# Durability of Immune Response to COVID-19 Vaccines in Persons with MS on B cell Depleting Therapy

Sarah Flanagan Wesley[1], Zongqi Xia [2], Julia Davis-Porada [1], Ceren Tolzu [3], Claudia Aiello [1], Sugeidy Ferreira Brito [1], Kaho Onomichi [1], Adelle Ricci [1], Elizabeth Walker [2], Lili Zhang [2], Wen Zhu [2], Philip De Jager [1], Donna L Farber [1], Rebecca Straus Farber [1]

1Columbia University Irving Medical Center, New York, United States, 2University of Pittsburgh, Pittsburgh, United States, 3Cornell University Medical College, New York, United States

## Background & Objective

- Therapeutic agents for MS that work through B-cell depletion (BCD) are highly effective and widely used.
- Up to 30 days post-COVID-19 mRNA vaccination, persons with MS (PwMS) with few circulating B-cells do not mount a robust antibody response despite T-cell response being largely spared
- How this translates into longer lasting immunity is poorly understood.
- **Objective:** Prospectively characterize long-term anti-SARS-CoV-2 immune responses post-vaccination in PwMS, including antibody levels and T-cell subsets.

## Methods

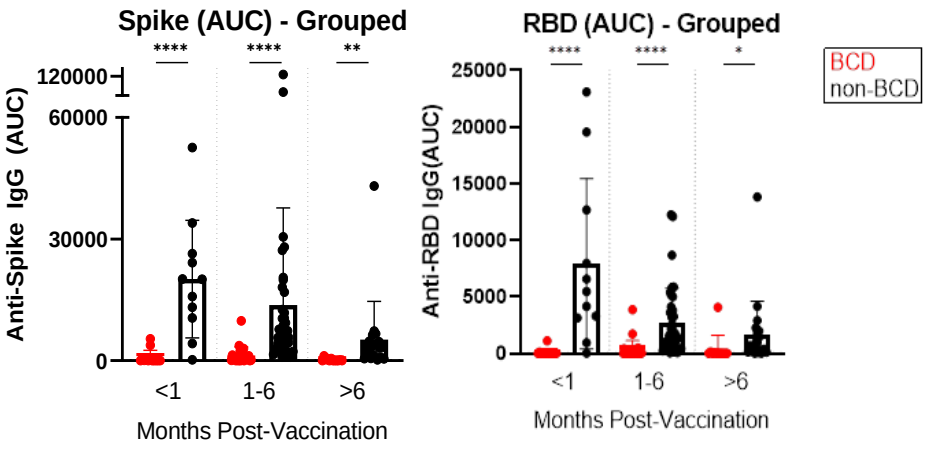
- Blood samples were collected from PwMS at following completion of mRNA vaccine series at <1 month(mo), 1-6 mos, and >6 mos
- Samples testing positive for anti-Nucleocapsid antibodies or samples from subjects reporting a history of clinical COVID19 infection were **excluded** from analysis. Samples obtained after 3rd/booster doses were excluded from analysis.
- Anti-Spike (S) and anti-Receptor binding domain (RBD) Abs were quantified by enzyme-linked immunoassays
- Vaccine specific T-cells were identified by expression of activation-induced markers following stimulation with peptide pools spanning the spike protein
- Levels of vaccine specific anti-S and anti-RBD antibodies and T-cell subsets were compared between PwMS on BCD at the time of vaccination versus non-BCD (either on alternative therapy or no therapy) at time of vaccination.
- T-cell data was log transformed. Comparisons between 2 or more groups were done with a Kruskal-Wallis test corrected for multiple comparisons using Dunn's test; for two groups a Mann-Whitney test was used. For T cell subset analysis, we used a 2-way-ANOVA corrected for multiple comparisons by Sidak test.

## Data

| | |
|---|---|
| Participants | n=106 subjects (121 samples) |
| Sex | Female:79 (75%) |
| Age | Mean: 49.2 (range 24-78) |
| Race | Asian: 3 (3%)<br>Black/AA: 18 (17%)<br>Native Am: 3 (3%)<br>White: 81 (76%)<br>Other/Unknown: 1 (1%) |
| Ethnicity | Hispanic/ Latino: 13 (12%) |
| Disease Modifying Therapy | Non-BCD: 60 (57%)<br>• None:14 (13%)<br>• cladribine: 2 (2%)<br>• fumarate: 10 (9%)<br>• glatiramer acetate: 9 (8%)<br>• interferons: 5 (5%)<br>• natalizumab: 13 (12%)<br>• S1-P inhibitors: 1 (1%)<br>• teriflunomide: 6 (6%)<br><br>Non-BCD: 46 (43%)<br>• ocrelizumab: 25 (24%)<br>• ofatumumab: 3 (3%)<br>• rituximab: 18 (17%) |

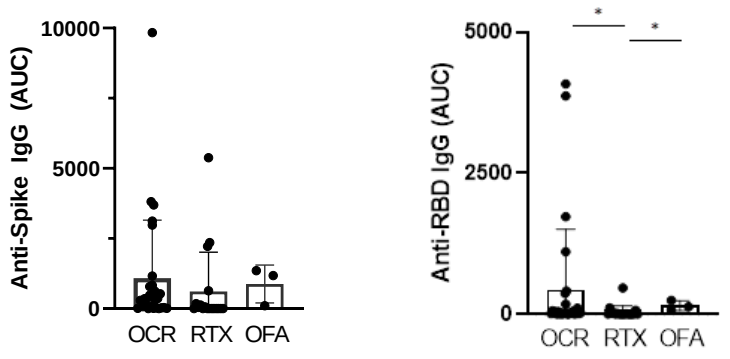
## Data Analysis

**Figure 1: Post-Vaccine Anti-S and Anti-RBD Response Over Time : Comparison of BCD vs. non-BCD**




With non-BCD therapies anti-S and anti-RBD titers were detectable and declined with time. Those on BCD therapy did not induce a robust humoral response and had significantly lower anti-S and anti-RBD titers at <1mo ($p < 0.0001$, $p<0.0001$), 1-6mo ($p < 0.001$, $p<0.001$), and >6mo ($p=0.002$, $p=0.01$) post-vaccination compared to non-BCD patients.

**Figure 2: Anti-S and Anti-RBD Response: Comparison between 3 BCDs**




There was no statistically significant difference in anti-S Ab levels between on the 3 different types of BCD therapy. There was a trend for those on RTX to have lower levels of both antibodies as compared to OCR and OFA.

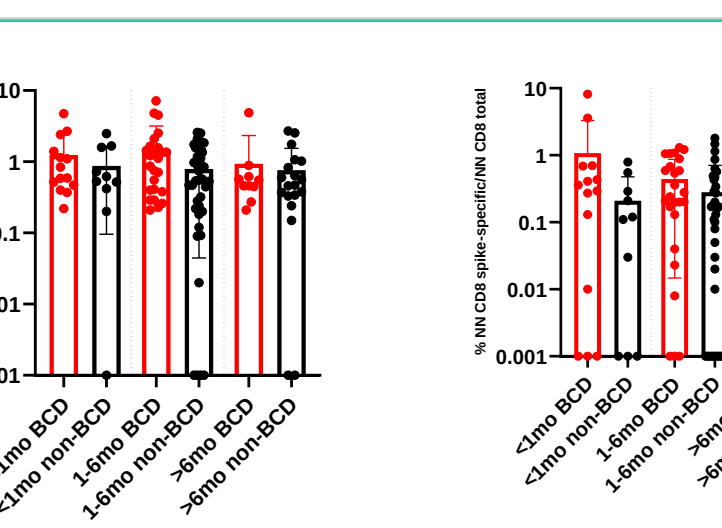
Anti-RBD levels were lower in those on rituximab (RTX) as compared to those on ocrelizumab (OCR) ($p=0.02$) or ofatumumab (OFA) ($p=0.03$)

**Figure 3: Spike-specific CD4 and CD8 responses over time: Comparison of BCD vs Non-BCD**



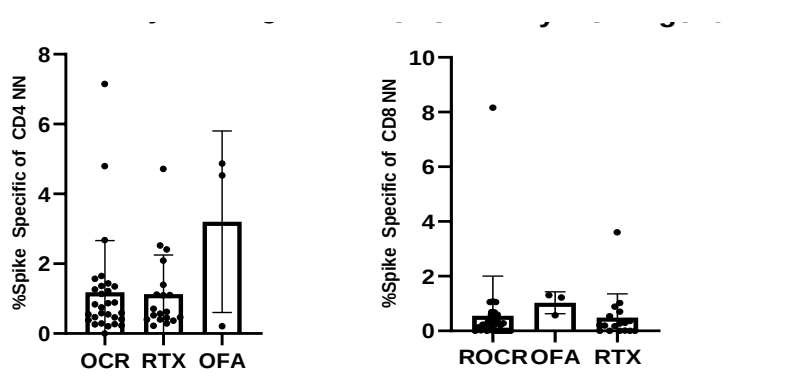

Patients on BCD and non-BCD therapies have similar levels of CD4 and CD8 S-specific memory T cells (ie non-naïve, excluding those that are CD45RA+CCR7+) at <1mo ($p=0.999$, $p=0.266$), 1-6mo ($p=0.6161$, $p=0.16349997$), and >6 mo ($p=>0.999$, $p=>0.999$) post-vaccination.

**Figure 4: Spike-specific CD4 and CD8 Responses In Aggregate: Comparison of BCD and Non-BCD**



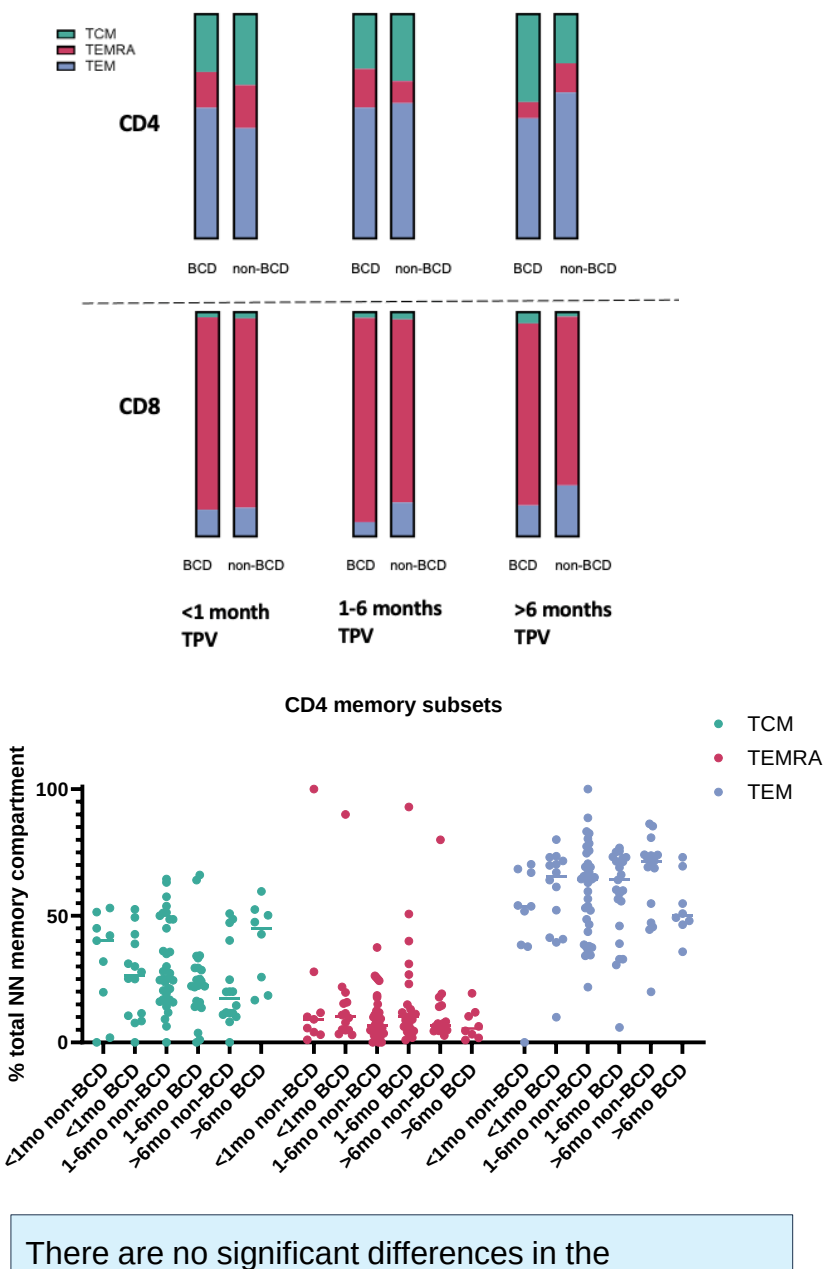

When evaluated in aggregate, BCD and non-BCD groups have similar levels of S-specific CD4 T cells, but subjects on BCD depletion have a larger CD8 response to vaccination.

**Figure 5: Spike-specific CD4 and CD8 responses over time: Comparison Between BCD Therapies**




There are no significant differences in the quantity of S-specific memory (non-naïve) T cells induced between subjects on various BCD agents.

**Figure 6: Spike-specific CD4 and CD8 Subtypes**




There are no significant differences in the phenotype of non-naïve S-Specific T cells between groups at any time point. There was a trend for BCD subjects to lose CD4 T effector memory (TEM) cells/ increase T Central Memory (TCM) cells while non-BCD subjects do the opposite over time.

## Conclusions

- B-cell depleting therapy diminishes the humoral response (anti-S and anti-RBD antibodies) that typically declines with time
- There may be some variability in the extent to which different BCD depleting therapies affect the humoral response, although data is limited by sample size especially for OFA
- Even in PwMS on BCD therapy, cellular response remains intact and endures with similar levels of spike-specific CD4 memory T cells
- Those on BCD therapy may actually have a more robust spike-specific CD8 memory T cell response than those not non BCD therapy
- BCD does not seem to significantly affect the phenotype (TCM, TEMRA, TEM) of non-naïve S-Specific T cells

**Disclosures: Study Source of Funding: Novartis**

S Wesley has received research support from Novartis and Biogen. Z Xia has served as a Consultant for Genentech/Roche and has received research support from the Pittsburgh Foundation and Genentech / Roche. P DeJager has consulted for Puretech, Biogen, Novo Nordisk and has research sponsored by Roche, Puretech, and Biogen. R Farber has consulted for Alexion, Roche/Genentech, Horizon Therapeutics, and has received research support from Novartis and Biogen. J Davis-Porada, C Tolzu, C Aiello, S Ferreira Brito, K Onomichi, A Ricci, E Walker, L Zhang, W Zhu, and D Farber have nothing to disclose.