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camidanlumab tesirine will make a difference after the results of phase 2 and 3 studies are reported.

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# Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma

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Multiple myeloma is a malignancy of plasma cells, which is highly associated with immune suppression. Consistent with this, reports of outcomes of COVID-19 infection in patients with multiple myeloma show higher rates of severe disease than in the general population.[1,2] Protection of this vulnerable patient group from COVID-19 infection is crucial but response to the new vaccines in patients with multiple myeloma is unknown. A recent report showing low anti-SARS-CoV-2 IgG response to the Pfizer vaccine in patients with cancer included 38 patients with haematological malignancies (nine patients with multiple myeloma) and showed only a 13% response rate, raising concerns that multiple myeloma might be associated with attenuated vaccine response.[3]

In the UK, both Pfizer and AstraZeneca vaccines have been used with spacing of 12 weeks between the first and second doses. We retrospectively assessed serological response following the first SARS-CoV-2 vaccine dose in patients with multiple myeloma in our centre. Patients were eligible if they had a diagnosis of multiple myeloma and an anti-SARS-CoV-2 spike protein S1 IgG antibody result 21 days or more post-vaccination. Details of the laboratory testing and data analysis are in the appendix (pp 1–2). Data collection and analysis was approved by the Royal Marsden Committee for Clinical Research.

Clinical characteristics of the 93 patients included are shown (table and appendix p 2). Patients had received a median of one (IQR 1–2, range 0–8) previous line of therapy and 66 (71%) patients were on therapy at the time of vaccination. 48 (52%) patients were in a complete response or very good partial response at the time of vaccination compared with 16 (17%) patients in partial response and 27 (29%) patients with stable disease or progressive disease. Immunoparesis was identified in 43 (46%) patients. Analysis of antibody status occurred at a median of 33 days (IQR 28–38, range 21–61) following vaccination.

Of the 93 patients, 52 (56% [95% CI 46–66]) tested positive for SARS-CoV-2 IgG antibodies on a blood test taken 21 days or more post-vaccination. There was no difference in the percentage of patients with a positive result between those who received the Pfizer and AstraZeneca vaccines (table).

On subgroup analysis there was no difference in seropositive rates based on age, sex, disease isotype, leucopenia, or time from vaccination to antibody test (table). However, seropositive rates were different between patients with a good response (complete response or very good partial response) or partial response and those with stable disease or progressive disease (table 1, appendix p 3). Other features with a

See **Online** for appendix

| | Positive antibody result (n=52) | Negative antibody result (n=41) | p value* |
|---|---|---|---|
| Vaccination type | | | 0·84 |
| Pfizer (n=48) | 26 (54%) | 22 (46%) | .. |
| AstraZeneca (n=45) | 26 (58%) | 19 (42%) | .. |
| Age (years) | 65 (47–84) | 70 (47–87) | 0·090 |
| Sex | | | 0·83 |
| Male (n=55) | 30 (55%) | 25 (45%) | .. |
| Female (n=38) | 22 (58%) | 16 (42%) | .. |
| Disease isotype | | | 0·31 |
| IgG (n=61) | 36 (59%) | 25 (41%) | .. |
| IgA (n=21) | 10 (48%) | 11 (52%) | .. |
| Light chain (n=9) | 6 (67%) | 3 (33%) | .. |
| Other (n=2) | 0 (0%) | 2 (100%) | .. |
| Disease status (per IMWG criteria) | | | 0·0046 |
| Complete response or very good partial response (n=48) | 30 (63%) | 18 (38%) | .. |
| Partial response (n=16) | 12 (75%) | 4 (25%) | .. |
| Stable disease or progressive disease (n=27) | 8 (30%) | 19 (70%) | .. |
| Unable to assess (n=2) | 2 (100%) | 0 (0%) | .. |
| Neutropenia (per CTCAE criteria) | | | 0·23 |
| ≥ Grade 2 neutropenia (n=13) | 5 (38%) | 8 (62%) | .. |
| < Grade 2 neutropenia (n=80) | 47 (59%) | 33 (41%) | .. |
| Lymphopenia (per CTCAE criteria) | | | 0·15 |
| ≥ Grade 2 lymphopenia (n=24) | 10 (42%) | 14 (58%) | .. |
| < Grade 2 lymphopenia (n=69) | 42 (61%) | 27 (39%) | .. |
| Immunoparesis | | | 0·039 |
| Immunoparesis (n=43) | 19 (44%) | 24 (56%) | .. |
| No immunoparesis (n=50) | 33 (66%) | 17 (34%) | .. |
| Days between vaccination and antibody test | 32 (21–56) | 34 (22–61) | 0·38 |
| Previous lines of therapy | 1 (0–3) | 1 (0–8) | 0·0059 |
| Previous autologous HSCT | | | 0·61 |
| ≤12 months (n=8) | 6 (75%) | 2 (25%) | .. |
| >12 months (n=69) | 37 (54%) | 32 (46%) | .. |
| No previous autologous HSCT (n=16) | 9 (56%) | 7 (44%) | .. |
| Therapy status | | | 0·037 |
| On therapy (n=66) | 32 (48%) | 34 (52%) | .. |
| Not on therapy (n=27) | 20 (74%) | 7 (26%) | .. |
| Therapy type† | | | |
| Immunomodulatory drug (n=44) | 20 (45%) | 24 (55%) | 0·60 |
| Not on an immunomodulatory drug (n=22) | 12 (55%) | 10 (45%) | .. |
| Proteasome inhibitor (n=18) | 10 (56%) | 8 (44%) | 0·58 |
| Not on proteasome inhibitor (n=48 ) | 22 (46%) | 26 (54%) | .. |
| Steroid (n=42) | 17 (40%) | 25 (60%) | 0·12 |
| Not on steroid (n=24) | 15 (63%) | 9 (38%) | .. |
| Anti-CD38 antibody (n=21) | 11 (52%) | 10 (48%) | 0·79 |
| Not on anti-CD38 antibody (n=45) | 21 (47%) | 24 (53%) | .. |
| Other therapy (bendamustine, cyclophosphamide, or belantamab mafodotin; n=10) | 1 (10%) | 9 (90%) | 0·013 |
| No other therapy (n=56) | 31 (55%) | 25 (45%) | .. |

Data are number of patients (%) or median (range). Percentages represent proportion of patients using the row totals. CTCAE=Common Terminology Criteria for Adverse Events. HSCT=haematopoietic stem-cell transplantation. *p values were calculated by use of the Fisher's Exact test (or Fisher-Freeman-Halton test where the contingency table was more than 2x2) for categorical characteristics and the Mann-Whitney test for continuous characteristics. Under "Therapy type", p values for each pair are given in the first row of the pair. †A total of 66 patients were on therapy at the time of vaccination; some patients were on more than one therapy so these groups are not mutually exclusive. IMWG=International Myeloma Working Group.

***Table:*** **Comparison of positive and negative anti-SARS-CoV-2 spike protein S1 IgG antibody groups**

significant difference included immunoparesis at the time of vaccination and more previous lines of therapy. Being on any therapy at the time of vaccination was associated with a lower rate of positive antibody result, but no specific treatment was associated with low rates compared with other treatments. Eight patients had an autologous haematopoietic stem-cell transplantation (HSCT) within 12 months before vaccination, of whom six (75%) had positive antibodies; all six patients were in at least a partial response.

Further analysis of 40 of the 41 patient samples that were IgG negative after vaccination was done using the Total antibody assay, which measures anti-SARS-CoV-2 IgG, IgM, and IgA levels. The Total antibody assay gave a positive result in 13 (33%) of these patients. A positive antibody result after first vaccination, either IgG or Total or both, was seen in 65 (70% [95% CI 61–79]) of 93 patients.

Positive IgG antibody results before vaccination were found in seven patients (with PCR-proven or highly clinically suspected COVID-19 infection in six of these patients) and not all patients had pre-vaccination antibody testing done in this real world study. To consider proven vaccine conversion rate (ie, antibody negative pre-vaccine to antibody positive post-vaccine), we looked at the subset of patients who were documented to be IgG antibody negative before vaccination (n=40). Of these, 19 (48%) patients became IgG antibody positive, rising to 28 (70%) patients when considering Total antibody response.

In summary, we found anti-SARS-CoV-2 IgG in 56% (95% CI 46–66) of patients after their first vaccination, which rises to 70% (95% CI 61–79) when measuring Total antibody. This rate is lower than in the vaccine trials, in which serological response is almost universal.[4,5] We found the same seropositive rates reported in trials when testing hospital staff with the same test as used in the patients with multiple myeloma (177 staff were tested post-vaccination, showing a SARS-CoV-2 IgG positive rate of 99% [175 of 177]). However, the IgG response rates seen in our patients are higher than that reported by Monin-Aldama and colleagues[3] in patients with cancer, although different laboratory tests and patient populations might have contributed to this difference. Importantly, we find no difference between the Pfizer and AstraZeneca vaccines, supporting the current advice for patients with multiple myeloma to receive whichever is available. Our data suggest lower positive antibody rates in patients with active multiple myeloma, patients with immunoparesis, and patients on any treatment. The only easily reversible risk factor of these is being on therapy, although we did not identify any specific treatment associated with a lower seropositive rate than others. Where possible in our centre, we advised patients to avoid vaccination on a day they were receiving anti-myeloma therapy except immunomodulatory agents. Omission of therapy pre-vaccination and post-vaccination should be balanced against the risk of disease relapse, so this decision making will need to be individualised. Importantly, positive antibody rates in patients vaccinated within a year of autologous HSCT were good. The strongest association with poor response to vaccination was having poorly controlled multiple myeloma, suggesting that active disease might play a major role in attenuation of vaccine effect.

In the vaccine clinical trials, IgG response was associated with protection from infection and from severe disease, although it is important to note that measured IgG antibodies are not equivalent to neutralising antibodies, and the strength of association between IgG response and clinical protection is uncertain, especially in an immunocompromised population.[4–6] However, our data suggest that most patients with multiple myeloma are likely to have some protection after one vaccination, which might improve after second vaccination. We saw no serious COVID-19 infections or associated deaths in this cohort during the period of data collection, but longer follow-up is needed to assess the degree of clinical protection from severe COVID-19 infection afforded by vaccination. That at least 30% of patients did not have a positive antibody test after first vaccination is concerning, and it will be important to track this group closely, as non-responders could be left vulnerable to severe COVID-19 infection. These patients might need to take extra precautions to reduce infection risk, although they might have some degree of protection through other immune mechanisms or after their second vaccination. Additional studies in patients with multiple myeloma and those with other malignancies—including studies testing the wider immune repertoire, such as antigen-specific T-cell induction—are urgently required.

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