Durability of Immune Response to COVID-19 Vaccines in MS Patients on B-Cell Depleting Therapy

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Background & Objective

- B-lymphocyte depleting therapies are commonly used for MS.
- Small studies have shown that individuals who are B-cell depleted (BCD) do not mount a robust antibody (Ab) response at 30 days post-SARS-CoV-2 vaccination [1]
- T-cell response has been largely spared in these smaller studies
- How this translates into longer lasting immunity is poorly characterized
- We aimed to characterize long-term immune responses to SARS-CoV-2 mRNA vaccines in subjects with treated and untreated MS.

Objective: Quantify anti-Spike and anti-Receptor binding domain (RBD) Abs, vaccine specific T-cells, and functional T-cell response in MS subjects pre-, 2-3 weeks post-, and 6 months post-mRNA vaccine series

Methods

- Subjects were recruited from Columbia Multiple Sclerosis Center and in New York City
- Data was collected from subjects with MS at one or more of the following: pre-, 2-3 weeks post-, and 6 months post- vaccine
- Donors with evidence of prior COVID infection (clinical history or nucleocapsid Abs) were excluded.
- Anti-Spike and 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 entire spike protein

Table 1: Subject Characteristics

Participants	N=127
Sex	Female: 69.3% (88)
Age	18-35: 36.3% (46) 36-55: 48.1% (61) 56+: 15.7% (20)
Race	Asian: 2.4% (3) Black/AA: 23.6% (30) Native Am: 3.9% (5) White: 51.2% (65) Other/multiracial: 18.9% (24)
Samples collected	252
Enrollment by DMT	Non-B cell: 46 • Cladribine: 2 • Dimethyl fumarate: 8 • Diroxyl fumarate: 2 • Fingolimod: 17 • Glatiramer acetate: 2 • Natalizumab: 8 • Siponimod: 1 • Teriflunomide: 6 B-cell depleting: 77 • Ocrelizumab: 53 • Ofatumumab: 10 • Rituximab: 14 No DMT : 4

Study Funding: Novartis

Data Analysis

Figure 1: Spike and RBD AB Titers

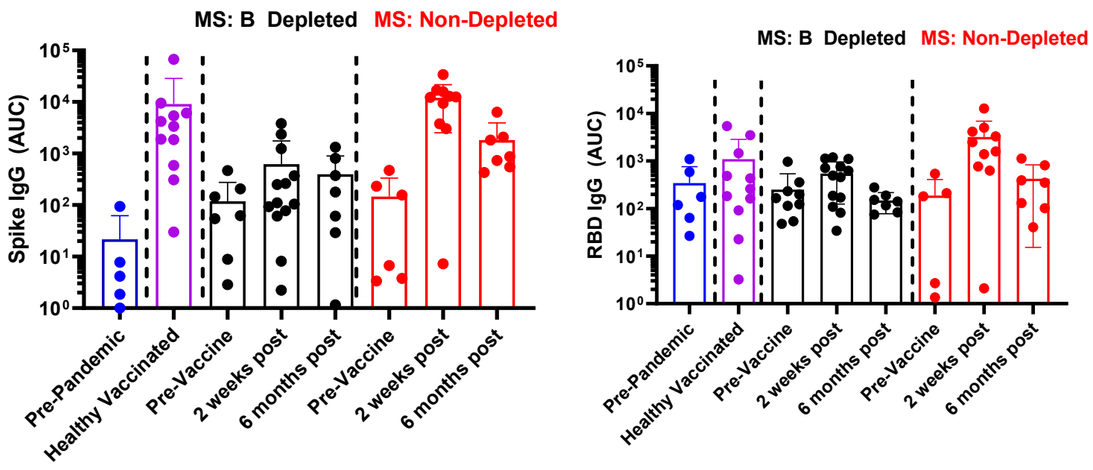


Figure 2: Post-Vaccine 2 WEEKS: Spike Ab Titers Comparing between BCD and Non-BCD, Amongst 3 BCDs

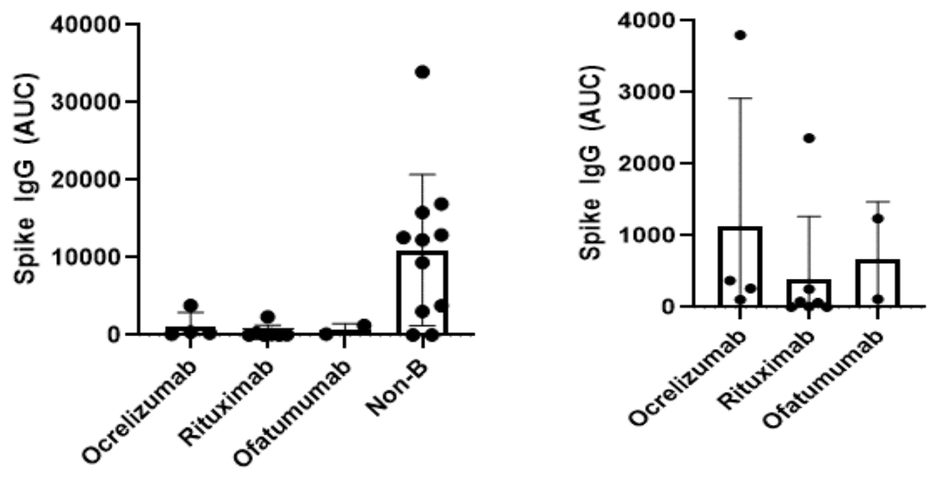


Figure 3: 6 Months Post-Vaccine: Spike Ab Titers Comparing between BCD and Non-BCD, Amongst 3 BCDs

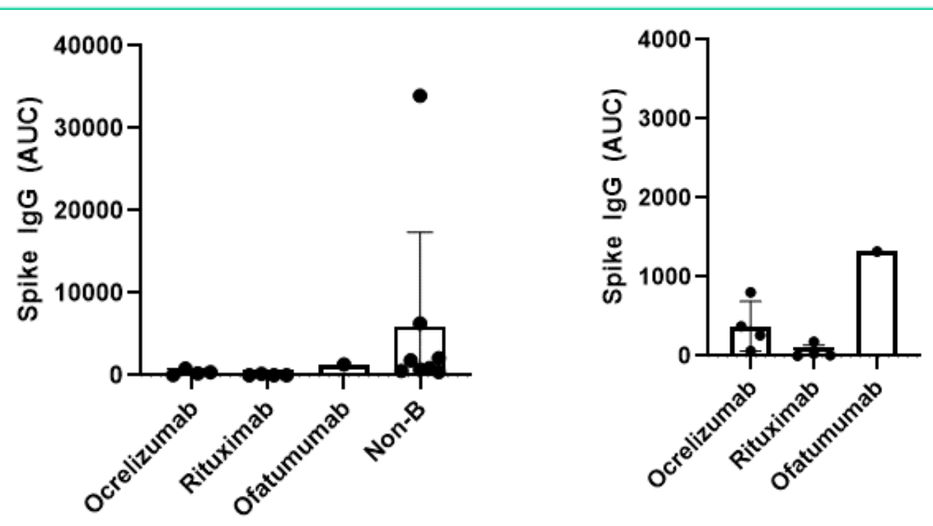
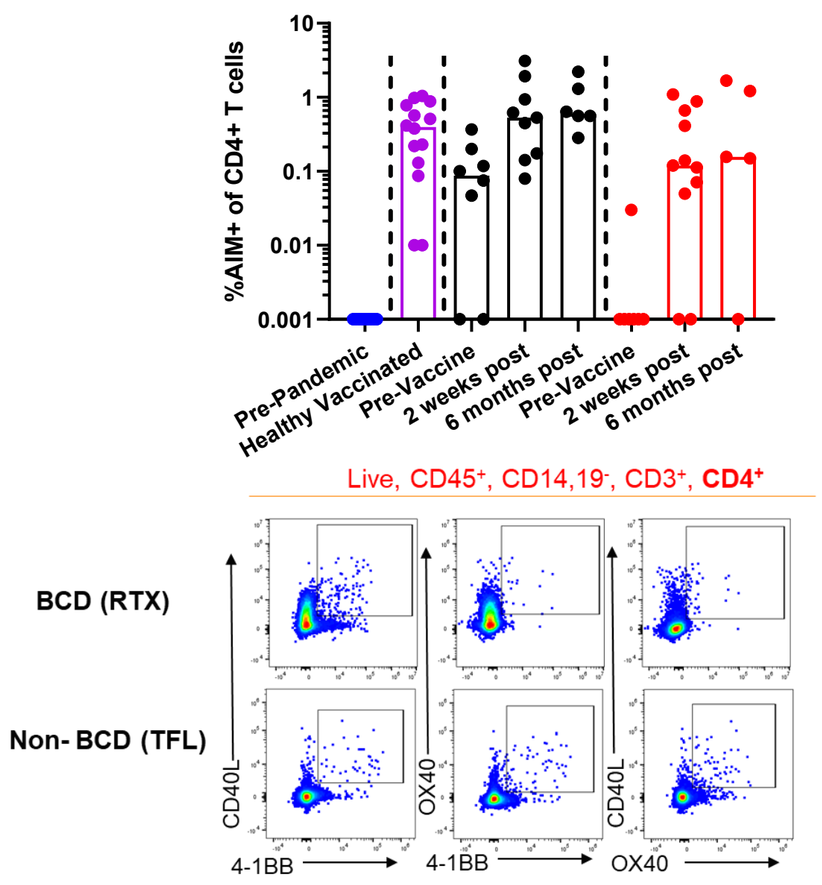


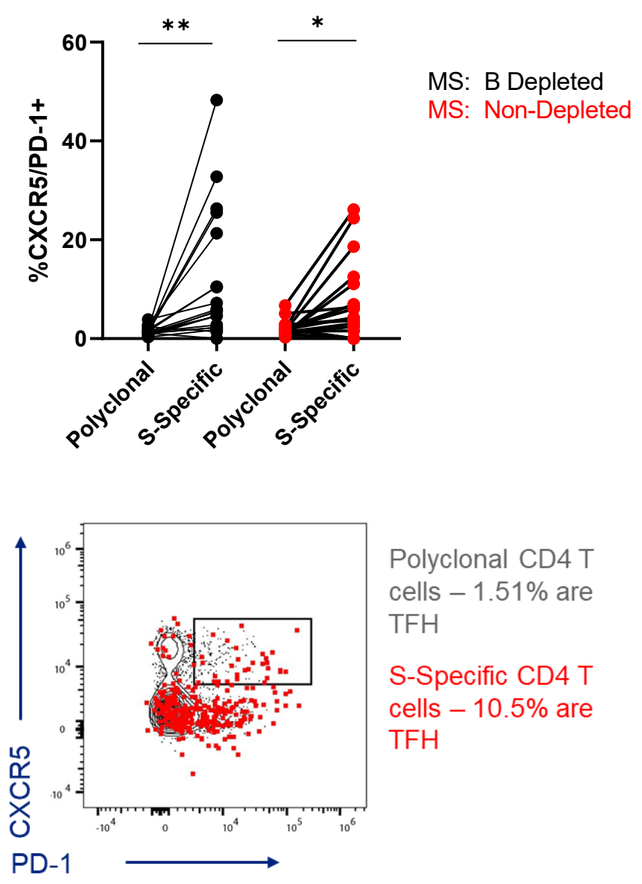
Figure 4: S-Specific CD4 T cells are induced in B cell depleted MS patients



Results

- In preliminary analysis of 48 samples, Ab titers increased following vaccination in all subjects.
- **At 2 weeks post-vaccination:** Mean titers of BCD (Spike 1546.1, RBD 699.3) were lower than those not BCD (Spike 11920.81, RBD 3093.2) at two weeks post-vaccination.
- The difference was significant (p=0.002) for Spike Ab titers and near significant (p=0.017) for RBD Ab titers.
- **At 6 months, post-vaccination:** Both groups' titers had dropped such that neither Spike Ab (p=0.101) nor RBD Ab titers (p=0.104) were different from one another.
- There was no trend towards a difference amongst the BCD agents in Spike Ab levels at 2 weeks post-vaccination, although the one sample from a subject on ofatumumab obtained 6 months post vaccination had Spike Ab titers of 1322 (versus a mean of 54 and 375 in rituximab and ocrelizumab, respectively).
- A robust CD4+ predominant T-cell response was induced in both BCD and non-BCD subjects. Percentage of Spike-specific CD4 T-cells was similar between the two groups at 2 weeks (p=0.097) and 6 months (p=0.734) post-vaccination.
- Enhanced levels of T follicular helper cells were seen in BCD and non-BCD subjects

Figure 5: Vaccination induces enhanced levels of circulating TFH in MS patients on any immunotherapy



Discussion

- B-cell depleting therapy alters the initial strength and the kinetics of the humoral vaccine response.
- Whether there is a difference in the extent or the kinetics of the humoral response between different BCD agents remains to be seen
- Long-term humoral immunity may not be significantly impaired.
- Cellular response remains intact and endures.
- The nature of the cellular response in BCD patients is similar in terms of the notable expansion of T follicular helper cells
- Data on cytokine production following antigen exposure is pending.

References

[1] Apostolidis SA, Kakara M, Painter MM, Goel RR, Mathew D, Lenzi K, Rezk A, Patterson KR, Espinoza DA, Kadri JC, Markowitz DM, E Markowitz C, Mexhitaj I, Jacobs D, Babb A, Betts MR, Prak ETL, Weiskopf D, Grifoni A, Lundgreen KA, Gouma S, Sette A, Bates P, Hensley SE, Greenplate AR, Wherry EJ, Li R, Bar-Or A. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat Med. 2021 Nov;27(11):1990-2001. doi: 10.1038/s41591-021-01507-2. Epub 2021 Sep 14.

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