody testing in patients with PCDs after each vaccine dose. Some had routine nucleocapsid antibody monitoring,[7] those receiving chemo-immunotherapy (CIT) have 4-weekly routine swabs. Patient and treatment characteristics were retrieved from medical records (Table SI). Full methods are described in Data S1.

A total of 188 patients [monoclonal gammopathy of undetermined significance/smouldering MM (10), MM (155), systemic AL amyloid (18), other PCD (5)], with a median age of 64 years, received both vaccine doses [BNT162b2 (69%), ChAdOx1 nCoV-19 (25%), unknown (6%)]. Excluding previous COVID-19 infection, 174 patients were tested after their second dose [median (range) 41·5 (10–96) days] and of these, 104 were also tested after their first dose [median (range) 44 (21–96) days].

The seropositivity rate after the first dose was 67% (70/104); of those with available negative baseline antibody test, 68% (30/44) seroconverted. After the second dose, 89% (154/174) were seropositive; of those with negative baseline antibody, 90% (61/68) seroconverted. Analysing paired samples, median titres were higher after the second dose than after the first dose (Fig 1A).

Active CIT, four lines of therapy, a less than partial response (PR) disease response, light-chain (LC) disease, male gender and not responding to first dose were significant factors for not responding to the second dose and remained significant after adjusting for disease response (Table I). No difference in response was found by CIT type, vaccine type, dosing intervals (>42 vs. 42 days) or time to serology sample. Dosing interval analysis showed no difference when re-categorised (28 $\pm$ 14, 43–69 and 84 $\pm$14 days), nor was there difference in titres with both categorisations (Fig 1C, D). Significantly higher titres occurred in females, non-LC isotype and four lines of treatment (Figure S1). Eligibility for booster dosing in the OCTAVE-DUO study will utilise 400 u/ml as cut-off based on lower third titres of the OCTAVE study.[8] We explored disease and patient-related factors associated with suboptimal response (defined here as 400 u/ml) after a second dose, found in 43% (75/174) of patients. Age $\geq$70 years, male gender, four lines of treatment were significant independent risk factors (anti-CD38 therapy of borderline significance) (Figure S2, Table SII). No difference was observed with vaccine interval, vaccine type or active CIT. We analysed patients with PCDs altogether (Figure S3A shows post second dose titres by underlying diagnosis), as future vaccination policy will be unlikely to discriminate between them. A larger cohort with similar dose-interval and vaccine-type analyses, by subgroups of patients with PCDs will help us understand differences in immune response and hence disease risks amongst these patients.

In all, 19 of 34 (56%) patients who were seronegative after the first dose, seroconverted after the second dose; however, antibody titres were significantly lower than in those who seroconverted after the first dose (Fig 1B). A total of 27 patients were tested twice after their second doses; titres declined over time (Fig 1E). Titres in 14 patients with previous COVID-19 infection, were over a 100-times higher after the first dose and remained significantly higher after the second dose, compared to those without previous infection (Fig 1F; Figure S3B).



This real-world analysis of opportunistic testing in patients with PCDs reports a 67% seropositive response rate after the first dose,[3] rising to 89% after the second dose despite extended dosing in our present cohort. Response rates and median titres remained lower than in healthy adults.[1,5] Nearly two-thirds of those seronegative after the first dose

Fig 1. All titres were quantified by Elecsys (Roche, Basel, Switzerland) anti-SARS-CoV-2 S assay (spike); lowest cut-off 0·4 u/ml, positive cut-off 0·8 u/ml, upper limit 2500 u/ml. (A) Comparison of all paired post first and post second dose measurements (n = 104). Post first dose median (IQR) 5·795 (0·4–27·20) u/ml *versus* post second dose 557·0 (18·80–2245) u/ml, $P < 0·0001$. (B) Comparison of post second dose antibody titres in patients who only seroconverted after second dose (n = 19) *versus* patients with positive response after one dose (n = 69); median (IQR) 54·8 (10·9–299) u/ml *versus* 1593 (506–2500) u/ml, $P < 0·0001$. (C) Comparison of post second dose titres based on vaccine dosing intervals ≤42 (n = 31) vs. >42 days (n = 143); ≤42-day interval median (IQR) 364 (69·4–696) u/ml *versus* >42-day interval 602 (54·8–2355) u/ml, P = 0·17. (D) Comparison of post second dose titres based on vaccine dosing intervals, 28 ± 14 days (n = 31), 43–69 days (n = 66) and 84 ± 14 days (n = 77); median (IQR) 364 (69·40–696) u/ml, 589 u/ml (IQR 36·75–2244) and 633 (83·1–2500) u/ml (28 ± 14 days vs. 84 ± 14 days, P = 0·11; 28 ± 14 days vs. 43–83 days, P = 0·37; 43–83 days vs. 84 ± 14 days, P = 0·48). (E) Paired repeated positive antibody titres post second dose. First [median (range) 26 (11–93) days] and second measurements [median (range) 61 (36–161) days] (n = 27), median (IQR) 1593 (596–2245) vs. 1233 (381–1993) u/ml, P = 0·0103. (F) Comparison of post first and post second dose positive response in patients with previous and no previous COVID-19 infection. Post first dose no previous COVID-19 n = 104 median 5·795 U/mL (IQR 0·4–27.20), previous COVID-19 (n = 12) median 2121 U/mL (IQR 23·48–2500) $P < 0·0001$, post second dose no previous COVID-19 (n = 154) median 684.5 U/mL (IQR 182·8–2391), previous COVID-19 (n = 14) median 2500 U/mL (IQR 2500–2500) $P < 0·0005$. IQR, interquartile range.

Table I. Univariate analysis of serological response to second vaccine dose including adjusted odds ratios for underlying plasma cell disorder response at the time (N = 174).

Variable	N (%)	Had serological (positive) response, n (%)	OR (95% CI)	P	Adjusted OR (95% CI)	P
Age at first vaccine dose, years						
<70	121 (69·5)	109 (90·1)	Reference	0·3	Reference	0·6
≥70	53 (30·5)	45 (84·9)	0·62 (0·24–1·62)		0·77 (0·28–2·14)	
Sex						
Male	100 (57·5)	83 (83·0)	Reference	0·02	Reference	0·02
Female	74 (42·5)	71 (95·9)	4·85 (1·36–17·22)		4·74 (1·30–17·25)	
Vaccine type						
BNT162b2 mRNA	118 (72·4)	103 (87·3)	Reference	0·5	Reference	0·7
ChAdox-nCoV-19	45 (27·6)	41 (91·1)	1·49 (0·47–4·77)		1·26 (0·38–4·13)	
Undisclosed	11					
Disease isotype						
IgG/IgA	122 (75·3)	113 (92·6)	Reference	0·03	Reference	0·02
κLC/λLC	40 (24·7)	32 (80·0)	0·32 (0·11–0·89)		0·29 (0·10–0·85)	
Not applicable	12					
Lines of treatment including current*						
0–1	75 (43·1)	69 (92·0)	Reference	0·01	Reference	0·03
2–3	73 (42·0)	67 (91·8)	0·97 (0·30–3·16)		1·13 (0·32–3·96)	
≥4	26 (14·9)	18 (69·2)	0·20 (0·06–0·64)		0·24 (0·07–0·86)	
Current response						
SD/PD	36 (22·9)	28 (77·8)	Reference	0·04	–	–
CR/VGPR/PR	121 (77·1)	110 (90·9)	2·86 (1·05–7·77)			
Unknown	17					
Currently on CIT						
No	31 (17·8)	31 (100)	Reference	0·02	Reference	N/A
Yes	143 (82·2)	123 (86·0)	N/A		N/A	
Immunoparesis						
No	26 (15·5)	24 (92·3)	Reference	0·5	Reference	0·4
Yes	142 (84·5)	124 (87·3)	0·57 (0·12–2·64)		0·39 (0·05–3·11)	
Unknown	6					
IgA (excluding those with IgA myeloma)						
<0·8	102 (71·8)	89 (87·3)	Reference	0·4	Reference	0·2
≥0·8	40 (28·2)	37 (92·5)	1·80 (0·48–6·69)		2·67 (0·57–12·56)	
Unknown	6					
IgM (excluding those with IgM myeloma)						
<0·4	133 (79·2)	115 (86·5)	Reference	0·3	Reference	0·2
≥0·4	35 (20·8)	33 (94·3)	2·39 (0·52–10·87)		3·72 (0·47–29·61)	
Unknown	6					

Table I. (*Continued*)

Variable	*N* (%)	Had serological (positive) response, *n* (%)	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
IgG (excluding those with IgG myeloma)						
<6·0	51 (71·8)	41 (80·4)	Reference	0·7	Reference	0·3
≥6·0	20 (28·2)	17 (85·0)	1·38 (0·34–5·65)		2·32 (0·41–13·05)	
Unknown	1					
Current proteasome inhibitor-based treatment						
No	120 (69·0)	105 (87·5)	Reference	0·5	Reference	0·5
Yes	54 (31·0)	49 (90·7)	1·40 (0·48–4·07)		1·47 (0·54–3·97)	
Current IMiD-based treatment						
No	131 (75·3)	118 (90·1)	Reference	0·3	Reference	0·2
Yes	43 (24·7)	36 (83·7)	0·57 (0·21–1·53)		0·57 (0·23–1·42)	
Current anti-CD38 treatment						
No	129 (74·1)	115 (89·1)	Reference	0·7	Reference	>0·9
Yes	45 (25·9)	39 (86·7)	0·79 (0·28–2·20)		0·99 (0·36–2·71)	
ASCT within 12 months						
No	153 (87·9)	133 (86·9)	Reference	0·1	Reference	N/A
Yes	21 (12·1)	21 (100)	N/A		N/A	
Dose interval, days						
28 (±14)	31 (28·7)	29 (93·5)	Reference	0·5	Reference	0·2
84 (±14)	77 (71·3)	69 (89·6)	0·59 (0·12–2·97)		0·22 (0·02–1·99)	
Outside either range	66					
Dose interval, days						
≤42	31 (17·8)	29 (93·5)	Reference	0·3	Reference	0·1
>42	143 (82·2)	125 (87·4)	0·48 (0·11–2·18)		0·21 (0·03–1·66)	
Response to first vaccine dose**						
No	34 (32·7)	19 (55·9)	Reference	<0·001	Reference	<0·001
Yes	70 (67·3)	69 (98·6)	54·47 (6·76–439·08)		52·25 (6·39–431·42)	
Unknown	70					
Time from second dose until sample, days						
≤28	84 (48·3)	75 (89·3)	Reference	0·8	Reference	>0·9
>28	90 (51·7)	79 (87·8)	0·86 (0·34–2·20)		1·01 (0·38–2·68)	

ASCT, autologous stem cell transplantation; CD, cluster of differentiation; CI, confidence interval; CIT, chemo-immunotherapy; CR, complete response; Ig, immunoglobulin; IMiD, immunomodulatory imide drug; LC, light-chain; N/A, not available; OR, odds ratio; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Disease response variable used for adjusted OR was CR/VGPR/PR *versus* SD/PD.

*The reported *P* value is from a likelihood ratio test comparing a logistic regression model with lines of treatment as a covariate to one without.

**There is a borderline association between presence of a post-dose 1 response and response post-dose 2 ($P = 0{\cdot}05$), with patients with missing dose 1 responses being more likely to respond post-dose 2. A sensitivity analysis assuming all missing data shows the opposite association to the observed data has an OR of 2·44 (95% CI 0·84–7·03), $P = 0{\cdot}1$. While not significant, still provides some evidence of a positive association between post-dose 1 and post-dose 2 response. One patient tested borderline above the defined positive cut-off for response post first dose (0·81 u/ml) and subsequently tested negative post second dose.

responded to the second dose. Previous COVID-19 infection produced significantly higher titres, in keeping with other COVID-19 infected patients with MM.[5]

We describe association of age ≥70 years, male gender, four lines of treatment with suboptimal humoral response. Lower humoral and cellular responses with older age have been reported.[9] Association with male gender and older age may be related to higher frequency of autoantibodies to type-1 interferons that impair their ability to block severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.[10,11] We found no association of anti-myeloma agent types with serological response in contrast to reports of B-cell maturation antigen (BCMA)-targeted[5] and anti-CD38 therapies.[4,5] A borderline significant effect on optimal response was observed in patients receiving anti-CD38 therapy. Only 36% of our present patients were exposed to anti-CD38 and even less to BCMA-targeted therapies (1·6%), as the latter are not yet widely available in the UK. We found no difference in response or titres with vaccine types, although BNT162b2 mRNA has shown higher vaccine effectiveness against the delta variant compared to ChAdOx1 nCoV-19 elsewhere.[12]

We did not assess cellular immunity, an important aspect of vaccine immunogenicity. Further studies of cellular and

humoral responses to vaccination are awaited as correlates of humoral response and immunogenicity markers with disease protection from COVID-19 in PCDs are unknown.[13,14] A third of our present seropositive patients with PCDs had a suboptimal response (<400 u/ml) and may be at risk of reduced protection despite measurable humoral response.

Patients with PCDs are at 33% estimated risk of death from SARS-CoV-2,[15] hence should be prioritised for shorter dosing intervals. Significant predictors of seronegative and suboptimal response after two doses can be utilised to select patients for booster doses; timing doses for when particular risk factors have been eliminated. Prophylactic strategies (e.g. anti-spike monoclonal antibodies) in patients identified at high-risk of vaccine response failure or in whom vaccination response is suboptimal should be explored. Results of these trials alongside correlates of protection applicable to PCDs will be eagerly awaited.

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Conflicts of interest

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

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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. Comparison of post second dose titres based on patient or disease-related factors.

Fig S2. Forest plot of univariate analysis of optimal response (defined as titres ≥400 u/ml).

Fig S3. Anti-SARS-CoV-2 S titre comparisons based on plasma cell diagnosis and available baseline anti-SARS-CoV-2 S Titres in patients with previous COVID-19 infection.

Table SI. Baseline patient and plasma cell disorder characteristics after first and second dose of a COVID-19 vaccine.

Table SII. Multivariate analysis of optimal response to second vaccine dose.

Data S1. Supplementary Methods.

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