Humoral and Cellular Immune Responses to COVID-19 Vaccination across Disease-Modifying Therapies in a Decentralized MS Cohort

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Background

COVID-19 vaccination has been broadly effective in reducing severe illness; however, disease-modifying therapies (DMTs) used in multiple sclerosis (MS) may differentially affect vaccine-associated immunity. Prior studies have largely focused on humoral responses, particularly among individuals receiving B-cell–depleting or sphingosine-1-phosphate receptor modulator (S1PR) therapies. Less is known about how DMTs influence cellular immune responses over time, particularly in real-world longitudinal cohorts.

Objective

This immunological substudy of COVER-MS (COVID-19 VaccinE Response in MS) evaluated longitudinal humoral (Spike IgG) and cellular (Ag1–Ag3 interferon-gamma release) immune responses to SARS-CoV-2 vaccination across DMT classes in a geographically distributed, decentralized MS cohort.

Methods

Participants were recruited through the iConquerMS research network and completed electronic consent and survey procedures remotely. Blood collection kits were mailed directly to participants, and biospecimens were collected either through local Quest Diagnostics Patient Service Centers or mobile phlebotomy services. Participants completed up to three visits approximately six months apart.

Cohort Characteristics

The analytic cohort included 183 participants at Visit 1, 161 at Visit 2, and 141 at Visit 3. Overall, 236 participants enrolled, representing 41 U.S. states and the District of Columbia, and 83% completed all three collections. Approximately 35% of participants were receiving B-cell–depleting therapies, 8% S1PR modulators, and 8% fumarates at baseline. 47-70% of participants reported a recent SARS-CoV-2 infection across the three visits, and most (77-88%) had received mRNA vaccination, predominantly BNT162b2 or mRNA-1273, within 178-365 days of collection. Approximately 18–19% had previously received Evusheld.

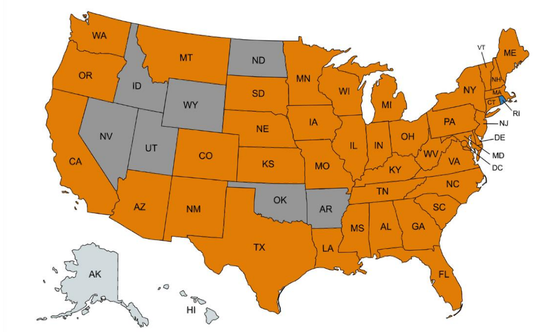


Figure 1: Nationwide coverage of the COVER-MS Substudy

Results

Humoral Immunity (Spike IgG)

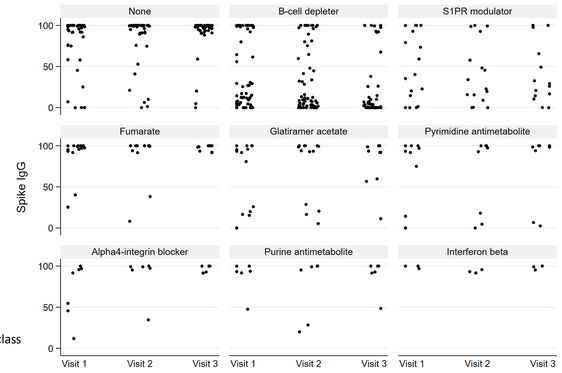
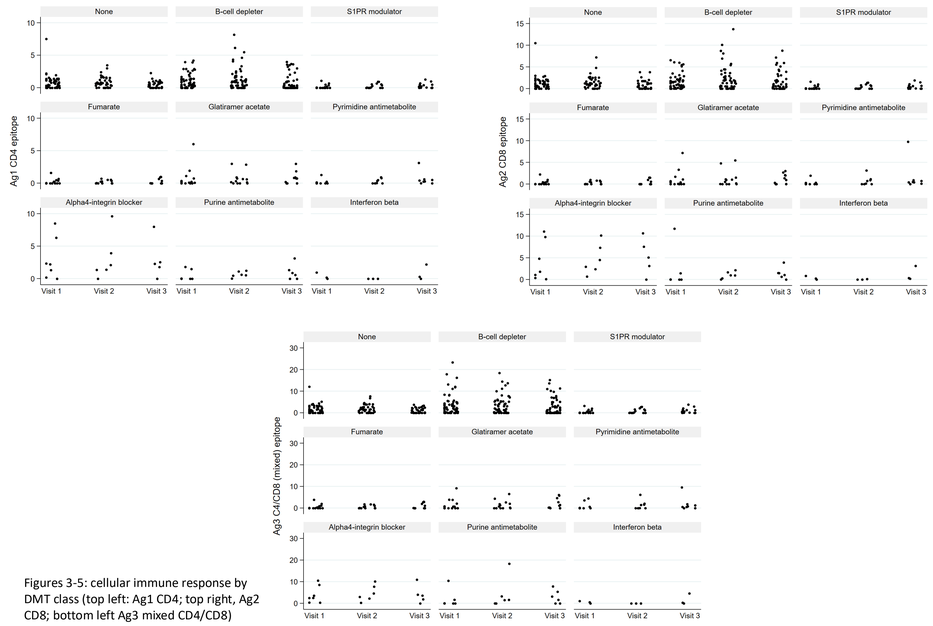


Figure 2: Spike IgG by DMT class across visits 1, 2, and 3

Humoral responses varied substantially across DMT classes. B-cell–depleting therapies and S1PR modulators were consistently associated with markedly reduced odds of higher Spike IgG levels across all visits. Prior SARS-CoV-2 infection and mRNA-1273 vaccination were associated with stronger humoral responses, particularly at earlier timepoints.

Cellular Immunity: Ag1 (CD4), Ag2 (CD8), Ag3 (Mixed)



Figures 3-5: cellular immune response by DMT class (top left: Ag1 CD4; top right, Ag2 CD8; bottom left Ag3 mixed CD4/CD8)

Distinct patterns emerged across Ag1, Ag2, and Ag3 cellular immune responses. S1PR modulators demonstrated broad suppression across all cellular assays, consistent with reduced circulating lymphocyte availability. In contrast, participants receiving B-cell–depleting therapies demonstrated preserved or increased Ag3 responses despite markedly attenuated antibody responses, suggesting dissociation between humoral and cellular immunity.

Key Findings

This study demonstrates that DMTs produce distinct immune-response profiles rather than uniformly suppressing immunity. Participants receiving B-cell–depleting therapies exhibited markedly impaired humoral responses (OR ~0.02–0.03 across visits) despite relatively preserved or enhanced cellular responses, particularly within the Ag3 mixed CD4/CD8 assay. In contrast, S1PR modulators demonstrated profound attenuation across both humoral and cellular immune compartments, including suppression of Ag1–Ag3 responses. Fumarates were also associated with reduced cellular responses across multiple models. Additionally, mRNA-1273 vaccination was associated with stronger early humoral responses compared with BNT162b2. Together, these findings support the importance of multidimensional immune assessment in people with MS.

Decentralized Trial Impact

The decentralized study infrastructure was designed to maximize accessibility and geographic reach while reducing barriers associated with traditional site-based research participation. Participants were able to complete longitudinal biospecimen collection without requiring travel to specialty MS centers.

Impact

- Broader geographic reach
- Reduced participant burden
- High longitudinal retention (~83%)

Conclusion

Distinct humoral and cellular immune-response patterns were observed across DMT classes in vaccinated people with MS. B-cell–depleting therapies were associated with markedly attenuated antibody responses but preserved cellular immunity, while S1PR modulators demonstrated broad immune attenuation. These findings support both multidimensional immune profiling and the use of decentralized research models for longitudinal immunologic studies in MS.

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