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SHORT REPORT

Immune responses to COVID-19 booster vaccinations in intensively anti-CD38 antibody treated patients with ultra-high-risk multiple myeloma: results from the Myeloma UK (MUK) *nine* OPTIMUM trial

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Summary
Multiple myeloma (MM) and anti-MM therapy cause profound immunosuppression, leaving patients vulnerable to coronavirus disease 2019 (COVID-19) and other infections. We investigated anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies longitudinally in ultra-high-risk patients with MM receiving risk-adapted, intensive anti-CD38 combined therapy in the Myeloma UK (MUK) *nine* trial. Despite continuous intensive therapy, seroconversion was achieved in all patients, but required a greater number of vaccinations compared to healthy individuals, highlighting the importance of booster vaccinations in this population. Reassuringly, high antibody cross-reactivity was found with current variants of concern, prior to Omicron subvariant adapted boostering. Multiple booster vaccine doses can provide effective protection from COVID-19, even with intensive anti-CD38 therapy for high-risk MM.

KEYWORDS
antibodies, anti-CD38, high-dose therapy, multiple myeloma, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

Martin F. Kaiser and Jennifer L. J. Heaney joint last authors.

Multiple myeloma (MM), a cancer of differentiated bone marrow plasma cells, causes wide-ranging immunodeficiency and immune dysregulation. Immunoparesis is well-documented and increases susceptibility to both bacterial and viral infections.[1–3] Infection-related morbidity and mortality is high, particularly in the first 3 months after diagnosis, where infections are responsible for half of early deaths.[4,5] Anti-CD38 monoclonal antibodies such as daratumumab (Dara) are highly effective anti-myeloma therapies and improve responses in patients with newly diagnosed MM (NDMM); however, they are also associated with hypogammaglobulinaemia and increased infection risk.

As a result of disease and therapy-related immunosuppression, which endures into remission,[6] patients with MM are extremely vulnerable to coronavirus disease 2019 (COVID-19). High mortality rates have been observed in patients with MM admitted to hospital due to COVID-19.[7] Certain patients with MM may be especially vulnerable to infection because of the treatment they receive. Anti-CD38 anti-MM therapy has been specifically associated with increased risk of severe COVID-19 and impaired responses to COVID-19 vaccination.[8] Initial guidance by the International Myeloma Working Group and the European Myeloma Network recommended COVID-19 vaccination preferably in treatment-free intervals.[9,10] However, particularly in patients requiring sustained intensive therapy, such as those with molecular ultra-high-risk (UHiR) MM, this is not feasible.

As treatment outcomes for UHiR NDMM remain poor, we performed the Myeloma UK (MUK) *nine* OPTIMUM trial (NCT03188172), in which patients with molecular UHiR MM received intensified induction, autologous stem cell transplantation (ASCT) and intensive long-term post-ASCT consolidation with 18 cycles of Dara, bortezomib, lenalidomide, dexamethasone (Dara-VRd), followed by Dara-R maintenance.[11] The trial therapy regime is illustrated in Supplementary Figure S1. Early results show very promising improvement in progression-free survival over the current standard of care.[12]

However, the COVID-19 vaccine response of an UHiR NDMM patient population in receipt of highly intensive anti-CD38 combined therapy is currently unknown, including the potential of antibody responses against Omicron variants of concern (VoC) such as BA.2, BA.4 and BA.5. As OPTIMUM therapy may emerge as a new standard for UHiR NDMM, such knowledge could be essential to help inform patient management and any required updates to the current vaccination programme, which in the UK includes regular booster vaccines for the entire MM patient population.

The present investigation (i) evaluated OPTIMUM UHiR risk MM patient's long-term response to vaccination in accordance with the UK booster programme, (ii) compared their responses to healthy individuals, and (iii) measured cross-reactivity of patients with MM with existing anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies with current VoC.

The study included samples from patients from the OPTIMUM trial[11]; a sub-cohort of up to 79% (n = 85/107) recruited trial patients were included in the present analyses. Samples were also analysed from a non-myeloma cohort: healthcare workers (HCW) who participated in the Immune response to SARS-CoV-2 infection (COCO) study.[13] Samples collected from donors before 2019 were included as negative controls. All participants from these UK trial/studies provided informed consent, which all had appropriate ethics committee approval in line with the Declaration of Helsinki. Samples were analysed using a total anti-immunoglobulins G, A, and M (IgGAM) SARS-CoV-2 spike glycoprotein enzyme-linked immunosorbent assay (ELISA) and IgG ELISAs against SARS-CoV-2 spike proteins, anti-Wuhan and anti-Omicron (BA.1, BA.4 and BA.5), described in detail previously.[14,15] Longitudinal antibody measurements were performed after doses of the original SARS-CoV-2 vaccines (Pfizer/BioNTech, AstraZeneca) and subsequent boosters (either Pfizer/BioNTech, AstraZeneca, Moderna). Both patients with MM and HCW received vaccinations at the recommended intervals in accordance with UK national recommendations and all serum samples were taken ≥28 days after vaccination. Live virus neutralisation assays were performed as previously described,[16] either after the second vaccine dose (HCW) or third dose (patients with MM).

The OPTIMUM patients with MM responses to the SARS-CoV-2 UK vaccination programme to date are shown in Figure 1. All patients had completed up to six cycles of induction with Dara-CVRd and a bortezomib-enhanced ASCT. The majority of patients (62.9%) had already completed at least six cycles of post-ASCT consolidation one with Dara-VRD and were receiving consolidation two with Dara-VR and 37.1% had completed 18 cycles of Dara-VR(D) consolidation one and two and were on maintenance with Dara-RD when they received the first vaccine dose. At time of the third dose of vaccine the majority (91.9%) of patients were in receipt of maintenance with Dara-R and 8.11% were on consolidation two with Dara-VR. The majority (97.6%) of patients were in receipt of maintenance with Dara-R and 2.5% of patients were in receipt of consolidation two with Dara-VR at the time of the fourth vaccine dose.

For Figure 2A,B, the majority of patients (63.2%) were on consolidation two with Dara-VR when they received their second vaccine dose. In all, 36.8% of patients were on maintenance with Dara-R at the time of the second vaccine dose. The majority of patients (94.1%) were on maintenance with Dara-R and 5.9% were on consolidation two with Dara-VR at the time of the third vaccine dose. For Figure 2C,D, the majority (96.7%) of patients had already completed consolidation two with Dara-VR and were on maintenance with Dara-R and 3.23% were on consolidation two with Dara-VR when they received their fourth vaccine dose. All of the patients were on maintenance with Dara-R at the time of the fifth vaccine dose. The third and fourth vaccine doses were given on average 6 and 4 months after the previous dose; therefore, patients will have received six and four Dara

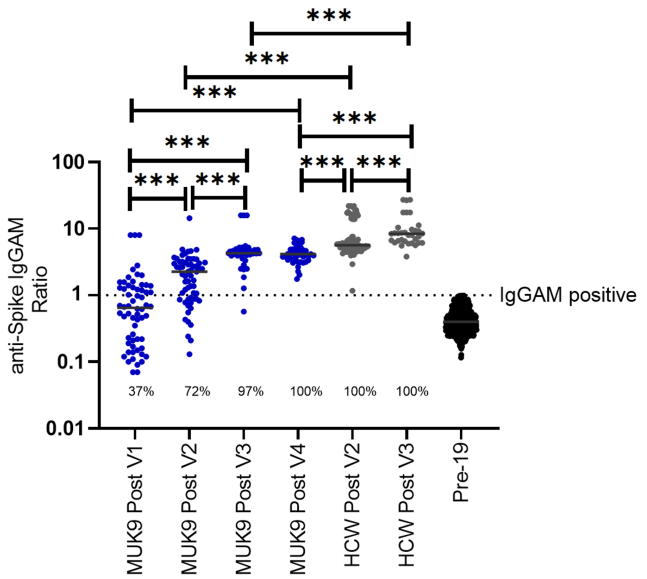

FIGURE 1 Responses to coronavirus disease 2019 (COVID-19) vaccinations in patients with multiple myeloma and healthcare workers (HCW). Results are shown for anti-Spike immunoglobulins G, A, and M (IgGAM) antibody ratio. Results for this enzyme-linked immunosorbent assay are reported as a ratio relative to a monoclonal Spike-specific calibration antibody standard: any ratio values >1 are classed as positive.[14] Serum samples collected pre-2019 prior to the COVID-19 pandemic are shown evidencing this ratio cut-off ($n = 746$). Data includes Myeloma UK MUK *nine* trial (MUK9) patients ($n = 62$) after the first (V1), second (V2) ($n = 61$), thitd (V3) ($n = 37$) and fourth (V4) ($n = 41$) COVID-19 vaccination doses, and HCW after V2 ($n = 91$) and V3 ($n = 33$). Percentages shown indicate proportion of patients with a positive IgGAM ratio. Differences within cohorts over time and between cohorts at the same timepoint (after V2 or V3) were tested using Kruskal–Wallis or Mann–Whitney tests as appropriate. Significant differences are indicated, $^{***}p < 0.001$.

administrations between vaccinations due to high compliance and minimal delays between monthly administrations.

Samples were measured for combined anti-spike IgG, IgA, IgM ratio (Figure 1).[14] Patients' anti-spike antibody levels increased over the course of the vaccination programme and data highlights the necessity of multiple vaccinations in these patients. After the first vaccine, only 37% of patients were seropositive; this proportion nearly doubled after the second dose but over a third of patients were still seronegative. The third dose significantly increased antibody levels again and converted the majority of patients (97%) to seropositive. Results demonstrate the fourth vaccination as essential to achieve seroconversion across all patients with MM. In contrast, all HCW achieved seropositivity after the second vaccination, although median antibody levels still increased from the second to third dose. When comparing cohorts at equivalent time points (after the second and third doses), patients with MM had significantly lower IgGAM antibody ratios compared with the HCW (Figure 1). Data demonstrates MM responses are weakened compared to healthy individuals and are reliant on multiple vaccinations. Even after four vaccinations, in the patients with MM, the median antibody ratios still had not caught up and were significantly lower than the HCW after only two or three vaccinations.

Immunoglobulin G contributed to most anti-spike antibodies measured, with little derived from IgA and IgM (Supplementary Figure S1). No differences in antibody responses were observed based on patient's response to anti-MM therapy (Supplementary Figure S3).

Supplementary Figure S2 shows that most of the patients with MM antibodies also exhibited effective neutralisation responses when measured against Wuhan. Although, despite having received three vaccine doses compared to the two received by the HCW, the patients with MM responses were still significantly lower. Of the patients with MM, 81% demonstrated neutralisation of >50% compared with 96.5% of the HCW. A previous report found most patients treated with anti-CD38 therapy attained suboptimal antibody responses (<50% neutralisation) after primary vaccination.[17] Our findings suggest booster vaccination can markedly increase neutralising antibody response in these patients.

Figure 2A,B displays IgG anti-spike antibody levels for MM and HCW for SARS-CoV-2 variants anti-Wuhan and anti-Omicron (BA.1). Again, the patients with MM antibody response against these SARS-CoV-2 variants was inferior compared to the HCW. Although antibody levels were lower, the majority of patients with MM were IgG seropositive after receiving two or three vaccinations: 94% and 97% for anti-Wuhan and BA.1 respectively.

Omicron variants BA.4 and BA.5 are currently driving transmission and infections. The most recent serum samples (either after the fourth or fifth vaccine dose) in the patients with MM were analysed to see if their antibodies were able to react with these VoC. Figure 2C,D shows all patients with MM were IgG positive against BA.4 and BA.5. This 100% positivity was also seen in the HCW who had received three doses. Although all samples analysed were IgG positive, it should be acknowledged that the patients with MM still had lower median antibody levels compared with the HCW, despite having received more doses.

All the HCW received Pfizer/BioNTech (messenger RNA [mRNA]) vaccination only; no switching took place. For patients with MM who received four or more vaccine doses, 2% received only AstraZeneca vector vaccine for all doses, 42% received only Pfizer/Moderna mRNA vaccines for all doses, and the remaining 56% of patients received AstraZeneca for the first two primary doses, then switched to mRNA Pfizer BioNTech/Moderna vaccine for subsequent booster doses. There were no significant differences in antibody levels (either anti-Wuhan or anti-Omicron variants) based on vaccine schedules. At individual time points, no differences were seen between the types of vaccine (vector/mRNA), nor were there any differences between patients who switched from vector to mRNA for booster doses and those who received mRNA for all doses.

Four instances of hospitalisations due to COVID-19 infection were recorded in this cohort of trial patients. Two of these cases occurred prior to first vaccination dose and in one case vaccination status was unknown. However, one

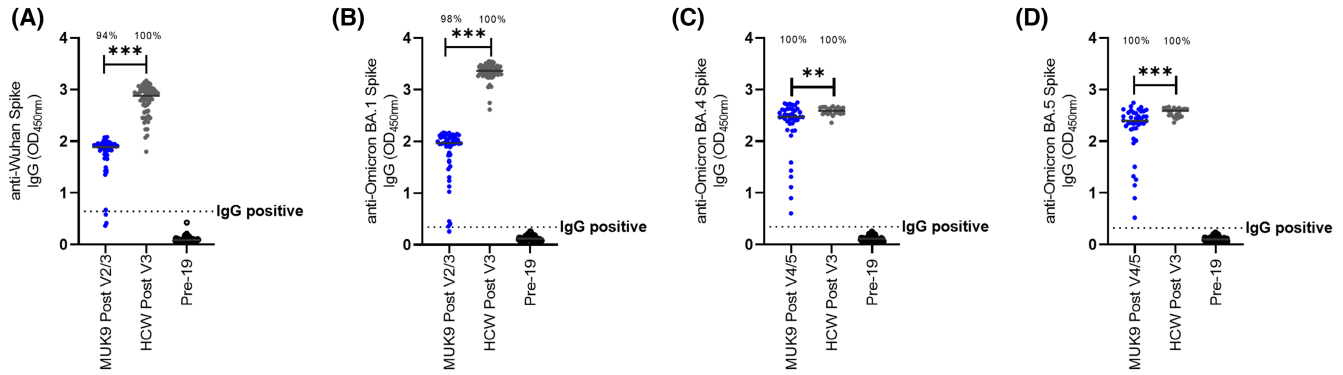

FIGURE 2 Anti-Wuhan and anti-Omicron spike immunoglobulin (Ig)G antibodies in patients with multiple myeloma (MM) and healthcare workers (HCW). IgG positivity thresholds are indicated, and serum samples collected before 2019 (pre-19) prior to the coronavirus disease 2019 (COVID-19) pandemic are shown ($n = 47$ [**A**], $n = 73$ [**B**], $n = 86$ [**C**], $n = 85$ [**D**]). Panels **A** and **B** show anti-spike IgG antibody levels for Wuhan (**A**), Omicron BA.1 (**B**) in Myeloma UK MUK *nine* trial (MUK9) patients with MM ($n = 53$) who had received either two ($n = 19$) or three ($n = 34$) vaccinations (post V2/V3) at the time of the sample and in HCW ($n = 60$) after three vaccinations (post V3). Panels **C** and **D** show anti-spike IgG antibody levels for Omicron BA.4 (**C**) and Omicron BA.5 (**D**) in MUK9 patients with MM ($n = 42$) who had received either four ($n = 31$) or five ($n = 11$) vaccinations (post-V4/5) and HCW ($n = 20$) after three vaccinations (post V3). Cohorts were compared using Mann–Whitney tests and significant differences are indicated, $^{**}p < 0.01$, $^{***}p < 0.001$.

hospitalisation did occur after the first two doses, prior to boosters. This patient did not respond to the first two vaccine doses (seronegative) and only mounted a positive response after their third vaccination dose. These findings concur that despite the effectiveness of vaccines in reducing severity of disease, hospitalisation, and deaths, patients with existing diseases remain at higher risk and thus remain a priority for additional boosters.[18] Our observed overall low hospitalisation rate is difficult to compare to other studies. However, there were no deaths due to COVID-19 in our study, with all patients recovering from infection. Treatment with anti-CD38 monoclonal antibody within 6 months of COVID-19 infection has recently been found to be an independent predictor for intensive care unit admission.[19] In general, studies in MM populations have mainly focused on inpatients and subsequent mortality,[18,19] rather than infection rates and risk of hospitalisation. In addition, the efficacy of vaccination in preventing non-severe breakthrough infections and re-infection in MM populations requires investigation within future studies.

Overall, our findings demonstrate that antibodies induced as part of the UK vaccination programme to date display high cross-reactivity with Omicron VoC. It is encouraging that patients with MM who are up to date with boosters may already have some degree of protection against these circulating variants. While data demonstrates antibody binding with BA.4 and BA.5, neutralisation data were only available for the Wuhan strain. Further, cellular data, such as T-cell responses to vaccination, were not investigated in this study and should be examined in patients with MM.

CONCLUSIONS

Myeloma is one of the most immunosuppressive of all blood cancers, and novel intensive treatment approaches including anti-CD38 combinations for UHiR patients as in OPTIMUM exert additional immunosuppressive effects. Despite this, patients with UHiR MM can mount an effective antibody response to vaccination providing multiple doses are administered. As these patients were receiving sustained intensified therapy, we advocate that breaks in treatment are not necessary to facilitate administration of COVID-19 vaccinations. As patients with MM require an additional two vaccinations to reach the higher antibody levels and full seroconversion rate seen in non-cancer populations, it is essential to prioritise the timely offering and uptake of booster vaccinations in clinical practice, irrespective of whether the patient is undergoing therapy. The high-cross-reactivity of patients' existing SARS-CoV-2 antibodies with current VoC are reassuring in the interim while patients await additional booster vaccinations adapted for Omicron subvariants BA.4 and BA.5.

AUTHOR CONTRIBUTIONS

Jennifer L. J. Heaney and Martin F. Kaiser wrote the manuscript. Jennifer L. J. Heaney, Martin F. Kaiser and Mark T. Drayson interpreted the data. Mark T. Drayson, Alex Richter, Jennifer L. J. Heaney designed the antibody investigation. Sian E. Faustini carried out all antibody measurements and Andrew Hall and Sian E. Faustini analysed the data. Harriet Hill and Zania Stamataki performed antibody neuralisation measurements. Sarah Brown, Sadie Roberts, Matthew W. Jenner, Roger G. Owen, Guy Pratt, Gordon Cook (members of the MUK *nine* OPTIMUM trial management group) collected data and reviewed the final manuscript. The Protective Immunity from T cells to COVID-19 in Health workers (PITCH) consortium supported antibody analysis and all members reviewed the final manuscript. Martin F. Kaiser is chief investigator of the MUK *nine* OPTIMUM trial. All authors reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Martin F. Kaiser has consulted for Abbvie, consulted for and received honoraria from Amgen, consulted for and received honoraria, research support, and travel support from BMS/Celgene, consulted for and received honoraria and travel support from Janssen, consulted for GSK, consulted for Karyopharm, consulted for Pfizer, consulted for Regeneron, consulted for Seattle Genetics, and consulted for and received honoraria and travel support from Takeda. Mark T. Drayson owns stock in Abingdon Health Ltd. Roger G. Owen has consulted for and received honoraria from Janssen. Matthew W. Jenner has consulted for Janssen, BMS and Pfizer and received sponsorship for meeting attendance from Janssen. All other authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data in this Report concern patient data and are not available in a public repository. Data from the laboratory analysis included in this study are available on request.

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SUPPORTING INFORMATION

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

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