Immunologic Responses After COVID-19 Vaccination in Patients With Membranous Nephropathy Receiving Anti–CD38 Felzartamab Therapy: Results From the Phase 1b/2a M-PLACE Study

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INTRODUCTION

Mass vaccination against SARS-CoV-2 has been one of the pivotal public health strategies to curb the COVID-19 outbreak. Currently, there are insufficient data on the immune response to COVID-19 vaccines in patients with autoimmune kidney diseases, especially those receiving immunosuppressive drugs. Patients who are immunocompromised are at a higher risk of a severe disease course if infected with SARS-CoV-2 and are less likely to mount an adequate immune response to vaccination.1

Primary membranous nephropathy (MN) is an autoimmune kidney disease and a leading cause of nephrotic syndrome in adults worldwide.2 Approximately 75% of primary MN cases arise because of autoantibodies that target the phospholipase A2 receptor (PLA2R) on podocytes.2 High titers of anti-PLA2R autoantibodies have been associated with more severe disease courses and a longer time to achieve remission.3 The probable source of anti–PLA2R antibodies is CD38 high-expressing plasmablasts and plasma cells.4,5

Depleting B cells (plasma cell precursors) has been recognized as a promising therapeutic strategy for autoimmune diseases, with a number of agents currently under development or approved for clinical use.4,6 However, these treatments have been associated with impaired humoral response after COVID-19 vaccination.1,7

Felzartamab (MOR202), an investigational, fully human IgG1 anti-CD38 monoclonal antibody that depletes plasmablasts and plasma cells via antibody-dependent cell-mediated cytotoxicity and antibody-dependent cell-mediated phagocytosis, is currently being evaluated for the treatment of anti-PLA2R antibody-positive MN.2,8

To elucidate whether the plasma cell-depleting effect of felzartamab precludes response to vaccination against SARS-CoV-2, the Roche Elecsys anti-SARS-CoV-2 S assay was used to investigate the humoral immune responses of COVID-19 vaccines in patients with anti-PLA2R antibody-positive MN treated with felzartamab in the ongoing phase 1b/2a M-PLACE study (NCT04145440).2 (Supplementary Methods).

RESULTS

Of the 31 patients enrolled in the M-PLACE study, 19 (61.3%) were vaccinated against SARS-CoV-2. Among these patients, the median age was 63 years, 73.7% received at least 2 doses of a COVID-19 vaccine, the majority (68.4%) were vaccinated with the Pfizer-BioNTech vaccine, and 47.4% received their first vaccination after initiation of felzartamab treatment (Table 1, Supplementary Figure S1, and Supplementary Table S1).

Patients with MN treated with felzartamab showed a comparable humoral response to COVID-19 vaccination to that observed after vaccination in a healthy
expression regarding vaccination status, are shown in patients with positive titers, but with missing information after initiating felzartamab treatment (Figure 1b). Vaccine used or whether vaccination took place before or after initiating felzartamab treatment (median 1,768.0 binding antibody unit/ml), and those vaccinated after initiating felzartamab treatment (median 816.7 binding antibody unit/ml). The anti-SARS-CoV-2 antibody titer in response to infection, indicating that felzartamab treatment does not preclude immune responses to SARS-CoV-2 infection (Supplementary Figure S3). No correlation between felzartamab treatment and severity of subsequent SARS-CoV-2 infection was confirmed.

### Table 1. Demographics and COVID-19 vaccination details of patients included in the M-PLACE study

| Patient data                  | Patients vaccinated (N = 19) |
|-------------------------------|-----------------------------|
| Patient characteristics      |                             |
| Age, median (yrs)            | 63                          |
| Female, n (%)                 | 4 (21.1)                    |
| Prior IST, n (%)              | 10 (52.6)                   |
| Number of felzartamab doses, n (%) |                             |
| 1–3                          | 2 (10.5)                    |
| 4–6                          | 3 (15.8)                    |
| 7–9                          | 14 (73.7)                   |
| Number of COVID-19 vaccination doses, n (%) |                 |
| 1                            | 5 (26.3)                    |
| 2                            | 13 (68.4)                   |
| 3                            | 1 (5.3)                     |
| COVID-19 vaccine, n (%)       |                             |
| Pfizer-BioNTech (Comirnaty)  | 13 (68.4)                   |
| Moderna (Spikevax)           | 3 (15.8)                    |
| AstraZeneca (Vaxzevria)       | 3 (15.8)                    |
| Time of first vaccination, n (%) |                             |
| Median (Q1, Q3), days        |                             |
| Before felzartamab treatment start | 10 (52.6)                |
| After felzartamab treatment start | 9 (47.4)                 |
| During felzartamab treatment  | 6 (31.6)                    |
| Post-felzartamab treatment   | 3 (15.8)                    |
| Anti-SARS-CoV-2 antibody titer (BAU/ml), median (Q1, Q3) | 205 (190, 208) |
| Patients vaccinated before felzartamab treatment start | 816.7 (92.5, 2,336.3) |
| Patients vaccinated after felzartamab treatment start | 768.0 (716.9, 2,082.0) |
| During felzartamab treatment  | 876.0 (269.5, 1,788.8)     |
| Post-felzartamab treatment   | 2,082.0 (1,925.0, 14,041.0) |

BAU, binding antibody units; IST, immunosuppressive therapy; Q1, first quartile; Q3, third quartile.

*Anti–SARS-CoV-2 antibody titer at baseline (cycle 1, day 1) used for analysis.

*Best anti–SARS-CoV-2 antibody titer used for analysis.

In the M-PLACE study, a total of 5 patients, with or without COVID-19 vaccination, were reported with SARS-CoV-2 infection (Supplementary Table S2). Of these, 3 patients were reported with treatment emergent adverse events as follows: 2 patients with mild COVID-19 disease (patients S2.1 and S2.3) and 1 patient with severe COVID-19 disease course (patient S2.2) during felzartamab treatment. The remaining 2 patients were reported with non-treatment-emergent COVID-19 disease. Of these, 1 patient was reported with a mild asymptomatic SARS-CoV-2 infection during the screening period (patient S2.4), and the other patient was reported with non-treatment-emergent COVID-19 of moderate severity 43 days after the last felzartamab dose (patient S2.5). Patients with mild or moderate SARS-CoV-2 infection recovered with or without medical intervention, while the patient with severe infection required hospitalization to treat pulmonary, gastrointestinal tract, and other generalized COVID-19 manifestations and was recovering at the time of latest follow-up. More specifically, this 43-year-old unvaccinated patient who was newly diagnosed with MN and had not received any prior immunosuppressive therapy experienced a severe SARS-CoV-2 infection, which was not suspected to be related to felzartamab (as assessed by the investigator, considering the patient’s underlying disease status, relevant medical history, and general risk during an ongoing COVID-19 pandemic) of contracting COVID-19 and was managed with medical intervention including oxygen therapy (no intubation or intensive care unit admission required). The patient had received 6 doses of felzartamab over a 2-month period before the infection yet was able to generate a very high anti–SARS-CoV-2 antibody titer in response to infection, indicating that felzartamab treatment does not preclude immune responses to SARS-CoV-2 infection (Supplementary Figure S3). No correlation between felzartamab treatment and severity of subsequent SARS-CoV-2 infection was confirmed.

### Discussion

B cell depletion with anti–CD20 immunosuppressive monoclonal antibodies, such as rituximab and ocrelizumab, has been associated with impaired humoral response to COVID-19 vaccination, although most of these patients subsequently developed at least T cell responses to SARS-CoV-2.4,5,10 The failure in humoral response may be attributed to the fact that anti–CD20 therapeutic approaches completely eradicate the circulating B cell compartment, except for terminal differentiated CD20−/CD38+ plasma cells. B cells are an essential cell population of the adaptive immune system, as they...
Figure 1. Comparison of anti-SARS-CoV-2 antibody titers in patients from the M-PLACE study. Patients vaccinated after start of felzartamab treatment: results before, after first, or after second vaccination (a). Patients vaccinated before (left graph) or after (right graph) the start of felzartamab treatment (b). BAU, binding antibody units; LLOQ, lower limit of quantification; Q1, first quartile; Q3, third quartile; ULOQ, upper limit of quantification.
recognize and react to newly encountered antigens, such as vaccines, by activation and antibody secretion. Therefore, the timing of COVID-19 vaccine administration in patients receiving B cell depletion therapies is a key factor to consider. Currently, any recommendations on the optimal interval between COVID-19 vaccination and anti-CD20 antibody therapy are being extrapolated from previous vaccine studies and B cell repopulation kinetics.\textsuperscript{511–514}

The potential impact of anti-CD38 antibody therapies on COVID-19 vaccination efficacy has been investigated in several studies, primarily in patients with multiple myeloma receiving daratumumab or isatuximab. Results of these studies are mixed, but there is accumulating evidence that anti–CD38 antibody therapies can impair immune response to SARS-CoV-2 vaccine in these patients.\textsuperscript{6–9} However, because of the underlying disease pathology and continuous therapies that may alter the humoral immune response, such data cannot be used to draw inferences for patients with autoimmune kidney diseases.

This analysis from the M-PLACE study suggests that maintenance of the earlier B cell compartment may correlate with the capability of patients with MN to have a positive humoral response to COVID-19 vaccination, irrespective of felzartamab treatment. Notably, humoral responses were comparable in patients vaccinated before or after initiating felzartamab treatment, implying that the timing of COVID-19 vaccine administration may not be critical. A reduction in SARS-CoV-2 antibody titer over time was also observed, mainly in patients vaccinated before initiating felzartamab treatment. Although SARS-CoV-2 antibody titers remained detectable for all patients throughout the felzartamab treatment phase and with the observed reduction being in line with data on antibody kinetics in healthy individuals,\textsuperscript{512} a final conclusion on the impact of felzartamab treatment on SARS-CoV-2 antibody kinetics cannot yet be made, as direct comparison to an untreated population is not available.

Limitations of these analyses include the small sample size. Assessment of neutralizing SARS-CoV-2 antibody titer was not performed; however, a good correlation between the cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript Biotech Corporation, Piscataway, NJ), which has been issued Emergency Use Authorization by the US Food and Drug Administration,\textsuperscript{516} and the Roche binding antibody units used in this analysis has been previously reported.\textsuperscript{517,518} Cellular immune response was not evaluated in this study.

Felzartamab is currently under investigation in 2 phase 2a trials to assess its efficacy, safety, and pharmacokinetic or pharmacodynamic properties in patients with anti-PLA2R antibody-positive MN (NewPLACE; NCT04733040) and IgA nephropathy (IGNAZ; NCT05065970), in a phase 2 rescue therapy trial in patients with MN (MONET; NCT04893096), and in a phase 2 prospective trial in kidney transplant recipients with late antibody-mediated rejection (NCT05021484).

In conclusion, patients with MN receiving felzartamab can achieve a robust immune response when vaccinated with currently available replication-competent vector vaccines or mRNA vaccines against SARS-CoV-2, before initiating or during treatment. Nevertheless, because of the small sample size and the generally observed heterogeneous response to COVID-19 vaccinations in humans, results should be interpreted with caution and additional evidence is needed to confirm these findings.

**DISCLOSURE**

I-Mab has licensed rights to exploit felzartamab (MOR202/TJ202) in the greater China territory. I-Mab has initiated a phase 2 (NCT03860038) and a phase 3 (NCT03952091) study to evaluate felzartamab in patients with multiple myeloma, and a phase 1 study (NCT05140824) in patients with systemic lupus erythematosus. BHR is a scientific advisor for MorphoSys AG. RB, AT are employees of MorphoSys AG. PMR is a consultant for MorphoSys AG.

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**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)
Supplementary Methods.
Supplementary References.
Figure S1. Patient flow chart.
Figure S2. Patients with positive SARS-CoV-2 antibody titer at the start of felzartamab treatment who were excluded from analysis, as vaccination status data are missing.
Figure S3. Anti-SARS-CoV-2 antibody titer in the patient with severe SARS-CoV-2 infection after exposure to felzartamab (patient S2.2 in Supplementary Table S2).
Table S1. Overview of treatment, vaccination details and anti-SARS-CoV-2 antibody titers of patients included in the M-PLACE study.
Table S2. Overview of patients with COVID-19 infection in the M-PLACE study.
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