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SHORT REPORT

Depletion of CD38-positive regulatory T cells by anti-CD38 monoclonal antibodies induces a durable response to SARS-CoV-2 vaccination in patients with plasma cell dyscrasia

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Summary

This study reports the relationship between CD38$^+$ regulatory T cells (Tregs) and messenger RNA coronavirus disease 2019 (mRNA-COVID-19) vaccination in 60 patients with plasma cell dyscrasia. Patients treated with anti-CD38 monoclonal antibodies (mAbs) had significantly lower CD38$^+$ Tregs than those not treated (0.9 vs. 13.2/μl). Late-responders, whose antibody titres increased from weeks 4–12 after the second vaccination, had significantly lower CD38$^+$ Treg counts than non-late-responders (2.5 vs. 10.3/μl). Antibody titres in patients with lower CD38$^+$ Treg levels were maintained from weeks 4–12 but decreased in those with higher CD38$^+$ Treg levels. Therefore, depletion of CD38$^+$ Tregs by anti-CD38 mAbs may induce a durable response to mRNA-COVID-19 vaccination.

KEYWORDS
anti-CD38 monoclonal antibody, coronavirus disease 2019 (COVID-19), multiple myeloma, regulatory T cell, vaccines

INTRODUCTION

Patients with multiple myeloma (MM) have severe humoral and cellular immune response impairment due to disease nature and treatment. Of the patients with MM who had coronavirus disease 2019 (COVID-19) in New York City, 29% died.[1] Moreover, patients with MM have an insufficient response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination.[2] Anti-CD38 monoclonal antibody (mAb) use and lymphopenia decrease antibody production.[2]

The anti-CD38 mAb is the key drug for treating MM. Previously, our group reported that depletion of CD38-positive (CD38$^+$) regulatory T cells (Tregs) by daratumumab leads to durable treatment response.[3] This effect is caused not only by the direct effect on CD38$^+$ myeloma cells but also by the indirect effect of CD8$^+$ T cell expansion.[4] Moreover, CD38$^+$ Tregs are more immunosuppressive than CD38-negative Tregs.[5] Another available anti-CD38 mAb, isatuximab, also decreases the proliferation of Tregs.[6]

Ageing influences the immune response, such as Type 1 T-helper cells (Th1) cells, polyfunctional CD8$^+$ T cells, germinal centre reactions, and Tregs, which finally induces low vaccine response in healthy older adults.[7,8] Moreover, in patients with COVID-19, lower Treg counts cannot inhibit host pro-inflammatory immune cell expansion, which induces severe cytokine storms.[9] Therefore, Tregs affect the immune response to both tumours and microbes. However, because the SARS-CoV-2 vaccine has been approved only recently, there is still a paucity of literature on the relationship between Tregs and SARS-CoV-2 vaccination. Moreover, the

relationship between antibody titres and Tregs in patients with MM remains unclear.

Thus, we hypothesised that the depletion of circulating $CD38^+$ Tregs could maintain the SARS-CoV-2 vaccine response in patients with MM. This study will make a significant contribution to increasing the efficacy of SARS-CoV-2 vaccination in patients treated with plasma cell dyscrasia (PCD).

PATIENTS AND METHODS

This study included 60 patients with PCD (54 MM, four untreated smouldering MM, and two untreated monoclonal gammopathy of undetermined significance) (Table 1). All patients received two doses of messenger RNA (mRNA)-based vaccines (59 BNT162b2 and one mRNA-1273). Two patients were newly diagnosed with MM after the two vaccine doses, and one patient with MM had COVID-19 after the first BNT162b2 vaccine. Serum samples were collected at 4 weeks (T1, median [range] 31.5 [10–65] days; $n = 60$) and at 12 weeks (T2, median [range] 89 [60–133] days; $n = 53/60$) after the second vaccination. The gating method for Tregs ($n = 48/60$ at T1 and $n = 12/60$ at T2), represented by the $CD4^+CD25^{high}CD127^{dim}$ population in peripheral lymphocytes, is shown in Figure S1A, as previously reported.[3] No patients changed the treatment regimen between T1 and T2. In all, 25 and 34 patients were receiving anti-CD38 mAb (18 daratumumab and seven isatuximab) and immunomodulatory imide drugs (IMiDs; 19 lenalidomide, 14 pomalidomide, and one iberdomide) respectively, at the measurement of Treg counts.

Antibody responses were analysed using Elecsys® Anti-SARS-CoV-2 on a Cobas 8000 e801 module (Roche Diagnostics), which measures the antibodies of the SARS-CoV-2 spike (S) protein receptor-binding domain protein. We defined S-immunoglobulin (Ig)G ≥0.8 u/ml as seropositive and ≥200 u/ml as 'clinically protective'. We determined this value from our unpublished data (T. Terao, *Int J Hematol* 2022); 92.6% of healthy subjects showed a S-IgG of ≥200 u/ml after the second BNT162b2 vaccination. We also defined 'late-responders' as patients whose antibody titres increased from T1 to T2. We compared the continuous variables by Mann–Whitney *U*-test or Wilcoxon signed-rank test. All statistical analyses were conducted using the RStudio or the EZR software,[10] a user interface for R version 3.1.2. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The median (range) antibody titres at T1 and T2 were 74.4 (0.4–7171) u/ml and 77.4 (0.4–3530) u/ml, seropositive 90.0% and 94.3%, and clinical protective 35.0% and 30.2%, respectively (Figure 1A). In all, 18 patients (34.0%) were late-responders. Compared to non-late-responders, these late-responders included a significantly higher percentage

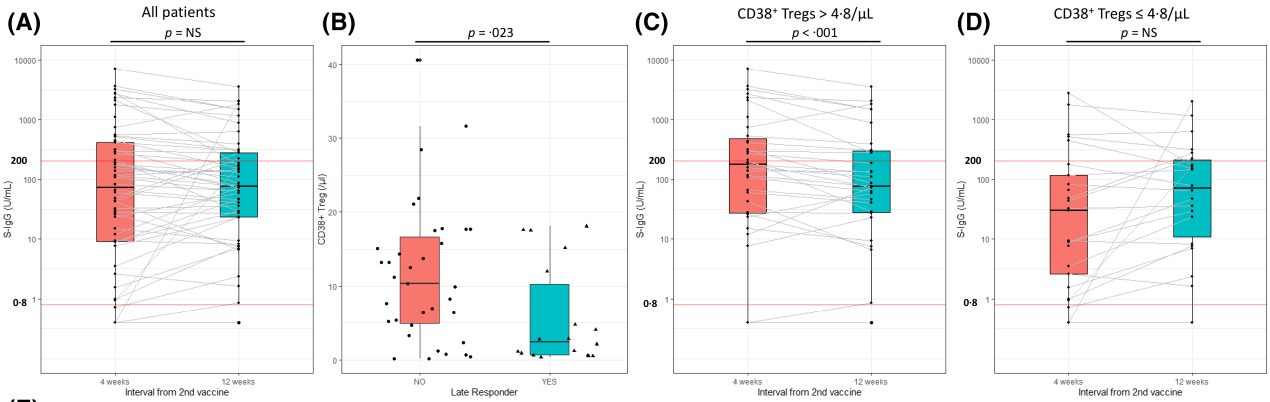
TABLE 1 Patients' characteristics

Characteristic	Value
Number of patients	60
Age, years, median (range)	75 (47–95)
Sex, male (%)	23 (38.3)
Disease, *n* (%)	
MM	54 (90.0)
sMM	4 (6.7)
MGUS	2 (3.3)
Heavy-chain type, *n* (%)	
IgG	34 (56.7)
IgA	17 (28.3)
Light-chain only	7 (11.7)
Others	2 (3.3)
Light-chain type, kappa, *n* (%)	38 (63.3)
ISS, Stage III, *n* (%)	32 (59.3)
Absolute lymphocyte count, /μl, median (range)	1281 (468–4896)
(Estimated) polyclonal IgG, g/l, median (range)[a]	6.28 (2.49–26.31)
Time from diagnosis to vaccination, months, median (range)	42.8 (0–200)
Treatment at second vaccination, *n* (%)	
DVd	2 (3.3)
DRd	10 (16.7)
Dara monotherapy	6 (10.0)
IsaPd	6 (10.0)
Isa monotherapy	1 (1.7)
ERd	1 (1.7)
EPd	5 (8.3)
VRd	3 (5.0)
IRd	5 (8.3)
Rd	1 (1.7)
Pd	3 (5.0)
Iberdomide and dexamethasone	1 (1.7)
VMP	2 (3.3)
Kd	2 (3.3)
Off-treatment[b]	12 (20.0)
S-IgG at 4 weeks after second vaccination, u/ml, median (range)	74.4 (0.4–7171)
S-IgG at 12 weeks after second vaccination, u/ml, median(range)	77.4 (0.4–3530)

Abbreviations: Dara, daratumumab; DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; EPd; elotuzumab, pomalidomide, and dexamethasone; ERd, elotuzumab, lenalidomide, and dexamethasone; Ig, immunoglobulin; IRd, ixazomib, lenalidomide and dexamethasone; Isa, isatuximab; IsaPd, isatuximab, pomalidomide, and dexamethasone; ISS, international staging system; Kd, carfilzomib and dexamethasone; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; sMM, smouldering multiple myeloma; VMP, bortezomib, melphalan, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

[a]Polyclonal IgG was estimated from total IgG minus monoclonal IgG if IgG-type plasma cell dyscrasia.

[b]12 patients included six with MM, four with sMM, and two with MGUS. Four patients with MM had a good treatment response and did not receive any treatment at vaccination. The other two patients with MM were newly diagnosed after their second vaccination.



(E)

	Anti-CD38 antibody (+) IMiDs (+) n = 17	Anti-CD38 antibody (+) IMiDs (-) n = 9	Anti-CD38 antibody (-) IMiDs (+) n = 17	Anti-CD38 antibody (-) IMiDs (-) n = 17
Late-responder	7/14 (50·0%)	5/9 (55·6%)	5/15 (33·3%)	1/15 (6·7%)
Total Tregs (/μL, range)	58·3 (35·5-104·2)	40·4 (2·4-145·7)	51·6 (21·1-101·8)	67·3 (17·7-128·1)
CD38⁺ Tregs (/μL, range)	0·8 (0·2-17·9)	1·1 (0·2-2·3)	10·3 (0·9-21·9)	15·1 (5·2-40·6)
S-IgG at 4 week after 2nd vaccination (U/mL, range)	25·9 (0·4-511)	43·7 (1·53-2756)	108 (0·4-3176)	313 (15-7171)
S-IgG at 12 weeks after 2nd vaccination (U/mL, range)	29·6 (0·4-317)	175 (1·63-1162)	72·7 (0·85-2077)	187 (9·4-3530)
Median difference from T2 to T1 by the Wilcoxon signed-rank test (U/mL, *p*-value)	0·8 (0·76)	5·4 (0·82)	-44 (0·11)	-83 (0·004)

FIGURE 1 (**A**) The kinetics of the antibody titres at 4 weeks (T1) and 12 weeks (T2) after second vaccine are shown. The median S-IgG were 74.4 and 77.4 u/ml at T1 (red) and T2 (blue) respectively. (**B**) Late-responders, in blue, showed significantly lower CD38$^+$ Tregs than non-late-responders (2.5 vs. 10.3/μl, $p = 0.023$). (**C** and **D**) S-IgG levels decreased from T1 (red) to T2 (blue) in patients with higher CD38$^+$ Treg counts (median S-IgG difference between T1 and T2; −38.6 u/ml, $p < 0.001$, median; 176.0 and 77.4 u/ml, **C**); however, increased in those with lower CD38$^+$ Treg counts (median S-IgG difference between T1 and T2; 4.5 u/ml, $p = 0.53$, median; 29.7 and 71.9 u/ml, **D**). (**E**) The relationship between anti-CD38 mAbs and IMiD use, and vaccine response factors is shown. Regardless of the IMiD administration, the percentage of late-responders was higher and the number of CD38$^+$ Tregs was lower in patients treated with anti-CD38 mAbs (late-responder and CD38$^+$ Tregs; 50.0% and 0.8/μl and 55.6% and 1.1/μl in patients treated with anti-CD38 mAbs with and without IMiDs vs. 33.3% and 10.3/μl and 6.7% and 15.1/μl in those not treated with anti-CD38 mAbs, treated with or not treated with IMiDs respectively). There were no differences in terms of total Tregs between groups. Patients treated with IMiDs, regardless of anti-CD38 mAb administration, maintained vaccine response between T1 and T2. However, patients not treated with anti-CD38 mAbs and IMiDs had a significant decrease in S-IgG titre from T1 to T2 ($p = 0.004$, median S-IgG at T1 and T2; 313 and 187 u/ml). CD38$^+$ Tregs, CD38-positive regulatory T cells; Ig, immunoglobulin; IMiDs, immunomodulatory imide drugs; mAbs, monoclonal antibodies; NS, not significant [Colour figure can be viewed at wileyonlinelibrary.com]

of patients receiving anti-CD38 mAbs 3 months before the first vaccination (66.7% vs. 31.4%, $p = 0.020$) and had lower median polyclonal IgG (4.23 vs. 6.72 g/l, $p = 0.014$); however, there was no difference in IMiD use (66.7% vs. 48.6%, $p = 0.25$) nor in treatment response to MM (very good partial response or better 88.9% vs. 78.9%, $p = 0.43$). The antibody titres at T1 and T2 in patients treated with anti-CD38 mAbs were significantly lower than those of patients that were not treated with anti-CD38 mAbs (T1, 26.2 vs. 201 u/ml, $p = 0.002$, T2, 35.8 vs. 122 u/ml, $p = 0.023$). In patients treated with anti-CD38 mAbs, the S-IgG levels at T1 and T2 were unchanged ($p = 0.54$), but S-IgG levels in those not treated with anti-CD38 mAb showed a significant decrease of 44 u/ml at T2 compared to T1 ($p = 0.001$).

We analysed the lymphocyte subsets of the peripheral blood. In line with a previous study,[4] patients treated with anti-CD38 mAbs 3 months before first vaccination, compared to non-treated patients, respectively, had higher CD8$^+$ (median, 546 vs. 296/μl, $p = 0.004$) and human leucocyte antigen-DR isotype (HLA-DR)$^+$ T cells (median; 609 vs. 304/μl, $p = 0.002$), but lower CD19$^+$ (median; 31 vs. 100/μl, $p = 0.064$) and CD56$^+$ cells (median; 22 vs. 283/μl, $p < 0.001$). These patients had significantly lower number of CD38$^+$ Tregs than those that were not treated (1.0 vs. 13.5/μl, $p < 0.001$), but similar number of total Tregs (57.1 vs. 56.8/μl, $p = 0.72$). In late-responders, the absolute number of CD38$^+$ Tregs and CD19$^+$ cells were significantly lower compared to non-late-responders (CD38$^+$ Tregs, 2.5 vs. 10.3/μl, $p = 0.023$, Figure 1B; and CD19$^+$ cells, 28 vs. 103/μl, $p = 0.021$).

Next, we analysed the effects of CD38$^+$ Tregs in vaccine response over time. The optimal cut-off level of CD38$^+$ Tregs to predict late-responders was set at 4.8/μl using receiver operating characteristics curve analysis (the area under the curve was 0.69). Patients with low CD38$^+$ Treg numbers ($n = 25$) showed lower vaccine response at T1 than those with high CD38$^+$ Treg counts ($n = 35$) (median 29.7 vs. 176.0 u/ml, $p = 0.016$). However, at T2 the difference between the low and high CD38$^+$ Treg groups decreased (median 71.9 vs. 77.4 u/ml, $p = 0.61$). In patients with high CD38$^+$ Tregs, S-IgG levels from T1 to T2 showed a significant decrease of −38.6 u/ml

($p < 0.001$; median S-IgG at T1 and T2, 176.0 and 77.4 u/ml, Figure 1C), but S-IgG levels in those with low $CD38^+$ Tregs was unchanged ($p = 0.53$; median S-IgG at T1 and T2, 29.7 and 71.9 u/ml, Figure 1D).

Regarding anti-CD38 mAbs and IMiD administration, and vaccine response (Figure 1E), of the 60 patients, 17 of those treated with anti-CD38 mAbs received IMiDs, and 17 of the 34 patients who did not receive anti-CD38 mAbs received IMiDs. Regardless of IMiD administration, the percentage of late-responders was higher and the number of $CD38^+$ Tregs was lower in patients treated with anti-CD38 mAbs (Figure 1E). Patients treated with IMiDs but not with anti-CD38 mAbs maintained S-IgG titres at T1 and T2 (108 and 72.7 u/ml, respectively). However, patients not treated with anti-CD38 mAbs and IMiDs had the most significant decrease from T1 to T2 ($p = 0.004$, median S-IgG at T1 and T2; 313–187 u/ml).

In myeloma, treatment with anti-CD38 mAbs leads to a marked decrease in B and natural killer cells. The expression of CD38 in Tregs is downregulated by anti-CD38 mAb therapy,[3] while it is upregulated by IMiDs.[11] Our results showed that patients treated with anti-CD38 mAbs had lower initial vaccine response and lower $CD38^+$ Tregs and included more late-responders than those not treated with anti-CD38 mAbs. The lower initial response to the vaccine may be associated with not only older age, lymphopenia, lower polyclonal Ig levels, and receiving multiple lines of treatments, as previously reported, but also with the removal of normal plasma cells, $CD38^+$ Tregs, and B cells by anti-CD38 mAbs; while one of the reasons for the delayed and durable response may be the removal of $CD38^+$ Tregs.

Reports on the detailed immune profile of COVID-19 vaccine response in patients with haematological malignancies are largely lacking. In these patients, anti-CD38 mAbs use, classical monocytes, neutrophils, CD4 and CD8 effector memory $CD127^-$ T cells were related to lower vaccine response.[12] Marasco et al.[13] reported that these patients showed lower levels of spike-specific Th1-associated cytokine release than healthy controls. Although the exact cause of this longitudinal vaccine response was unclear, it is possible that the differences in immune profiles and the elimination of $CD38^+$ Tregs may be associated with the duration of the vaccine response.

In general, Treg function is activated in the elderly,[14] which reduces the effectiveness of influenza virus and varicella-zoster virus (VZV) vaccines.[15,16] Moreover, the lower number of Tregs are also implicated in autoimmune diseases such as immune thrombocytopenia or transfusion-related acute lung injury.[17,18] However, there are very few reports on the effect of Tregs on COVID-19 vaccines, as aforementioned. Based on our finding that lower numbers of $CD38^+$ Tregs show a durable COVID-19 mRNA vaccine response in patients with PCD, we considered that patients without PCDs with low Tregs would also show durable COVID-19 vaccine response like influenza or VZV vaccine; however, there are no other reports that support this supposition.

Our study had several limitations. First, owing to the nature of the observational study, we could not provide direct evidence that $CD38^+$ Tregs maintained a durable vaccine response, although, there was a correlation between $CD38^+$ Tregs and late-responders. Second, we did not measure the neutralising antibody titre and the expression of transcription factor forkhead box protein 3 (FoxP3) on Tregs. Third, all patients received mRNA-based vaccines, not adenovirus vector-based or other types of COVID-19 vaccines. Our results were based on the immunity to the proteins expressed by the vaccine, rather than the individual vaccine types. Thus, we believe that other COVID-19 vaccines would demonstrate similar results.

In conclusion, our results showed that 34.0% of patients with PCD are late-responders for SARS-CoV-2 mRNA vaccination. Although anti-CD38 mAb administration is one of the detrimental factors in initial vaccine response, the depletion of $CD38^+$ Tregs can maintain vaccine response in patients with PCD. Further studies are warranted to validate our results and to elucidate the detailed mechanisms of our new insights.

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CONFLICT OF INTERESTS

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Toshiki Terao conceived and designed the study, collected data, performed the statistical analysis, wrote the manuscript, and provided patient care. Toshiki Terao and Takashi Naduka analysed Tregs. Daisuke Ikeda, Ami Fukumoto, Yuya Kamura, Ayumi Kuzume, Rikako Tabata, Takafumi Tsushima, Daisuke Miura, Kentaro Narita, and Masami Takeuchi collected data and provided patient care. Kosei Matsue initiated, conceived, and supervised the study, and wrote the manuscript. All authors reviewed and approved the manuscript.

ETHICS APPROVAL

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was approved by the institutional review board (Approval Number: 21–025).

CONSENT TO PARTICIPATE

All participants or their family members provided written informed consent for study participation.

CONSENT FOR PUBLICATION

Patients signed informed consent regarding publishing their data and photographs.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from Toshiki Terao or Kosei Matsue on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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