



Original article

Longitudinal humoral and cellular immune responses to COVID-19 vaccination in persons with multiple sclerosis across disease-modifying therapy classes

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ABSTRACT

Background: Humoral responses to COVID-19 vaccination are attenuated in some people with multiple sclerosis (PwMS), particularly those receiving B-cell-depleting therapies or sphingosine-1-phosphate receptor modulators (S1PR). Less is known about how disease-modifying therapies (DMTs) shape cellular responses over time.

Objective: Evaluate longitudinal SARS-CoV-2 Spike IgG and antigen-specific T-cell responses in vaccinated PwMS across DMT classes in a decentralized study.

Methods: COVER-MS participants underwent decentralized biospecimen collection through Quest Diagnostics Patient Service Centers or mobile phlebotomy, paired with electronic surveys through iConquerMS. The study included 183 participants at Visit 1, 161 at Visit 2, and 141 at Visit 3. Spike IgG was categorized into ordered levels, and SARS-CoV-2-specific T-cell responses were measured using QuantiFERON Ag1, Ag2, and Ag3 interferon-gamma release assays. Participant-level mixed-effects models evaluated associations for DMTs, visit, and DMT × visit interactions.

Results: Longitudinal immune-response patterns differed across DMTs for Spike IgG (omnibus DMT × visit $p=0.003$) and Ag1 ($p=0.025$). B-cell depleters were associated with lower Spike IgG responses, with further attenuation by Visit 3, while Ag1-Ag3 responses were preserved. S1PR modulators were consistently associated with lower Spike IgG and Ag1-Ag3 responses. Fumarate-treated PwMS had lower cellular responses at later visits, with a significantly more negative Visit 1 to Visit 2 change in Ag1. Prior SARS-CoV-2 infection was associated with higher humoral and cellular responses, and mRNA-1273 vaccination was associated with higher Spike IgG. **Conclusion:** DMT class was associated with distinct humoral and cellular SARS-CoV-2 immune-response profiles in vaccinated PwMS, supporting multidimensional immune assessment and decentralized longitudinal biospecimen collection in MS research.

1. Introduction

COVID-19 vaccination has been broadly effective in reducing morbidity and mortality across the general population. (Khouri et al., 2021; Pushparajah et al., 2021) For people with multiple sclerosis (PwMS), however, concerns arose early in the pandemic regarding

whether disease-modifying therapies (DMTs) would impair vaccine-induced immunity. (Achiron et al., 2021; Sabatino et al., 2022) This was particularly true for PwMS on B cell depletion therapy. (Apostolidis et al., 2021) Initial analyses from the COVER-MS (COVID-19 Vaccine Response in MS) study demonstrated that COVID-19 vaccination was safe in PwMS. (Briggs et al., 2022) A

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subsequent COVER-MS publication showed that while vaccination was clinically protective, breakthrough infections and reinfections were substantially more common among individuals using anti-CD20 and sphingosine-1-phosphate receptor modulator (S1PR) therapies. (Briggs et al., 2025)

Earlier studies of COVID-19 vaccine-induced immune response in PwMS focused primarily on humoral immunity (i.e., anti-spike antibody responses). However, cellular immunity, particularly T-cell responses, plays a central role in mitigating severe COVID-19 outcomes and may remain detectable even when antibody responses are poor. For example, individuals receiving anti-CD20 therapies often exhibit impaired antibody generation but may retain functional T-cell responses due to preserved T-cell compartments. (Apostolidis et al., 2021; Mrak et al., 2021) Similarly, patients receiving S1PR modulators exhibit lymphocyte sequestration and attenuated humoral responses, but the extent to which SARS-CoV-2-specific cellular responses remain detectable across time has been less clear. (Achiron et al., 2021)

Understanding T-cell responses in PwMS is important for interpreting vaccine-associated protection, risk stratification, and individualized counseling around vaccination and infection mitigation. To address these gaps, the COVER-MS Biological Substudy used a real-world, decentralized design to measure SARS-CoV-2-specific humoral and cellular immune responses across DMT classes over repeated timepoints, enabling longitudinal immune profiling without requiring travel to specialty MS centers.

The present manuscript integrates these biological substudy findings with prior COVER-MS work to provide a broader picture of vaccine-associated immunity across DMT categories in MS. By combining Spike IgG and SARS-CoV-2 antigen-specific interferon-gamma release assays in a geographically distributed cohort, this study evaluates how MS therapies differentially shape humoral and cellular immune responses under real-world conditions, including whether response trajectories over time differ across DMT classes.

2. Materials and methods

2.1. Ethics statement

The study was approved by an independent ethics review board (WCG IRB, formerly Copernicus Group IRB), and participants electronically provided informed consent prior to enrollment. Analysis of de-identified data was deemed research not involving human subjects by the Case Western Reserve University IRB (IRB No.: STUDY20210761).

2.2. Study design

The study was designed by a multidisciplinary team that included persons with MS (PwMS), experts in neurology, neuroinflammation, and MS epidemiology, and representatives from Accelerated Cure Project (ACP), Quest Diagnostics, and the National Multiple Sclerosis Society (NMSS). Oversight was provided by a multi-stakeholder Steering Committee.

Participants were recruited from iConquerMS members participating in COVER-MS, and who reported neurologist-confirmed MS diagnosis, U.S. residence, and COVID-19 vaccination. (Briggs et al., 2022; Briggs et al., 2025) Participant-reported treatment histories were reviewed to facilitate targeted recruitment of PwMS using DMTs of interest. Invitations were distributed in batches to moderate enrollment rates, and consent was completed electronically through the iConquerMS portal.

A total of 953 COVER-MS participants were contacted, of whom 236 consented and enrolled in this substudy, representing residents across 41 U.S. states and the District of Columbia. Blood collection kits containing blood collection tubes, cold packs, and shipping materials were mailed to participants with instructions for scheduling sample collection appointments. Participants scheduled collections through local Quest Diagnostics Patient Service Centers (PSCs) using their online scheduling

portal. Individuals unable to travel because of distance, disability, or transportation barriers were offered mobile phlebotomy services through a Quest mobile phlebotomy provider (Exam One). Following collection, samples were shipped to a Quest Diagnostics specialty laboratory for processing. Overall, 228 participants successfully provided at least one blood sample.

2.3. Sample collection and participant survey

Participants were instructed to complete an electronic survey through the iConquerMS portal following blood collection. Survey domains included COVID-19 vaccination history, recent SARS-CoV-2 infections and treatments, recent MS relapses, DMT use, corticosteroid exposure, and tixagevimab plus cilgavimab (Evusheld™) administration. After laboratory processing, clinically relevant antibody results were returned to participants through the COVER-MS study portal, hosted by a HIPAA-compliant, secure, commercial cloud-based vendor.

Approximately six months following the initial collection (Visit 1; V1), participants were invited to complete a second collection (Visit 2; V2), followed approximately six months later by a third collection (Visit 3; V3). Of the 228 participants who provided at least one blood sample, 206 completed at least two collections and 189 completed all three, corresponding to 83% biospecimen-collection retention through V3. Following linkage of survey and laboratory data and visit-specific quality-control procedures described below, the analytic samples included 183 participants at V1, 161 at V2, and 141 at V3 (eFigure 1). The resulting longitudinal analytic dataset contained 485 participant-visits from 183 unique participants.

2.4. Laboratory assays

Measurement of anti-SARS-CoV-2 antibodies. Anti-spike protein and neutralizing SARS-CoV-2 antibodies were measured by Quest Diagnostics (test code 39,820). (Asashima et al., 2023)

Measurement of Nucleocapsid SARS-CoV-2 antibodies. SARS-CoV-2 nucleocapsid antibodies were measured using the U.S. FDA Emergency Use Authorization (EUA)-approved Roche Cobas Elecsys Anti-SARS-CoV-2 immunoassay. (Marasco et al., 2022) This electrochemiluminescence assay qualitatively detects antibodies directed against recombinant SARS-CoV-2 nucleocapsid antigen using a sandwich immunoassay format. Chemiluminescent signals were compared against calibrated cutoff values and interpreted as reactive or non-reactive according to manufacturer specifications.

Measurement of T-Cell-Mediated Immune Responses. T-cell responses were evaluated with the Qiagen QuantiFERON SARS-CoV-2 Starter Set Blood Collection Tubes, which consists of two antigen tubes, SARS-CoV-2 Ag1 and SARS-CoV-2 Ag2. (Johnson et al., 2023) These assays contain proprietary SARS-CoV-2 peptide antigens designed to stimulate lymphocytes in heparinized whole blood involved in cell-mediated immune responses, along with internal negative (Nil) and positive (Mitogen) controls.

The Ag1 tube contains CD4+ epitopes derived from the S1 receptor binding domain of the spike protein and primarily stimulates helper T-cell responses. The Ag2 tube contains CD4+ and CD8+ epitopes derived from the S1 and S2 spike subunits. The Ag3 tube contains CD4+ and CD8+ epitopes from S1 and S2 in addition to immunodominant CD8+ epitopes derived from the broader SARS-CoV-2 genome. Plasma harvested from stimulated samples was used for detection of interferon-gamma (IFN- γ) using the QuantiFERON ELISA. The Mitogen control served as a positive control reflecting nonspecific T-cell IFN- γ responsiveness.

2.5. Analytic sample and data quality control

Prior to analysis, completed survey and laboratory data were harmonized by visit and underwent quality control procedures to ensure

temporal consistency between specimen collection, survey completion, vaccination, Evusheld™ administration, and DMT exposure dates. Participants were included for a given visit if they had both antibody assay data and a corresponding survey completed within seven days of blood collection. Records were excluded when survey completion preceded sample collection, when vaccination occurred between blood collection and survey completion such that vaccination status at collection could not be determined, or when reported Evusheld™ administration occurred after the collection date. DMT exposure dates were reviewed for implausible or ambiguous entries and reconciled with self-reported current treatment status when appropriate.

2.6. Outcome variables

Humoral and cellular immune responses were evaluated at each study visit (V1–V3). Spike-specific IgG concentrations were categorized into four ordered levels based on assay thresholds with prominent floor and ceiling values: 0 = <0.8 IU/mL (undetectable), 1 = 1–49 IU/mL, 2 = 50–99 IU/mL, and 3 = ≥100 IU/mL.

T-cell responses were quantified using background-subtracted IFN- γ release values (Ag–Nil) following stimulation with SARS-CoV-2 antigen pools Ag1 (CD4-biased), Ag2 (CD8-biased), and Ag3 (mixed CD4/CD8). For the primary longitudinal analyses, Ag1–Ag3 values were inverse-rank normalized across all available participant-visits to address the right-skewed distributions. For secondary visit-specific analyses, Ag1–3 responses were categorized into quartiles representing ordered gradients of cellular immune activation.

2.7. Disease-modifying therapy classification

Current DMTs at each visit were grouped into nine categories based on mechanism of action and clinical relevance: (1) B-cell depleters (e.g., ocrelizumab, ofatumumab, rituximab); (2) S1P receptor modulators (e.g., fingolimod, ozanimod, siponimod); (3) fumarates; (4) glatiramer acetate; (5) pyrimidine antimetabolites (e.g., teriflunomide); (6) alpha4-integrin inhibitors (e.g., natalizumab); (7) purine antimetabolites (e.g., cladribine); (8) interferon beta; and (9) CD52 monoclonal antibody therapies. Participants not actively receiving a DMT served as the reference group for DMT comparisons. For the primary longitudinal models, DMT exposure was treated as time-varying and collapsed into five categories to reduce sparse longitudinal strata: not actively on a DMT, B-cell depleters, S1PR modulators, fumarates, and other DMTs. The other-DMT category comprised glatiramer acetate, pyrimidine antimetabolites, alpha4-integrin inhibitors, purine antimetabolites, interferon beta, and CD52 monoclonal antibody therapies.

2.8. Statistical analyses

The primary analytic objective was to evaluate longitudinal differences in humoral and cellular immune responses across DMT groups while accounting for repeated measurements within participants. For Ag1, Ag2, and Ag3, pooled inverse-rank-normalized IFN- γ responses were analyzed using linear mixed-effects regression with participant-specific random intercepts. Spike IgG category was analyzed using mixed-effects ordered logistic regression. Visit was modeled categorically (V1, V2, V3), and models included current DMT group, visit, and a DMT-by-visit interaction. Omnibus Wald tests of the DMT-by-visit interaction were used to assess whether longitudinal response patterns differed across DMT groups. Linear combinations of model coefficients were used to estimate adjusted DMT-versus-no-DMT contrasts at each visit. Models adjusted for baseline age, sex, ethnicity, race, MS disease course, and disease duration, as well as visit-specific self-reported prior SARS-CoV-2 infection, vaccine type, days since most recent vaccination,

Evusheld™ exposure, and current DMT. Cellular-response models additionally adjusted for Mitogen–Nil IFN- γ response. Mitogen–Nil was not included in the Spike IgG model. The vaccination-related covariates were with respect to the most recent vaccine dose and did not capture all possible vaccines or boosters received between survey completion. Sensitivity analyses excluding PwMS with Evusheld exposure were conducted.

As secondary analyses, separate multivariable ordered logistic regression models were fit for each outcome, and retained the more detailed DMT classification and estimated the adjusted odds ratio (OR) of being in a higher immune-response category. Proportional odds assumptions were evaluated using standard model diagnostics. These visit-specific analyses provided complementary estimates to the primary longitudinal models.

Concordance between self-reported prior SARS-CoV-2 infection and anti-nucleocapsid antibody status was examined descriptively at each study visit. Because anti-N antibodies may wane over time and may be less reliably detected following infection among participants receiving B-cell-depleting therapies, anti-nucleocapsid positivity was not considered a gold-standard measure of prior infection. As a sensitivity analysis, the primary longitudinal models were repeated using an alternative time-varying infection definition in which participants were classified as infected if they either reported prior SARS-CoV-2 infection or were anti-nucleocapsid positive at that visit; participants reporting uncertain infection history who were anti-nucleocapsid negative remained classified as uncertain.

A two-sided $\alpha=0.05$ was considered statistically significant. All analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).

3. Data availability

COVER-MS data are available to qualified researchers from iConquerMS™.

4. Results

The cohort was predominantly middle-aged (mean 55.3 years (SD 11.4)) and female (87%), with representation across relapsing-remitting, secondary progressive, and primary progressive MS (Table 1). Most participants had long-standing MS and were receiving DMTs, with all major therapeutic classes represented, though the majority (35%) were on B-cell depleter DMTs. All participants had received at least one SARS-CoV-2 vaccine dose prior to enrollment, and 47% reported prior COVID-19 infection. Participants with complete data at V2 and V3 were similar in characteristics.

Baseline immunologic measures (Spike IgG, Ag1–Ag3 responses, and Mitogen–Nil) demonstrated substantial inter-individual variability, reflecting heterogeneity in both humoral and cellular responses over time. These immunological patterns differed markedly by DMT class (Figs. 1–4).

Self-reported prior SARS-CoV-2 infection and anti-nucleocapsid positivity showed substantial discordance (eTable 1). Among participants reporting prior infection, 20/86 (23.3%), 24/102 (23.5%), and 18/98 (18.4%) were anti-nucleocapsid positive at V1, V2, and V3, respectively. Conversely, anti-nucleocapsid positivity among participants reporting no prior infection was uncommon (4/83 [4.8%], 2/52 [3.8%], and 1/37 [2.7%], respectively). The small number of anti-nucleocapsid-positive/self-report-negative observations limited meaningful characterization of this discordant subgroup. Thus, discordance primarily reflected self-reported infection in the absence of detectable anti-nucleocapsid rather than anti-nucleocapsid positivity among participants denying prior infection.

Table 1

Attributes of the study population by study visit.

Attribute (Mean [SD] or n [%])		Visit 1	Visit 2	Visit 3
N		183	161	141
Age (years)		55.3 (11.4)	55.8 (11.6)	56.5 (11.3)
Female		160 (87.4%)	141 (87.6%)	122 (86.5%)
Hispanic/Latinx		16 (8.7%)	12 (7.5%)	9 (6.4%)
Race	White	170 (92.9%)	148 (91.9%)	131 (92.9%)
	Black	7 (3.8%)	7 (4.4%)	6 (4.3%)
	Other	4 (2.2%)	4 (2.5%)	3 (2.1%)
	Unknown	2 (1.1%)	2 (1.2%)	1 (0.7%)
	Relapsing remitting	114 (62.3%)	102 (63.4%)	88 (62.4%)
Subtype	Secondary progressive	40 (21.9%)	34 (21.1%)	30 (21.3%)
	Primary progressive	21 (11.5%)	18 (11.2%)	17 (12.1%)
	Clinically isolated syndrome	5 (2.7%)	4 (2.5%)	4 (2.8%)
Disease duration (years)	Unknown	3 (1.6%)	3 (1.9%)	2 (1.4%)
	No	15.0 (9.2)	15.6 (9.3)	16.2 (9.3)
COVID-19 infection	Yes	83 (45.4%)	52 (32.3%)	37 (26.2%)
	Unsure	86 (47.0%)	102 (63.4%)	98 (69.5%)
	Unsure	14 (7.7%)	7 (4.4%)	6 (4.3%)
Most recent vaccine manufacturer	BNT162b2 (Pfizer-BioNTech)	88 (48.1%)	76 (47.2%)	60 (42.6%)
	mRNA-1273 (Moderna)	90 (49.2%)	80 (49.7%)	75 (53.2%)
	Ad26.COV2.S (Johnson & Johnson's Janssen)	5 (2.7%)	5 (3.1%)	4 (2.8%)
Most recent vaccine was a booster	Nuvaxovid (Novavax)	0	0	2 (1.4%)
		160 (87.4%)	142 (88.2%)	109 (77.3%)
Days since most recent vaccine		178 (176)	328 (220)	365 (330)
Ever treated with Evusheld		33 (18.0%)	31 (19.3%)	27 (19.1%)
Days since Evusheld treatment		155 (95)	342 (125)	568 (133)
Current disease modifying therapy	Not actively on a DMT	50 (27.3%)	44 (27.3%)	44 (31.2%)
	B-cell depleter (Ocrevus, Kesimpta, Rituxan)	64 (35.0%)	57 (35.4%)	47 (33.3%)
	S1PR modulator (Gilenya, Mayzent, Ponvory, Tascenso)	15 (8.2%)	15 (9.3%)	12 (8.5%)
	Fumarate (Tecfidera, Vumerity)	15 (8.2%)	11 (6.8%)	9 (6.4%)
	Glatiramer acetate (Copaxone, Glatopa, Generic)	14 (7.7%)	12 (7.5%)	11 (7.8%)
	Pyrimidine antimetabolite (Aubagio)	9 (4.9%)	7 (4.4%)	7 (5.0%)
	Alpha4-integrin blocker (Tysabri)	7 (3.8%)	6 (3.7%)	5 (3.6%)
	Purine antimetabolite (Mavenclad)	6 (3.3%)	5 (3.1%)	3 (2.1%)
	Interferon beta (Plegridy, Rebif)	3 (1.6%)	3 (1.9%)	3 (2.1%)
	CD52 monoclonal antibody (Lemtrada)	0	1 (0.6%)	0
SARS-CoV2 Spike positive		157 (85.8%)	140 (87.0%)	118 (83.7%)
SARS-CoV2 Nucleocapsid positive		24 (13.0%)	26 (16.0%)	19 (13.3%)
SARS-CoV2 CD4 Eptope response (Ag1; IU/mL) ^a		0.80 (1.81)	0.78 (1.62)	0.72 (1.33)

Table 1 (continued)

Attribute (Mean [SD] or n [%])	Visit 1	Visit 2	Visit 3
SARS-Cov2 CD8 Eptope response (Ag2; IU/mL) ^a	1.21 (2.53)	1.29 (2.28)	1.30 (2.14)
SARS-Cov2 CD4/CD8 (Mixed) Eptope response (Ag3; IU/mL) ^a	1.88 (3.34)	1.79 (3.14)	1.84 (3.03)

^a Background-adjusted values

In the primary longitudinal analyses, there was evidence that immune-response trajectories differed across DMT groups for Ag1 (Wald χ^2 [8]=17.53, $p=0.025$) and Spike IgG (χ^2 [8]=23.08, $p=0.003$), whereas the omnibus DMT $\times$ visit interactions were not significant for Ag2 (χ^2 [8]=11.06, $p=0.198$) or Ag3 (χ^2 [8]=9.44, $p=0.307$) (eTable 2). Participant-level random intercepts were strongly supported for all four outcomes, consistent with within-person correlation across repeated measurements (all likelihood-ratio tests $p<0.001$; eTable 2).

4.1. Humoral (Spike IgG) responses

In the mixed-effects ordered logistic model (Table 2), B-cell depleters and S1PR modulators were both associated with markedly lower Spike IgG responses. At V1, B-cell depleter use was associated with substantially lower odds of being in a higher Spike category compared with no DMT (OR=0.014, 95% CI 0.0023–0.083, $p<0.001$), as was S1PR modulator use (OR=0.031, 95% CI 0.0030–0.32, $p=0.004$). The strongly negative V3 $\times$ B-cell interaction (interaction OR=0.024, $p<0.001$) indicated that the V1-to-V3 change in Spike IgG response was significantly more negative among B-cell-depleter participants than among those not actively receiving a DMT. Fumarate and other-DMT groups were not significantly different from the no-DMT group at V1, and their interaction terms were not significant.

Several covariates were independently associated with humoral response (Table 2). Prior SARS-CoV-2 infection was associated with higher odds of being in a higher Spike category (OR=6.40, $p<0.001$), as was mRNA-1273 vaccination compared with BNT162b2 (OR=6.35, $p<0.001$). Longer time since the most recent vaccination was associated with lower Spike response ($p=0.002$), while prior Evusheld exposure was associated with higher Spike IgG (OR=6.19, $p=0.025$).

4.2. Cellular immunity: Ag1 (CD4-biased response)

S1PR modulator use was associated with substantially lower Ag1 response at V1 compared with no DMT ($\beta=-1.51$, 95% CI -1.92 to -1.09 , $p<0.001$), and this relative deficit persisted across subsequent visits (Table 2). B-cell depletion was not associated with lower Ag1 response. Fumarate use was not significantly different from no DMT at V1 ($\beta=-0.32$, $p=0.128$), but the V2 $\times$ fumarate interaction was significantly negative ($\beta=-0.52$, 95% CI -0.90 to -0.13 , $p=0.008$), indicating a more negative V1-to-V2 change among fumarate users relative to the no-DMT group. This resulted in lower adjusted Ag1 responses among fumarate users at V2 and persisted at V3. Prior SARS-CoV-2 infection was associated with higher Ag1 response ($\beta=0.23$, $p=0.003$), and Mitogen-Nil response was strongly positively associated with Ag1 ($p<0.001$), consistent with greater overall IFN- γ responsiveness among participants with stronger Ag1 responses.

4.3. Cellular immunity: Ag2 (CD8-biased response)

For Ag2, there was no significant overall DMT $\times$ visit interaction (eTable 2), indicating no evidence that longitudinal trajectories differed across DMT groups. Nevertheless, S1PR modulator use was strongly associated with lower Ag2 response at V1 ($\beta=-1.48$, 95% CI -1.89 to -1.06 , $p<0.001$), with similarly reduced responses observed across subsequent visits (Table 2). B-cell depletion was not associated with reduced Ag2 response. Fumarate use showed a nonsignificant tendency

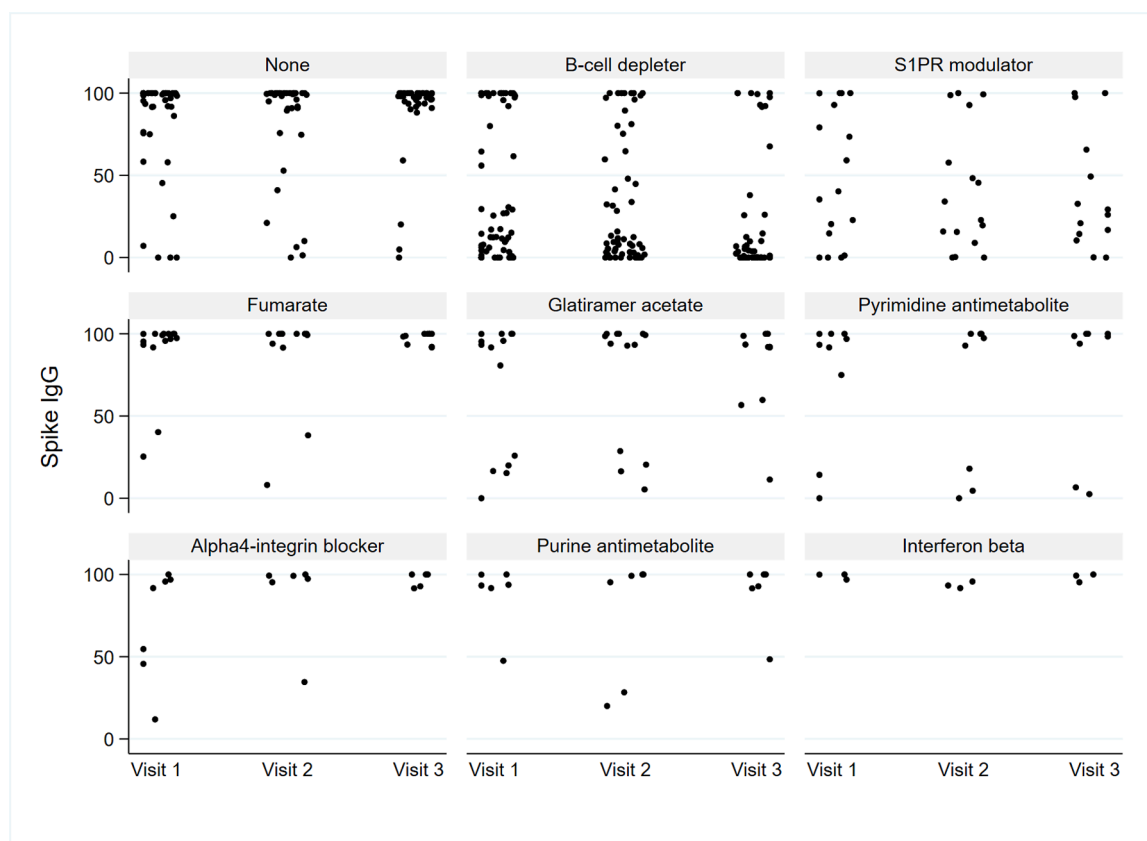


Fig. 1. Humoral responses to SARS-CoV-2 Spike IgG in persons with MS receiving various disease modifying therapies. Dot plots show anti-SARS-CoV-2 Spike IgG responses by current MS disease-modifying therapy group across three visits. The assay threshold for antibody detection was 0.8 IU/mL.

toward lower Ag2 response at V1 ($\beta = -0.37$, $p = 0.076$) and lower adjusted responses at later visits, although the individual interaction terms were not significant. Prior infection was associated with higher Ag2 response ($\beta = 0.22$, $p = 0.005$), greater Mitogen-Nil response was strongly associated with higher Ag2 response ($p < 0.001$), and longer time since vaccination was modestly associated with lower Ag2 response ($p = 0.035$).

4.4. Cellular immunity: Ag3 (mixed CD4/CD8 response)

The Ag3 model similarly showed no significant omnibus DMT $\times$ visit interaction (eTable 2). S1PR modulator use was associated with substantially lower Ag3 response at V1 ($\beta = -1.21$, 95% CI -1.61 to -0.82 , $p < 0.001$), which persisted across visits (Table 2). B-cell depletion was not associated with reduced Ag3 response. Fumarate use was not significantly different from no DMT at V1 ($\beta = -0.29$, $p = 0.161$), although the V2 $\times$ fumarate interaction was negative ($\beta = -0.43$, 95% CI -0.79 to -0.07 , $p = 0.021$); because the overall DMT $\times$ visit test was not significant, this finding should be interpreted cautiously as a visit-specific difference and not evidence of a distinct overall Ag3 trajectory. Prior infection ($\beta = 0.24$, $p = 0.001$) and Mitogen-Nil response ($p < 0.001$) were independently associated with higher Ag3 response.

4.5. Summary of immune response patterns

Overall, the longitudinal and secondary visit-specific analyses using the more granular DMT classification (eTables 3–6) demonstrated distinct DMT-associated immune-response profiles. Results were unchanged when using a combined self-reported prior infection and anti-nucleocapsid positivity variable as the infection covariate (data not shown). In sensitivity analyses excluding PwMS with prior Evusheld exposure, the principal DMT-associated associations persisted, including

markedly lower Spike IgG responses among participants receiving B-cell-depleting and S1PR-modulating therapies and lower cellular responses among S1PR modulator users; however, the omnibus DMT $\times$ visit interactions for Spike IgG and Ag1 were attenuated and no longer statistically significant in the reduced sample (eTables 7a–7b). S1PR modulators were consistently associated with attenuated humoral and cellular responses, with substantially lower Spike IgG and Ag1–Ag3 responses across visits. B-cell-depleting therapies showed a contrasting pattern, with reduced Spike IgG responses but preserved cellular immunity; in the secondary visit-specific analyses, B-cell depletion was associated with higher Ag2 response at V3 (eTable 5) and higher Ag3 responses across all visits (eTable 6). Fumarate therapy was associated with reduced cellular responses, with lower Ag1, Ag2, and Ag3 response categories across several visits (eTables 4–6) and longitudinal evidence of a greater V1-to-V2 decline in Ag1. Among less common DMTs, alpha4-integrin blockade was associated with higher cellular responses in the secondary analyses, particularly for Ag1 and Ag3 at V2 and V3 and Ag2 at V3, although estimates were imprecise because of small subgroup sizes (eTables 4–6). Glatiramer acetate, pyrimidine and purine antimetabolites, interferon beta, and CD52 monoclonal antibody therapy did not demonstrate consistent patterns across humoral and cellular outcomes.

5. Discussion

This real-world, decentralized substudy of COVER-MS provides a longitudinal evaluation of both humoral and cellular SARS-CoV-2 immune responses in vaccinated PwMS across DMT classes. Building on prior COVER-MS publications, (Briggs et al., 2022; Briggs et al., 2025) these findings show that MS therapies differentially affect Spike-specific antibody production and SARS-CoV-2 antigen-specific T-cell responses over time. The most consistent patterns were strong attenuation of Spike

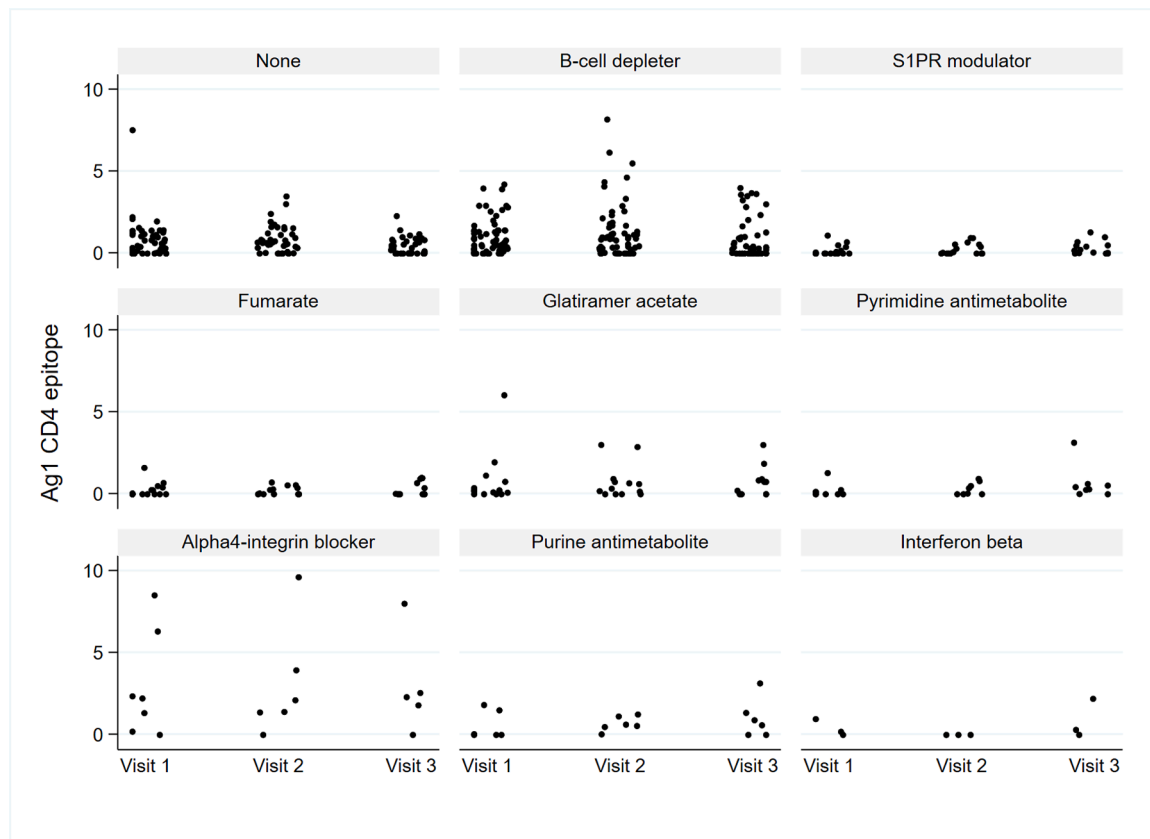


Fig. 2. CD4-biased SARS-CoV-2 T-cell responses in persons with MS receiving various disease modifying therapies. Dot plots show QuantiFERON Ag1 responses by current MS disease-modifying therapy group across three visits. Ag1 contains CD4 epitopes and is designed to evaluate CD4-biased interferon- γ responses.

IgG among participants receiving B-cell-depleting and S1PR-modulating therapies, profound and persistent suppression of Ag1-Ag3 IFN- γ responses among S1PR modulator users, and preserved or increased cellular responses among B-cell-depleted participants despite markedly reduced humoral responses. Fumarate-treated participants also demonstrated lower cellular responses at later visits, with the strongest evidence for a differential longitudinal pattern observed for Ag1. These results reinforce the importance of evaluating both antibody and T-cell compartments when assessing SARS-CoV-2 vaccine-associated immunity in immunologically heterogeneous MS populations. (Monschein et al., 2025)

5.1. Influence of DMTs on humoral and cellular immune responses

Consistent with prior COVER-MS findings and other studies, (Briggs et al., 2022; Briggs et al., 2025) humoral responses were sharply reduced among participants receiving B-cell-depleting and S1PR-modulating therapies. (Achiron et al., 2021; Briggs et al., 2025; Monschein et al., 2025; Sormani et al., 2021; Tolf et al., 2022) The current analyses extend these observations by evaluating antigen-specific IFN- γ responses across three SARS-CoV-2 antigen pools and repeated measurements. S1PR modulators showed the most consistent impairment across both humoral and cellular measures, with substantially lower Ag1-Ag3 responses throughout follow-up and lower Spike IgG responses across visits. This finding aligns with the mechanism of S1PR modulation, which limits lymphocyte egress from lymphoid tissues and reduces circulating lymphocyte availability for peripheral blood IGRA responses. Recent real-world longitudinal data similarly reported reduced serologic and cellular immunity among fingolimod-treated PwMS, in contrast to more preserved responses among those receiving several other DMTs. (Kalra et al., 2026)

B-cell-depleting therapies showed a distinct immune profile. As

expected, participants receiving B-cell depleters had markedly reduced odds of higher Spike IgG categories across all visits, with evidence that the longitudinal pattern differed from participants not actively receiving a DMT. In contrast, B-cell depletion was not associated with reduced Ag1, Ag2, or Ag3 responses in the primary longitudinal models. Secondary visit-specific analyses using the more granular DMT classification further suggested higher Ag3 response categories among B-cell-depleted participants across visits and higher Ag2 response at V3. This humoral-cellular dissociation has been observed in other studies of anti-CD20-treated PwMS, where impaired antibody production coexists with detectable or durable vaccine-induced T-cell responses. (Apostolidis et al., 2021; Jyssum et al., 2022; Davis-Porada et al., 2025; Novak et al., 2024) These findings align with longitudinal studies showing that ocrelizumab-treated PwMS often have attenuated anti-spike or spike anti-receptor binding domain antibody responses despite preserved T-cell reactivity, whereas fingolimod-treated PwMS may exhibit impairment across both humoral and cellular compartments. (Davis-Porada et al., 2025; Novak et al., 2024) Together, these data support the interpretation that B-cell depletion substantially compromises humoral immunity but does not necessarily eliminate vaccine-associated cellular immune responsiveness.

Spike IgG responses should also be interpreted in the context of prior tixagevimab/cilgavimab exposure, since Evusheld™ consists of exogenously administered anti-spike monoclonal antibodies. Higher measured Spike IgG among exposed participants may therefore partly reflect passive antibody exposure rather than endogenous vaccine- or infection-induced humoral immunity.

Other DMTs demonstrated more heterogeneous effects. Fumarates, which can be associated with variable lymphopenia, were associated with lower Ag1-Ag3 responses across visits in adjusted analyses, while humoral responses were not consistently reduced. In the longitudinal models, fumarate-treated participants were not significantly different

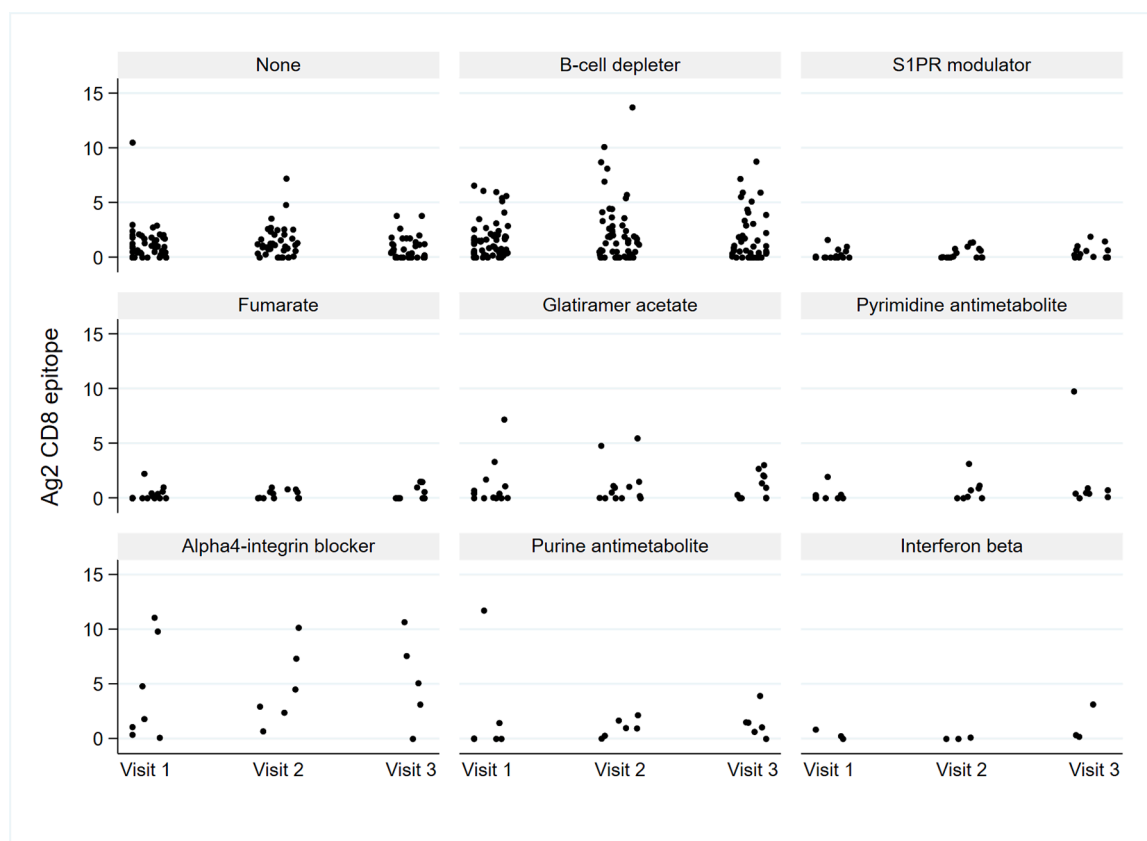


Fig. 3. CD8-biased SARS-CoV-2 T-cell responses in persons with MS receiving various disease modifying therapies. Dot plots show QuantiFERON Ag2 responses by current MS disease-modifying therapy group across three visits. Ag2 contains CD8 epitopes and is designed to evaluate CD8-biased interferon- γ responses.

from those not actively receiving a DMT at V1, but had lower Ag1 responses at V2 and V3, with a significant V2 $\times$ fumarate interaction supporting a more negative V1-to-V2 change. Lower Ag2 and Ag3 responses were also observed at later visits, although the omnibus DMT $\times$ visit interactions for these outcomes were not significant. Secondary visit-specific ordinal models similarly showed lower Ag1–Ag3 response categories among fumarate users across several visits, whereas humoral responses were not consistently reduced. This pattern may reflect effects on circulating lymphocyte populations or other immunomodulatory pathways, although interpretation should remain cautious given modest subgroup sizes.

Among less common therapies, secondary visit-specific analyses provided additional class-specific information. Cladribine, a purine antimetabolite that induces transient lymphocyte depletion followed by repopulation, showed a more nuanced pattern. Sample sizes were limited, reducing precision, but overall estimates did not suggest uniformly impaired humoral or cellular responses. This is broadly consistent with prior reports that cladribine-treated individuals can retain vaccine responsiveness, particularly when vaccination occurs outside periods of peak lymphocyte depletion. Platform therapies, including interferons and glatiramer acetate, generally demonstrated preserved humoral and cellular responses. These findings align with the immunomodulatory, rather than broadly immunosuppressive, profiles of these therapies. Natalizumab-treated participants displayed evidence of robust cellular immunity across several Ag1–Ag3 models, consistent with preserved peripheral immune function. Because natalizumab primarily blocks lymphocyte trafficking across the blood-brain barrier rather than depleting or sequestering circulating lymphocytes, preserved vaccine-induced T-cell responses are biologically plausible. However, estimates were imprecise because of small subgroup sizes and should be interpreted cautiously.

Across DMT classes, these findings underscore that MS therapies

exert distinct effects on humoral and cellular branches of the immune response. S1PR modulators were associated with the greatest impairment across both immune compartments, whereas B-cell depletion was characterized by humoral attenuation with relatively preserved of cellular responses. Fumarates showed a predominantly cellular pattern of attenuation, while several less common DMT classes demonstrated more heterogeneous or generally preserved responses.

5.2. Longitudinal immune dynamics and implications for MS care

Repeated immune measurements across three visits provided an opportunity to evaluate SARS-CoV-2 immune-response patterns under real-world conditions in PwMS over time and according to DMT status. Omnibus DMT $\times$ visit tests support differential longitudinal patterns for Spike IgG and Ag1, but not for Ag2 or Ag3. These longitudinal data support practical implications for risk stratification. PwMS receiving B-cell-depleting or S1PR-modulating therapies appear to represent immunologically vulnerable groups, but for different reasons: B-cell depletion primarily compromises antibody production, whereas S1PR modulation appears to impair both circulating antibody and T-cell IFN- γ responses. This distinction may help explain why breakthrough infections have been reported more frequently in these DMT groups in prior COVER-MS analyses, while severe outcomes remain uncommon in many vaccinated PwMS. (Briggs et al., 2022; Briggs et al., 2025) Preserved cellular immunity among B-cell-depleted participants may contribute to protection from severe disease even when circulating antibodies are low; however, circulating SARS-CoV-2-specific T-cell responses have not been established as a consistent correlate of clinical protection. In a large prospective BNT162b2 cohort, higher anti-Spike and neutralizing antibody levels were associated with lower risk of breakthrough infection, whereas measured CD4 and combined CD4/CD8 T-cell responses were not. (Seekircher et al., 2023) More



Fig. 4. Mixed CD4/CD8 SARS-CoV-2 T-cell responses in persons with MS receiving various disease modifying therapies. Dot plots show QuantiFERON Ag3 responses by current MS disease-modifying therapy group across three visits. Ag3 contains mixed CD4/CD8 epitopes and is designed to evaluate combined CD4/CD8 interferon- γ responses.

broadly, substantial inter- and intra-assay variability across SARS-CoV-2-specific T-cell assays has limited definition of standardized cellular correlates or protective thresholds. (Binayke et al., 2024) Accordingly, the preserved IFN- γ responses observed here should be interpreted as evidence of retained cellular immune responsiveness rather than as a surrogate for protection from infection or severe COVID-19; the present study was not designed to directly evaluate clinical protection.

Clinically, these results support continued attention to individualized vaccine planning, infection-prevention counseling, and rapid access to antiviral therapy for higher-risk PwMS. They do not imply that DMTs should routinely be interrupted for vaccination, but they do support discussions about vaccine timing when clinically feasible, particularly for therapies known to impair vaccine responsiveness. These decisions should remain individualized and balanced against the risk of MS disease activity. More broadly, these findings support risk-stratified vaccination strategies and closer surveillance of patients with impaired immune responsiveness. The real-world, repeated-sampling design of this study provides a template for monitoring immunologic durability across DMTs and suggests that longitudinal immune profiling may help guide vaccination practices in MS.

5.3. Decentralized and inclusive study design

A major strength of this substudy was its decentralized, real-world design, which demonstrated the feasibility of geographically distributed biospecimen collection and immune monitoring in PwMS. Participants from 41 states and the District of Columbia completed up to three blood draws through local Quest PSC or mobile phlebotomy, paired with electronic surveys through the iConquerMS portal. This approach enabled longitudinal sample collection without requiring participants to

travel to a specific specialty MS center. Operational challenges, including shipping delays, broken tubes, and temperature excursions, were mitigated through flexible scheduling, rapid reshipment, and use of local collection sites and home phlebotomy.

By reducing reliance on site-based clinic visits, the decentralized design broadened geographic participation and enhanced accessibility for PwMS who may face barriers related to disability, transportation, rural residence, or limited access to specialty care. This model is particularly relevant for MS research, where such barriers can reduce participation in traditional clinic-based studies. Together, these findings support decentralized biospecimen collection as a feasible and inclusive framework for longitudinal immunologic research in PwMS, including during public health emergencies.

5.4. Strengths and limitations

This study has several important strengths. First, the decentralized, real-world design enabled geographically broad participation across the U.S., with representation across MS disease courses and DMT classes. Repeated sampling across three visits allowed evaluation of longitudinal immune-response patterns rather than relying on a single cross-sectional assessment. In addition, the combined assessment of humoral immunity (Spike IgG) and cellular immunity (Ag1-Ag3 IFN- γ release) provided a multidimensional view of SARS-CoV-2 vaccine-associated immunity in PwMS and enabled detection of distinct immune-response profiles across DMT mechanisms. Finally, integration with prior COVER-MS publications on vaccine reactogenicity and breakthrough infections situates these immunologic findings within a broader real-world framework for understanding COVID-19 vaccine response and clinical risk in PwMS.

Several limitations should be considered. The observational design

Table 2Spike IgG mixed-effects ordered logistic model^a and cellular immune-response models^b.

Term	Higher Spike category OR (95% CI); p	Ag1 β (95% CI); p	Ag2 β (95% CI); p	Ag3 β (95% CI); p
Visit				
Visit 2	0.57 (0.14, 2.22); p=0.416	0.13 (-0.06, 0.32); p=0.176	0.15 (-0.04, 0.34); p=0.133	0.14 (-0.04, 0.31); p=0.128
Visit 3	3.66 (0.70, 19.08); p=0.124	-0.0048 (-0.20, 0.19); p=0.962	0.12 (-0.08, 0.32); p=0.229	0.09 (-0.10, 0.27); p=0.344
DMT main effects				
B-cell depleter	0.014 (0.0023, 0.083); p<0.001	0.09 (-0.18, 0.35); p=0.520	0.14 (-0.13, 0.41); p=0.310	0.21 (-0.05, 0.46); p=0.109
S1PR modulator	0.031 (0.0030, 0.32); p=0.004	-1.51 (-1.92, -1.09); p<0.001	-1.48 (-1.89, -1.06); p<0.001	-1.21 (-1.61, -0.82); p<0.001
Fumarate	5.14 (0.22, 119.8); p=0.308	-0.32 (-0.73, 0.09); p=0.128	-0.37 (-0.79, 0.04); p=0.076	-0.29 (-0.69, 0.11); p=0.161
Other DMT	0.37 (0.059, 2.27); p=0.280	-0.04 (-0.32, 0.24); p=0.772	-0.0060 (-0.29, 0.28); p=0.967	0.04 (-0.23, 0.31); p=0.761
Visit x DMT interactions				
Visit 2 x B-cell depleter	0.63 (0.12, 3.17); p=0.571	-0.05 (-0.28, 0.19); p=0.709	0.0005 (-0.24, 0.24); p=0.997	-0.08 (-0.31, 0.14); p=0.468
Visit 2 x S1PR modulator	2.54 (0.32, 20.07); p=0.377	0.28 (-0.07, 0.63); p=0.119	0.30 (-0.06, 0.66); p=0.106	0.07 (-0.26, 0.40); p=0.685
Visit 2 x Fumarate	1.22 (0.046, 32.40); p=0.903	-0.52 (-0.90, -0.13); p=0.008	-0.29 (-0.69, 0.10); p=0.143	-0.43 (-0.79, -0.07); p=0.021
Visit 2 x Other DMT	3.75 (0.55, 25.41); p=0.176	0.02 (-0.25, 0.29); p=0.902	0.06 (-0.22, 0.34); p=0.674	0.03 (-0.23, 0.28); p=0.844
Visit 3 x B-cell depleter	0.024 (0.0031, 0.18); p<0.001	0.10 (-0.14, 0.35); p=0.409	0.12 (-0.14, 0.37); p=0.359	0.04 (-0.20, 0.27); p=0.766
Visit 3 x S1PR modulator	0.26 (0.024, 2.79); p=0.266	0.28 (-0.10, 0.66); p=0.148	0.24 (-0.15, 0.63); p=0.224	0.11 (-0.25, 0.46); p=0.561
Visit 3 x Fumarate	0.58 (0.014, 24.13); p=0.774	-0.34 (-0.75, 0.07); p=0.103	-0.34 (-0.76, 0.08); p=0.110	-0.34 (-0.73, 0.05); p=0.086
Visit 3 x Other DMT	1.64 (0.18, 15.34); p=0.665	0.26 (-0.02, 0.54); p=0.073	0.21 (-0.08, 0.50); p=0.165	0.12 (-0.14, 0.39); p=0.366
Demographic covariates				
Age at Visit 1 (per year)	1.07 (1.00, 1.15); p=0.046	-0.0002 (-0.01, 0.01); p=0.972	-0.0032 (-0.01, 0.0083); p=0.586	-0.0022 (-0.01, 0.0094); p=0.706
Female	0.48 (0.072, 3.23); p=0.452	-0.09 (-0.42, 0.25); p=0.613	-0.06 (-0.39, 0.26); p=0.701	-0.06 (-0.39, 0.27); p=0.725
Hispanic/Latinx	0.28 (0.028, 2.89); p=0.287	0.20 (-0.20, 0.60); p=0.331	0.20 (-0.19, 0.59); p=0.318	0.11 (-0.29, 0.50); p=0.600
Ethnicity unknown	0.016 (0.0000, 709.8); p=0.449	-1.85 (-3.98, 0.27); p=0.087	-1.01 (-3.08, 1.07); p=0.342	-1.53 (-3.62, 0.57); p=0.153
Black	8.64 (0.41, 181.0); p=0.165	0.47 (-0.07, 1.00); p=0.087	0.35 (-0.17, 0.87); p=0.187	0.08 (-0.44, 0.61); p=0.762

Table 2 (continued)

Term	Higher Spike category OR (95% CI); p	Ag1 β (95% CI); p	Ag2 β (95% CI); p	Ag3 β (95% CI); p
Other race	2.85 (0.049, 164.7); p=0.612	-0.07 (-0.79, 0.65); p=0.853	-0.10 (-0.80, 0.60); p=0.785	-0.21 (-0.92, 0.50); p=0.560
Race unknown	5.40 (0.0036, 8143.1); p=0.652	1.28 (-0.16, 2.73); p=0.082	0.85 (-0.56, 2.27); p=0.236	0.66 (-0.76, 2.08); p=0.364
MS characteristics				
Secondary progressive MS	0.66 (0.14, 3.01); p=0.590	-0.0076 (-0.29, 0.27); p=0.957	0.03 (-0.24, 0.30); p=0.841	0.04 (-0.23, 0.32); p=0.762
Primary progressive MS	0.31 (0.039, 2.44); p=0.266	0.05 (-0.33, 0.43); p=0.810	0.02 (-0.35, 0.39); p=0.916	0.03 (-0.35, 0.40); p=0.894
Clinically isolated syndrome	NA	0.03 (-0.63, 0.68); p=0.936	-0.14 (-0.78, 0.49); p=0.657	-0.21 (-0.86, 0.43); p=0.514
MS subtype unknown	31.09 (0.050, 19243.0); p=0.295	0.19 (-0.62, 1.00); p=0.648	-0.0057 (-0.80, 0.79); p=0.989	-0.20 (-1.00, 0.60); p=0.623
MS disease duration at V1 (per year)	1.00 (0.93, 1.09); p=0.939	0.0002 (-0.01, 0.01); p=0.977	-0.0014 (-0.02, 0.01); p=0.837	-0.0072 (-0.02, 0.0067); p=0.311
Infection / vaccination / prophylaxis				
Prior infection: Yes	6.40 (2.25, 18.21); p<0.001	0.23 (0.08, 0.39); p=0.003	0.22 (0.07, 0.37); p=0.005	0.24 (0.09, 0.38); p=0.001
Prior infection: Unsure	1.90 (0.27, 13.39); p=0.519	0.30 (-0.01, 0.60); p=0.058	0.15 (-0.16, 0.46); p=0.337	0.02 (-0.28, 0.31); p=0.914
Moderna vs Pfizer	6.35 (2.27, 17.78); p<0.001	0.11 (-0.05, 0.26); p=0.188	0.15 (-0.0079, 0.31); p=0.063	0.05 (-0.10, 0.20); p=0.526
Janssen vs Pfizer	0.95 (0.026, 34.43); p=0.976	-0.18 (-0.89, 0.53); p=0.619	-0.16 (-0.85, 0.54); p=0.655	0.27 (-0.43, 0.97); p=0.454
Novavax vs Pfizer	2.22 (0.017, 284.9); p=0.748	0.20 (-0.51, 0.91); p=0.583	0.0073 (-0.72, 0.74); p=0.984	0.18 (-0.49, 0.86); p=0.593
Days since most recent vaccination (per day)	1.00 (1.00, 1.00); p=0.002	-0.0002 (-0.0005, 0.0001); p=0.181	-0.0003 (-0.0006, -0.0000); p=0.035	-0.0002 (-0.0005, 0.0000); p=0.084
Evusheld: Yes	6.19 (1.26, 30.50); p=0.025	0.03 (-0.24, 0.31); p=0.808	0.09 (-0.19, 0.36); p=0.540	0.15 (-0.12, 0.42); p=0.281
Assay positive control				
Mitogen-Nil (per IU/mL)	-	0.05 (0.04, 0.06); p<0.001	0.05 (0.04, 0.06); p<0.001	0.050.04, 0.06); p<0.001

^a Mixed-effects ordered logistic model and represent greater odds of being in a higher Spike IgG category. Reference categories are Visit 1, not actively on a DMT, male, not Hispanic/Latinx, White race, relapsing-remitting MS, no prior infection, Pfizer-BioNTech vaccine, and no Evusheld. DMT main-effect ORs apply at Visit 1. Mitogen-Nil was omitted from the Spike model. N=481 person-visits from 182 participants. The CIS estimate reflects sparse-data separation and is not interpretable.

^b Beta values are on the inverse-rank-normalized Ag response scale. Reference categories are Visit 1, not actively on a DMT, male, not Hispanic/Latinx, White race, relapsing-remitting MS, no prior infection, Pfizer-BioNTech vaccine, and no Evusheld. DMT main effects are DMT-versus-no-DMT contrasts at Visit 1; Visit x DMT terms are differences in change from Visit 1 relative to the no-DMT group. Models included a participant-specific random intercept. N=482 person-visits from 182 participants for each Ag model.

precludes causal inference regarding DMT effects on immune response, and DMT exposure may change over time; immune responses following a treatment switch may also reflect effects of prior therapies rather than the therapy reported at a given visit. Sample sizes for several DMT subgroups, including interferons, glatiramer acetate, purine antime-tabolites, and CD52 monoclonal antibody therapy, were very modest, limiting power and precision. Accordingly, the primary longitudinal analyses grouped less common therapies into an “Other DMT” category, while more granular individual-class estimates were retained as sec-ondary visit-specific analyses and should be interpreted cautiously. Infection history, vaccination timing, Evusheld™ exposure, and DMT use were participant-reported and may be subject to recall or reporting error, although temporal quality-control procedures were applied. Prior SARS-CoV-2 infection was modeled as a time-varying history of infec-tion by each visit, but available data did not allow reliable character-ization of reinfections or precise time since each infection. Nucleocapsid antibody status may underestimate prior infection, particularly among B-cell-depleted participants who may fail to seroconvert or may lose detectable nucleocapsid antibodies over time. Because vaccination sur-veys focused primarily on the most recent dose, cumulative vaccine-dose number and complete homologous versus heterologous vaccine se-quences could not be reliably reconstructed across visits; heterogeneous booster histories also limited separation of calendar time, time since vaccination, and cumulative vaccine exposure. Because Evusheld™ contains anti-spike monoclonal antibodies, Spike IgG measurements among exposed participants may partly reflect passive antibody expo-sure rather than endogenous vaccine- or infection-induced antibody production. However, sensitivity analyses excluding participant-visits with prior Evusheld exposure preserved the principal DMT-associated patterns, although evidence for DMT-specific longitudinal change was attenuated in the reduced sample (eTables 7a–7b). The IGRA platform measures antigen-specific IFN- γ release in peripheral blood but does not fully characterize T-cell phenotype, memory subsets, neutralizing anti-body capacity, mucosal immunity, or memory B-cell function. Partici-pants not actively receiving a DMT should not be considered an untreated control group, as they may differ from treated participants in prior treatment exposure, disease characteristics, and reasons for not receiving therapy. No formal adjustment for multiple testing was applied; therefore, nominally significant findings, particularly from secondary and subgroup analyses, should be interpreted cautiously. Finally, study visits occurred across an evolving pandemic period characterized by changes in circulating SARS-CoV-2 variants, vaccina-tion practices, prior infection prevalence, and preventive therapies. These real-world temporal changes may contribute to observed immune-response patterns and cannot be completely disentangled from visit ef-fects.; however, this heterogeneity also reflects the clinical context in which PwMS and clinicians make vaccination and risk-mitigation decisions.

6. Conclusion

In this longitudinal, decentralized COVER-MS substudy, DMT class was associated with distinct SARS-CoV-2 immune-response profiles in vaccinated PwMS. B-cell-depleting therapies were linked to markedly attenuated Spike IgG responses with relatively preserved cellular responses, whereas S1PR modulators showed broad attenuation across both humoral and cellular measures. Fumarate-treated participants demonstrated lower cellular responses at later visits, with the strongest evidence for a differential longitudinal pattern observed for Ag1. These findings support the value of assessing both antibody and T-cell responses when evaluating vaccine-associated immunity in PwMS and may inform DMT-specific vaccine planning and infection-risk coun-seling. Operationally, the study demonstrates that decentralized bio-specimen collection paired with electronic survey data is feasible for longitudinal immunologic research in MS and may provide a useful model for future vaccine studies and emerging infectious disease

monitoring.

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CRediT authorship contribution statement

Farren B.S. Briggs: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Stephanie Buxhoeveden:** Writing – review & editing, Writing – original draft, Investigation. **Hollie Schmidt:** Writing – review & editing, Data curation, Conceptualization. **Julia Larsen:** Writing – review & editing, Methodology, Conceptualization. **Bruce F. Bebo:** Writing – review & editing, Investigation, Conceptualization. **Phyllis Klein:** Writing – review & editing, Methodology. **Robert N. McBurney:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Michael K. Racke:** Writing – review & editing, Su-pervision, Methodology, Investigation, Funding acquisition, Conceptu-alization. **Sara Loud:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition.

Declaration of competing interest

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Supplementary materials

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