Research paper

# Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy

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## ARTICLE INFO

## ABSTRACT

*Background:* Sphingosine-1-phosphate receptor (S1P) modulators and anti-CD20 therapies impair humoral responses to SARS-CoV-2 mRNA vaccines. Relatively few studies have assessed the impact of an array of disease modifying therapies (DMTs) for multiple sclerosis (MS) on T cell immune responses to SARS-CoV-2 vaccination.
*Methods:* In 101 people with MS, we measured humoral responses via an immunoassay to measure IgG against the COVID-19 spike S1 glycoprotein in serum. We also measured T cell responses using FluoroSpot assay for interferon gamma (IFN-$\gamma$) (Mabtech, Sweden) using cryopreserved rested PBMCs and then incubated in cRPMI with $1\mu$g/ml of pooled peptides spanning the entire spike glycoprotein (Genscript, 2 pools; 158 peptides each). Plates were read on an AID iSpot Spectrum to determine the number of spot forming cells (SFC)/$10^6$ PBMCs. We tested for differences in immune responses across DMTs using linear models.
*Findings:* Humoral responses were detected in 22/39 (56.4%) participants on anti-CD20 and in 59/63 (93.6%) participants on no or other DMTs. In a subset (n=88; 87%), T cell responses were detected in 76/88 (86%), including 32/33 (96.9%) participants on anti-CD20 therapies. Anti-CD20 therapies were associated with an increase in IFN-$\gamma$ SFC counts relative to those on no DMT or other DMTs (for anti-CD20 vs. no DMT: 425.9% higher [95%CI: 109.6%, 1206.6%] higher; $p<0.001$; for anti-CD20 vs. other DMTs: 289.6% [95%CI: 85.9%, 716.6%] higher; $p<0.001$).
*Interpretation:* We identified a robust T cell response in individuals on anti-CD20 therapies despite a reduced humoral response to SARS-CoV-2 vaccination. Follow up studies are needed to determine if this translates to protection against COVID-19 infection.
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## 1. Introduction

The COVID-19 pandemic has impacted people with multiple sclerosis (MS), both directly, as a result of morbidity and mortality from COVID-19 as well as indirectly through uncertainty in how best to optimize MS care during this time [1]. For example, certain disease modifying therapies (DMTs) may impact the risk of contracting COVID-19 or developing severe COVID-19 infection,[2,3] and, it is unclear whether certain DMTs should be held or modified in how they are used [3].

The introduction of highly effective vaccines, such as the SARS-CoV-2 mRNA vaccines produced by Pfizer and Moderna, provides an effective intervention to reduce the risk and severity of COVID-19 infection [4,5]. Multiple studies indicate that COVID-19 vaccination results in both a humoral and cell-mediated immune response that is likely to play a role in their protective effects [6].

Certain MS DMTs such as anti-CD20 therapies or sphingosine-1-phosphate (S1P)-receptor modulators can impact responses to a

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## Research in context

### Evidence before this study

We searched PubMED for the term (("COVID-19") or ("SARS-CoV-2") or ("coronavirus")) AND (("vaccination") or ("vaccine")) AND ("multiple sclerosis"), published between January 1, 2020 and September 10, 2021. 14 studies evaluated the humoral response to SARS-CoV-2 vaccination in people with MS on a variety of disease modifying therapies (DMTs) and noted a reduction in humoral response to vaccination in patients on anti-CD20 and sphingosine-1-phosphate receptor modulators. One study (Moor et al.), evaluated humoral and cellular vaccine responses in rituximab treated patients, but included only 5 people with MS and noted blunted humoral and cellular response to SARS-CoV-2 vaccination. We also searched Medrxiv for the same terms and identified two pre-prints (Apostolidis et al. and Madelon et al.) that identified robust T cell responses in anti-CD20 treated people with MS, but these studies did not evaluate responses in people with MS on other DMTs.

### Added value of this study

We conducted this study to address the gap in current knowledge regarding T cell responses to SARS-CoV-2 vaccination in people with MS and the effect of DMTs on this response. In a study involving 101 people with MS, we confirmed previous findings that the humoral response to SARS-CoV-2 vaccination was reduced in people with MS on anti-CD20 therapy. We also noted that prolonged time from last infusion of anti-CD20 therapy was associated with higher chance of a positive humoral response to SARS-CoV-2 vaccination. We found that the majority of people with MS mounted a T cell response to SARS-CoV-2 vaccination with those on anti-CD20 mounting a more robust T cell response than those not on a treatment or on other DMTs.

### Implications of all the available evidence

Use of anti-CD20 agents is associated with lower humoral response to SARS-CoV-2 vaccination in people with MS. Identification of a more robust T cell response in people with MS suggests at least partial efficacy of vaccines and some potential for protection from severe COVID-19 disease even in the absence of a humoral immune response.

variety of existing vaccines,[7,8] and emerging studies suggest these therapies impair humoral response to SARS CoV-2 vaccines [9,10]. Still, despite a lack of humoral response, prior studies suggest the T cell immune response may be maintained following administration of other common vaccines in patients treated with anti-CD20 therapies [11]. Some conflicting data has emerged regarding the effect of these therapies on T cell response to SARS-CoV-2 vaccine in people with MS and rheumatologic diseases [12−14]. Additionally, to our knowledge, limited studies have assessed the effect of a range of DMTs on T cell responses to SARS-CoV-2 vaccination in people with MS. Thus, to address these gaps, we assessed both humoral and T cell responses to vaccination in people with MS on a range of DMTs.

## 2. Methods

### 2.1. Ethics Statement

This study was completed in accordance with the principles in the Declaration of Helsinki and received approval from the Johns Hopkins Medicine Institutional Review Board (IRB00246910). All participants provided written consent prior to blood collection.

### 2.2. Recruitment and Sample Collection

We recruited patients with multiple sclerosis that were part of an ongoing clinical observational study [3] at the Johns Hopkins MS Centre and had recently received a COVID-19 vaccine. No MS patients were excluded from the study based on type of disease modifying therapy, COVID-19 vaccine (all patients received either Pfizer, Moderna, or Johnson & Johnson vaccines), or any other demographic or disease characteristic. All participants received a complete vaccine series. Recruited patients underwent phlebotomy either 4 or 8 weeks after the terminal COVID-19 vaccination dose. We selected these timepoints as 1) large, randomized trials demonstrate COVID-19 vaccines are expected to be efficacious in this time interval (e.g., by 4 or 8 weeks post terminal dose)[5,15,16], and 2) to maximize recruitment of patients willing to provide a blood sample in this window.

### 2.3. Humoral response assay

Serum was isolated by centrifuging coagulated blood using a standardized protocol. Experimenters blinded to sample identity measured serum humoral responses using an ELISA quantifying IgG specific to the COVID-19 spike S1 glycoprotein (EUROIMMUN, Germany, EI 2606-9601-2G), which was given emergency use authorization by the Food and Drug Administration[12]. This ELISA was performed in a Clinical laboratory improvement amendments (CLIA) certified laboratory at the Johns Hopkins Department of Pathology [17]. This assay has high sensitivity and specificity and correlates with presence of neutralizing antibodies. The cut-off value for the presence of a humoral response on this assay is 1.24 and details on performance of this assay and determination of this cut-off have been reported previously [17].

### 2.4. T cell response assay

Peripheral blood mononuclear cells (PBMCs) were isolated via centrifugation in a Ficoll gradient (using SepMate PBMC isolation tubes; STEMCELL technologies, cat. #85415) and cryopreserved in media containing 10% DMSO. PBMCs were thawed and rested for 12 hours in complete culture media (RPMI + 10% Fetal Bovine Serum). Blinded experimenters plated PBMCs into a 96-well FluoroSpot assay plate for interferon gamma (IFN-$\gamma$) (Mabtech, Sweden, FSP-0102-10) at $2.5 \times 10^5$ cells per well for stimulation. Pooled peptides spanning the length of the entire spike glycoprotein (2 pools of 158 peptides each; Genscript, RP30020) were used for stimulation at a concentration of $1\mu$g/mL per peptide. Positive controls were stimulated with anti-CD3/anti-CD28 and negative controls received no stimulation. Three technical replicates were completed for each condition. After 22 hours of stimulation, cells were discarded and FluoroSpot plates were prepared per manufacturer's instructions. Plates were read on an AID iSpot Spectrum in the Johns Hopkins Immune Monitoring Core lab. Results were expressed as spot forming cells (SFC)/$10^6$ PBMCs and were obtained by subtracting the average counts for the negative control from the average counts for each peptide pool and then summing the counts for the two peptide pools. A negative T cell response was defined as the lack of response to both peptide pools − stimulation index (counts for the peptide pool divided by count in the negative control) of less than 3 or count of <20 SFC/$10^6$ PBMCs for each peptide pool [18].

### 2.5. Statistical methods

Initial descriptive statistics assessed differences in demographic or MS characteristics across therapy groups. We tested for differences across groups using generalized linear models. We categorized patients on glatiramer acetate and interferon-beta into an any injectable therapy category. We also collapsed dimethyl fumarate

and teriflunomide into an oral therapies group; we did not include fingolimod in the oral therapies group because of initial findings of other groups suggesting a lack of humoral vaccine response for individuals on this therapy specifically. We assessed the association between therapy class and odds of humoral vaccine response using a logistic regression model adjusted for age, sex, and time from first dose of the vaccine to blood collection (as samples were collected variably - 4 or 8 weeks following terminal vaccine dose). Sensitivity analyses restricted to participants for whom samples were collected 8 weeks following the terminal vaccine dose. A similar model assessed whether time from last infusion was associated with odds of a humoral response in individuals treated with anti-CD20 therapies. We next assessed the association between therapy classes and log-transformed IFN-$\gamma$ SFC adjusted for age, sex and time from first dose of the vaccine also using a linear model. As only 3 individuals were treated with fingolimod, we did not perform formal analyses assessing differences in IFN-$\gamma$ SFC counts for this therapy. No formal sample size determination or randomization was performed in this study. The personnel performing humoral and T cell assays were blinded to patient identity and any demographic details. Inclusion and exclusion criteria for this study are mentioned above under the "Recruitment and Sample Collection" section.

### 2.6. Role of funders

No funding sources had any role in study design, data collection, data analysis, result interpretation, or writing of the report.

### 3. Results

We enrolled 101 participants (82% female), 94% of whom received an mRNA vaccine (94%) with blood collection an average 6.8 weeks after terminal vaccine dose (Table 1).

### 3.1. Humoral response to SARS-CoV-2 vaccination

All participants on no therapy (n=14), injectables (n=16) or natalizumab (n=16) and the majority on non-S1P modulating oral therapies (12/14; 86%) demonstrated a humoral response to vaccination (Figure 1a). In contrast, only 22/39 (56%) of participants exposed to anti-CD20 therapy and 1/3 participants on S1P modulating therapy exhibited a humoral response to vaccination (Figure 1a). Among patients on anti-CD20 therapy, a 30 day increase in time from last infusion was associated with 1.45 increased odds of a positive humoral response to vaccination (Figure 1b; OR: 1.51; 95% CI: 1.05-2.17).

### 3.2. T cell response to SARS-CoV-2 vaccination

Most participants (76/88, 86%) across all DMTs demonstrated a T cell immune response to SARS CoV-2 vaccination. Interestingly, participants on anti-CD20 or non-S1P modulating oral therapies had significantly higher IFN-$\gamma$ SFC counts compared to those on no DMT (Figure 1c). Participants on anti-CD20 therapy in particular had on average 1.36 higher log(IFN-$\gamma$ SFC counts) when compared to individuals on other DMTs (mean difference in log[IFN-$\gamma$ SFC counts] versus other DMTs: 1.36; 95% CI: 0.62, 2.10; p<0.001 [from linear model]). Results were similar in sensitivity analyses restricting to participants in which samples were collected at least 8 weeks following the terminal vaccine dose.

### 4. Discussion

In this study, we found that most patients treated with non-anti-CD20 therapies developed a robust humoral and cellular response to SARS-CoV-2 vaccination. Patients treated with anti-CD20 therapy had impaired humoral response to SARS-CoV-2 vaccination,

**Table 1**
Demographic characteristics of study cohort.

| | Disease Modifying Therapy Category | | | | | | $P^*$ |
|---|---|---|---|---|---|---|---|
| | None | Injectable | Natalizumab | Other oral | AntiCD20 | Fingolimod | |
| **N** | 14 | 16 | 16 | 14 | 38 | 3 | |
| **Age, years, mean (SD)** | 57.42 (12.84) | 50.17 (8.52) | 47.63 (9.01) | 49.12 (11.27) | 47.78 (9.64) | 47.93 (9.36) | 0.07 |
| **Male sex, n (%)** | 3 (21.4) | 3 (18.8) | 1 (6.2) | 2 (14.3) | 9 (23.7) | 0 (0.0) | 0.66 |
| **Race, n (%)** | | | | | | | 0.38 |
| White | 12 (85.7) | 16 (100.0) | 15 (93.8) | 14 (100.0) | 34 (89.5) | 3 (100.0) | |
| Black | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.9) | 0 (0.0) | |
| Other | 2 (14.3) | 0 (0.0) | 1 (6.2) | 0 (0.0) | 1 (2.6) | 0 (0.0) | |
| **Hispanic or Latino ethnicity, n (%)** | 0 (0.0) | 0 (0.0) | 3 (18.8) | 0 (0.0) | 1 (2.6) | 0 (0.0) | 0.19 |
| **Vaccination manufacturer, n (%)** | | | | | | | 0.73 |
| J&J | 0 (0.0) | 0 (0.0) | 2 (12.5) | 2 (14.3) | 3 (7.9) | 0 (0.0) | |
| Moderna | 6 (42.9) | 8 (50.0) | 5 (31.2) | 4 (28.6) | 10 (26.3) | 0 (0.0) | |
| Pfizer | 8 (57.1) | 7 (43.8) | 9 (56.2) | 7 (50.0) | 23 (60.5) | 3 (100.0) | |
| Unsure | 0 (0.0) | 1 (6.2) | 0 (0.0) | 1 (7.1) | 2 (5.3) | 0 (0.0) | |
| **Weeks from initial vaccine dose, mean (SD)** | 10.57 (1.99) | 13.62 (6.38) | 11.62 (4.27) | 11.29 (4.68) | 10.21 (2.02) | 12.00 (0.00) | 0.09 |
| **MS subtype, n (%)** | | | | | | | 0.21 |
| PPMS | 2 (14.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.9) | 0 (0.0) | |
| RRMS | 9 (64.3) | 16 (100.0) | 14 (87.5) | 14 (100.0) | 32 (84.2) | 3 (100.0) | |
| SPMS | 3 (21.4) | 0 (0.0) | 2 (12.5) | 0 (0.0) | 3 (7.9) | 0 (0.0) | |
| **Individual DMT, n (%)** | | | | | | | |
| none | 14 (100.0) | - | - | - | - | - | |
| rituximab | - | - | - | - | 1 (2.6) | - | |
| ocrelizumab | - | - | - | - | 37 (97.4) | - | |
| dimethyl fumarate | - | - | - | 13 (92.9) | - | - | |
| teriflunomide | - | - | - | 1 (7.1) | - | - | |
| fingolimod | - | - | - | - | - | 3 (100.0) | |
| glatiramer acetate | - | 7 (43.8) | - | - | - | - | |
| interferon beta | - | 9 (56.2) | - | - | - | - | |
| natalizumab | - | - | 16 (100.0) | - | - | - | |
| **Disease duration, years, mean (SD)** | 9.15 (9.77) | 12.00 (6.56) | 13.07 (9.24) | 12.86 (10.75) | 9.51 (7.31) | 9.33 (7.64) | 0.61 |
| **DMT therapy duration, mean (SD)** | - | 10.84 (28.40) | 2.28 (2.20) | 1.43 (1.94) | 1.95 (0.88) | 3.75 (4.79) | 0.24 |

\* P values were derived from generalized linear models using appropriate link functions to test for differences in demographic or clinical characteristics with respect to MS disease modifying therapy category.
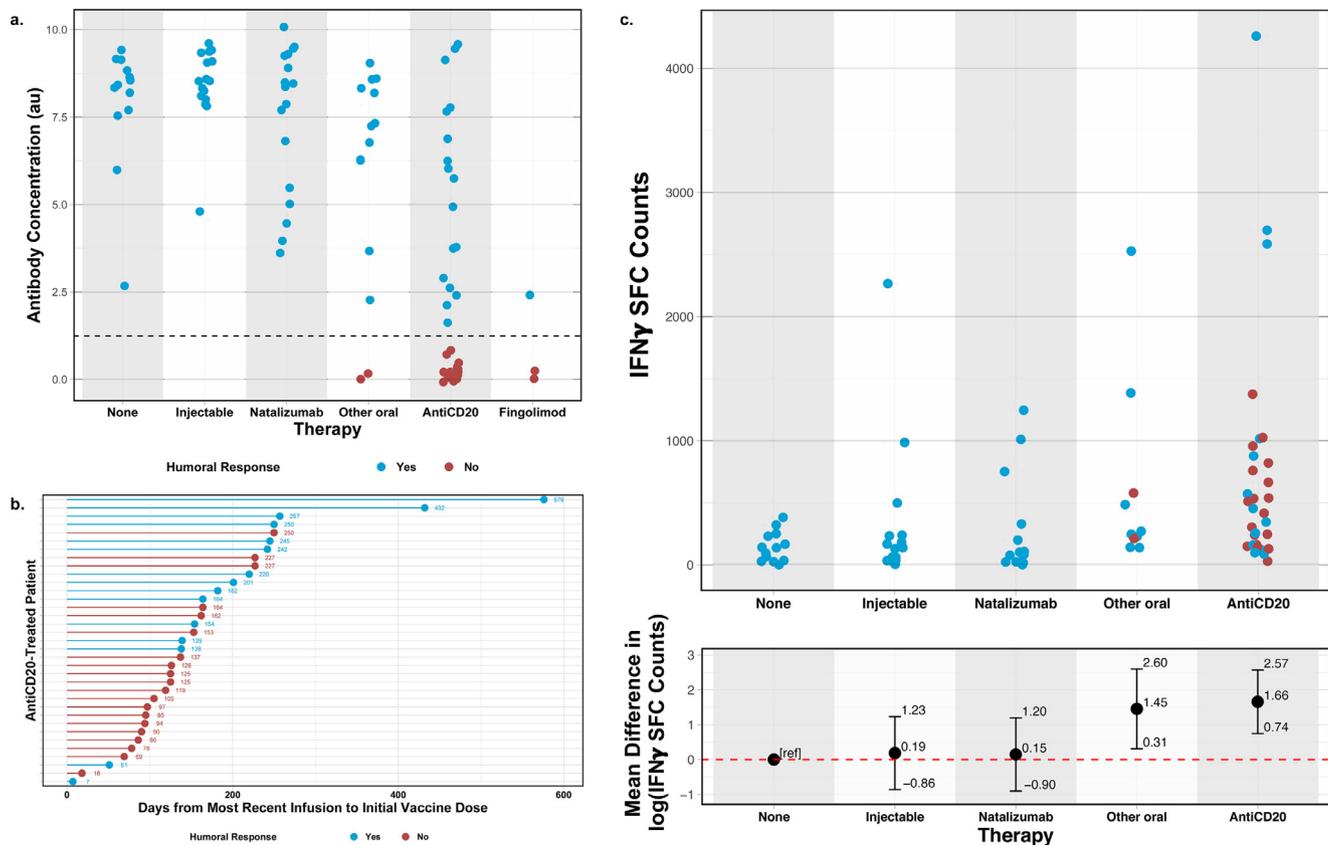
**Figure 1. Humoral and cell mediated responses to SARS-CoV-2 vaccination in people with multiple sclerosis. a.** Dot plot of IgG levels against S1 subunit of spike glycoprotein by disease modifying therapy (DMT) category; dotted line is cut-off for positivity of antibody response to vaccination (n=101). **b.** Time from last infusion of B-cell depleting agent in the study population (n=36; this information was unavailable in two participants); lines are colour coded based on antibody response status to vaccination and displayed values note the number of days from most recent infusion to first vaccination dose; mean (SD) time from last infusion was 165 (109) days. **c.** Dot plot of T cell response to spike glycoprotein peptides (number of IFN-$\gamma$ producing cells/$10^6$ PBMCs) by DMT category [above]. The bottom panel depicts the age and sex-adjusted mean difference in log-transformed IFN-$\gamma$ SFC counts relative to MS patients not on a DMT (error bars represent 95% confidence intervals for the difference in log[means]; n=86 patients displayed).

consistent with previous reports [9,10]. We also found that longer interval from last infusion of anti-CD20 therapy was associated with a higher chance of a positive humoral response, in line with recent studies linking humoral response to repopulation of B cells in anti-CD20 treated patients [13,19]. Interestingly, the T cell response to SARS-CoV-2 vaccination was more robust in anti-CD20 treated patients relative to patients not on a DMT or those on other DMTs, even in those anti-CD20 treated patients lacking an antibody response.

As the use of immunosuppressive medications was an exclusionary criterion in phase 3 clinical trials for most SARS-CoV-2 vaccines [5,15,16], a critical gap in our understanding of their safety and efficacy in patients being treated for MS and other autoimmune conditions emerged. Further, recent studies also find that immunocompromised individuals have lower rates of vaccine efficacy when compared to non-immunocompromised individuals (e.g., in the US: 63% versus 90%) with respect to hospitalization for breakthrough infection [20].

Our finding of robust T-cell responses in patients with B cell depletion is in agreement with pre-printed results in MS patients [12,13]. Interestingly, a similar study in primarily non-MS patients treated with B cell depleting therapies found decreased SARS-CoV-2 specific T cell activation after vaccination [14], though differing methodologies in assessing T cell activation could account for this discrepancy. For example, in addition to including 95% non-MS patients, in the Moor et al. study, the whole blood incubation period was 1 hour, whereas in our study, PBMCs were stimulated for a 22-hour period. Alternatively, the majority of participants in that study were on an additional immunosuppressive medication (such as steroids) which

may also have contributed to this discrepancy. B cells, in addition to producing antibodies, also present antigens and are important activators of CD4+ and CD8+ T cells [21]. Our results suggesting that B cell depletion increases T cell vaccine responses are therefore surprising and warrant further investigation. Also in agreement with our results a recent study showed that patients with X-linked agammaglobulinemia mounted a stronger T cell response to SARS-CoV-2 vaccination compared to healthy controls [22]. Possible mechanisms underlying this finding include depletion of regulatory B cells, alleviating their inhibition of T cell activation [23], decreased activation of regulatory T cells in the absence of B cells [24], or alterations in the local inflammatory milieu at the site of vaccination.

Another takeaway, from our study is that testing of antibodies to COVID-19 spike antigens following vaccination in MS patients on anti-CD20 therapy provides an incomplete picture of their response to the vaccine, since it neglects the T cell response; physicians should be aware of this limitation of currently clinically available tests to evaluate SARS-CoV-2 vaccine response.

While most patients with MS are not at significantly higher risk of morbidity and mortality from COVID-19 infection, the use of anti-CD20 therapies has been linked to greater COVID-19 severity in registry studies [2,25]. The greater severity of infection is likely linked to the lack of a humoral response to COVID-19 infection [26], similar to reduced humoral response to vaccination noted in our study and other prior studies [9]. The reduction of humoral responses in these patients has raised concerns that people on anti-CD20 therapy may have a greater COVID-19 infection risk despite vaccination and has prompted discussion of booster doses, perhaps in conjunction with delaying therapy infusions, to mitigate this risk. However, since

stronger SARS-CoV-2 specific T cell responses in the setting of natural infection have been linked to lower disease severity [6], our data demonstrating robust T cell responses to SARS-CoV-2 vaccination in patients on anti-CD20 therapy suggests that vaccination likely confers some promise of protection, even in the absence of detectable humoral responses. Since some patients on anti-CD20 therapy appear to clear their COVID-19 infection despite the lack of a humoral response [26], presumably due to T cell response to infection, the augmentation of this response could potentially ameliorate disease severity in this sub-group at higher risk for more severe COVID-19 infection. Confirmation of this observation will require follow-up studies examining post-vaccination breakthrough infections in patients on anti-CD20 therapies, which is an important next step building on the results of this study. We are following potential downstream COVID-19 infections and outcomes post-vaccination for participants in this study as well as those in our larger registry study [3] to address this question in future studies.

There are several important limitations of this study. We did not have baseline (pre-vaccination) samples available, and it is possible that a small proportion may have had prior natural infection. It is possible that immunity could develop later than the 4- week post terminal vaccine dose timepoint, which was one of the timepoints we selected. While theoretically possible, we think this is unlikely based on reports of vaccine efficacy by 2 weeks [5,15,16], and the lack of difference in sensitivity analysis limited to samples drawn 8 weeks following terminal vaccine dose. Another limitation was the relatively small number of patients treated with oral agents, especially S1P modulators, limiting our ability to draw conclusions in this group. Finally, we lack longitudinal follow up on these participants to comment on longevity of response or the effect of our findings on risk or severity of breakthrough infection.

In conclusion, this study provides novel information regarding T cell responses to SARS-CoV-2 vaccination in people with MS on a variety of DMTs, notably identifying robust T cell responses even in patients on anti-CD20 therapy who do not mount a humoral response to SARS-CoV-2 vaccination.

## Contributors

Conception and design of study − PAC, EMM, KCF and PB; Acquisition, analysis, and verification of data − SPG, MRM, LJ, SH, MD, MDS, KCF and PB; Drafting a significant portion of the manuscript or figures − SPG, MRM, PAC, EMM, KCF and PB. All authors read and approved the final version of the manuscript. PB and KCF have verified the data underlying this study.

## Data Sharing Statement

All primary data in this study will be made available upon request to the corresponding authors for individuals with appropriate data sharing agreements in place.

## Declaration of Competing Interest

SPG has nothing to disclose.
MRM has nothing to disclose.
LJ has nothing to disclose.
SH has nothing to disclose.
MD has nothing to disclose.
MDS has nothing to disclose.
PAC has received consulting fees from Disarm and Biogen and is PI on grants to JHU from Genentech, Principia, and Annexon.
EMM reports receiving research funding as site PI or for investigator-initiated studies from Biogen, Genentech, and Teva. She receives royalties for editorial duties from UpToDate.
KCF has nothing to disclose.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2021.103636.

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