Longitudinal Analysis of Adaptive Immunity Following Additional SARS-CoV-2 Vaccination in MS Patients on Anti-CD20 Therapies and Sphingosine-1-phosphate Receptor Modulators

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Introduction

- Adequate response to the SARS-CoV-2 vaccine is of high interest in caring for patients with multiple sclerosis (MS) during the SARS-CoV-2 pandemic.
- Previous studies have demonstrated reduced spike-specific immunoglobulin G (IgG) responses to the 1st and 2nd SARS-CoV-2 vaccines in MS patients on two specific DMT types: sphingosine-1-phosphate (S1P) receptor modulators and anti-CD20 monoclonal antibodies (mAb)[1].
- However, the effect of additional (3rd or booster) vaccinations on immune (both humoral and cellular) responses in MS patients treated with these DMTs is unknown.

1 Sabatino, et al. Multiple sclerosis therapies differentially impact SARS-CoV-2 vaccine-induced antibody and T cell immunity and function. JCI Insight. 2022

Objectives and Methods (1/2)

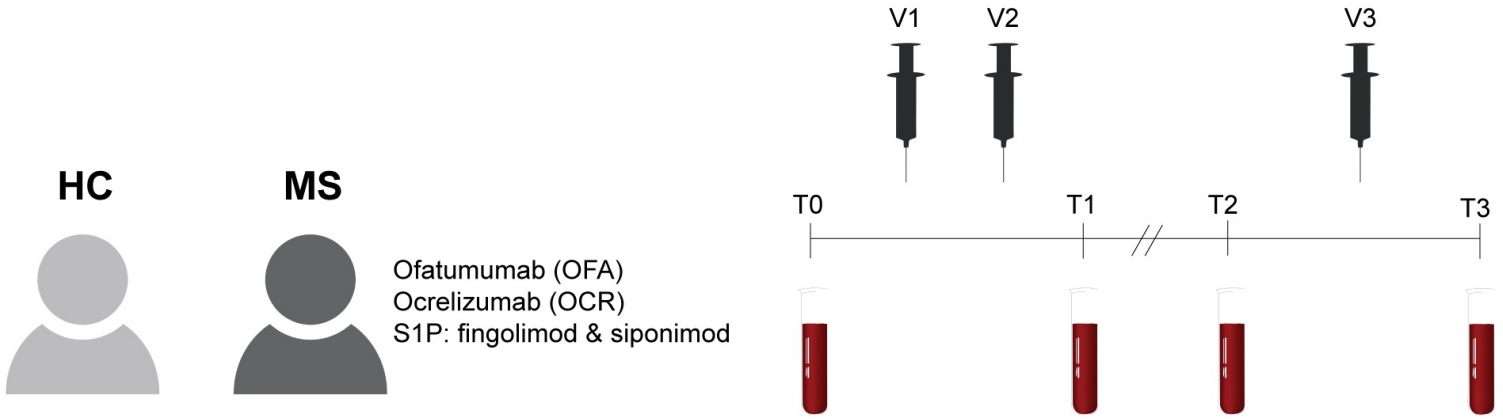
Objectives

As part of the ongoing longitudinal study on SARS-CoV-2 vaccine response, the goal of this interim analysis was to determine the effects of a 3rd SARS-CoV-2 vaccine (booster) on antibody and T-cell responses in healthy adults and MS patients treated with anti-CD20 antibodies (ocrelizumab and ofatumumab) and S1P receptor modulators (fingolimod and siponimod).

- All eligible subjects were included if they were 18 years of age or older at time of vaccination and MS patients had to be on one of the study treatments at time of receiving one of the FDA-approved or authorized vaccines (Comirnaty/BNT162b2 from Pfizer/BioNTech, mRNA-1273 from Moderna, or Ad26.COV2 from Johnson and Johnson)
- Blood samples were collected before and after SARS-CoV-2 vaccination (Figure 1)
  - Blood samples were collected ~2 weeks after vaccination
  - This analysis focused on immune response to 3rd vaccine (booster), where sample size was largest
- Total spike protein and spike receptor binding domain-specific IgG responses were measured by Luminex bead-based assay in a UCSF research lab. Spike-specific CD4+ and CD8+ T cell responses were measured by activation-induced marker (AIM) expression following stimulation with spike peptide pools
  - IgG reactivity against **total spike** protein demonstrates antibody reactivity against all potential epitopes within the spike protein, including reactivity that may not be neutralizing
  - IgG reactivity against the **spike receptor binding domain** (RBD) indicates reactivity against only the RBD portion of the spike protein, which is a surrogate for antibody-mediated neutralization of SARS-CoV-2
  - RBD is a subset of total spike and is a more specific and a better correlate for neutralizing antibodies against SARS-CoV-2 vaccination

Objectives and Methods (2/2)

Figure 1. Study design overview



- Cohort of healthy controls (HC) with no treatment and MS patients while on treatment with anti-CD20s (ofatumumab or ocrelizumab), or sphingosine-1-phosphate (S1P) receptor modulators (fingolimod or siponimod) were longitudinally assessed for antibody and T-cell responses before and following SARS-CoV-2 vaccinations (V1-3).
  - Blood samples were collected at the independent timepoints (T). T0 indicates blood samples collected at baseline, prior to vaccine 1. T1 indicates blood samples collected after receiving full two-dose vaccination series. T2 indicates blood samples collected prior to 3rd vaccine (booster). And T3 indicates seropositivity after 3rd vaccine (booster).
- Not all patients had blood samples available at all time points.

Results (1/6)

Table 1. Overview of study subject characteristics†

Study Group	N*	Age (mean years)	Female	Time from V2 to V3 (mean days)	Time from V3 to T3 (mean days)	Tx Duration to V3 (mean months)	Tx Duration to V3 including prior anti-CD20/S1P treatment (mean months)
HC	11	36.1	73%	277	15	N/A	N/A
Anti-CD20s							
OFA	11	48.1	64%	189	42	10.2	53.5**
OCR	25	44.2	64%	147	23	37.8	Not available at time of analysis
S1P	13^	48.8	69%	152	33	67.3	Not available at time of analysis

- Healthy controls tended to be younger and have longer time between V2 and V3.
- When accounting for prior treatment with another anti-CD20 or S1P, total length of treatment is significantly longer than ofatumumab treatment duration alone (>4 years and <1 year, respectively).

†All patients received mRNA vaccines, except for two S1P (both fingolimod) who received JNJ vaccine for first vaccine.

*Not all patients had blood samples available at all time points.

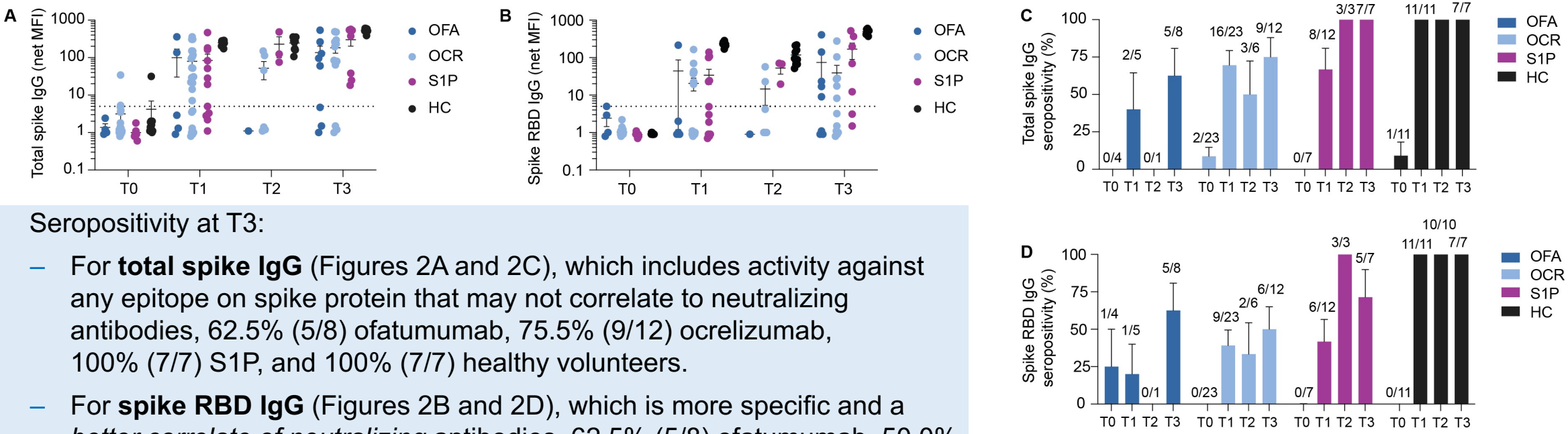
**Indicates treatment duration of ofatumumab-treated patients who were previously on another anti-CD20 (ocrelizumab or rituximab) therapy or S1P (fingolimod or siponimod).

^Includes 11 fingolimod and 2 siponimod.

Results (2/6)

Figure 2. Antibody responses to SARS-CoV-2 vaccination for the different groups at each time point

- IgG levels to total spike (A) and spike RBD (B) for the different groups at each time point. The dotted line indicates the cut-off for seropositivity.
- The frequency of seropositive subjects at each time point is shown for total spike IgG (C) and spike RBD IgG (D).
- The number of seropositive subjects is shown over the total number of samples available at each time point.



- Seropositivity at T3:
  - For **total spike IgG** (Figures 2A and 2C), which includes activity against any epitope on spike protein that may not correlate to neutralizing antibodies, 62.5% (5/8) ofatumumab, 75.5% (9/12) ocrelizumab, 100% (7/7) S1P, and 100% (7/7) healthy volunteers.
  - For **spike RBD IgG** (Figures 2B and 2D), which is more specific and a *better correlate of neutralizing* antibodies, 62.5% (5/8) ofatumumab, 50.0% (6/12) ocrelizumab, 71.4% (5/7) S1P, and 100% (7/7) healthy volunteers.

Results (3/6)

Table 2. Seropersistence – The number of patients in each group **that had results at both time points** who were seropositive following both V2 and V3 for patients for total spike IgG and spike RBD IgG.

Group	Total spike IgG	Spike RBD IgG
HC	7/7	7/7
OFA	1/1	Not applicable*
OCR	8/8	5/5
S1P	5/5	4/4

- All participants who were seropositive at V2 remained seropositive at V3.

* No seropositive samples available following V2

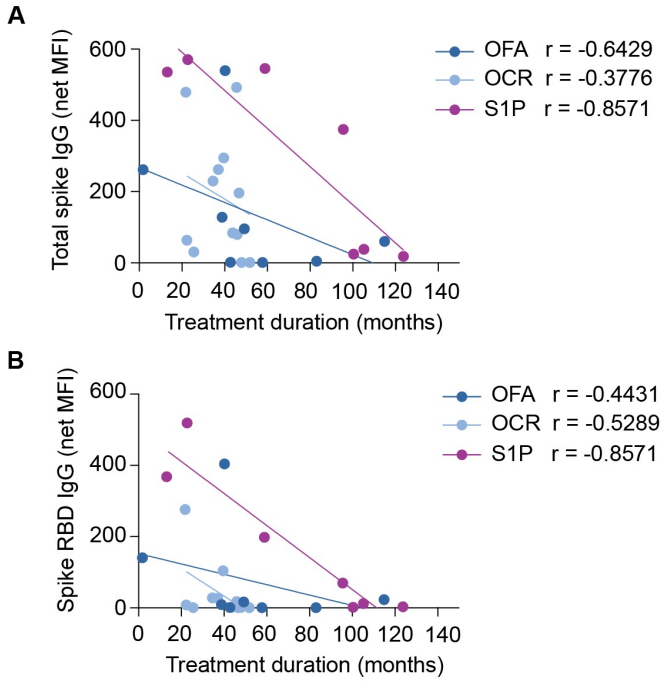
Table 3. Seroconversion – The number of patients in each group **that had results at both time points** who were seronegative following V2, and then seroconverted following V3 for total spike IgG and spike RBD IgG.

Group	Total spike IgG	Spike RBD IgG
OFA	0/3	1/4
OCR	1/4	0/7
S1P	2/2	1/3

- Among patients who were seronegative at V2, a subset of patients seroconverted at V3.

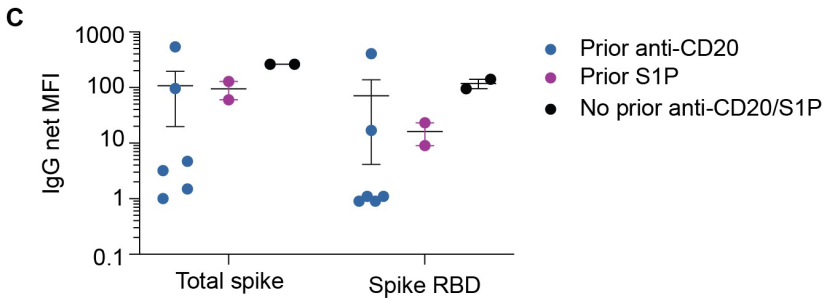
Results (4/6)

Figures 3A and 3B. Spearman correlation analysis of treatment duration on vaccine-elicited antibody responses (Figures 3A and 3B) and impact of prior treatment among ofatumumab-treated patients.



- As duration of treatment increases, immune response tended to decrease.

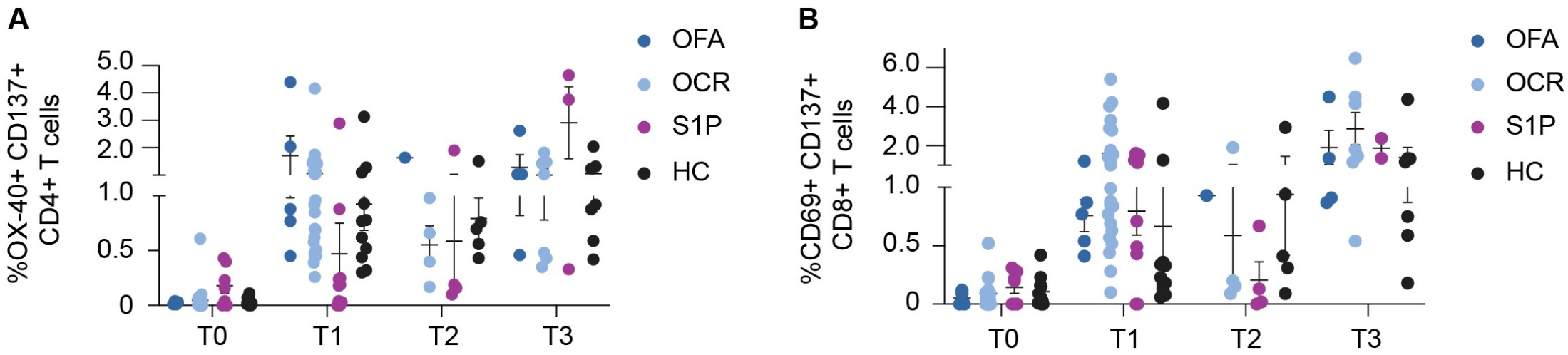
Figure 3C. Total spike IgG and spike RBD IgG levels in ofatumumab patients based on history of treatment prior to ofatumumab, including other anti-CD20, S1P, or neither anti-CD20/S1P.



- Prior treatment with ocrelizumab, rituximab, fingolimod or siponimod, may impact immune response among patients treated with ofatumumab.

Results (5/6)

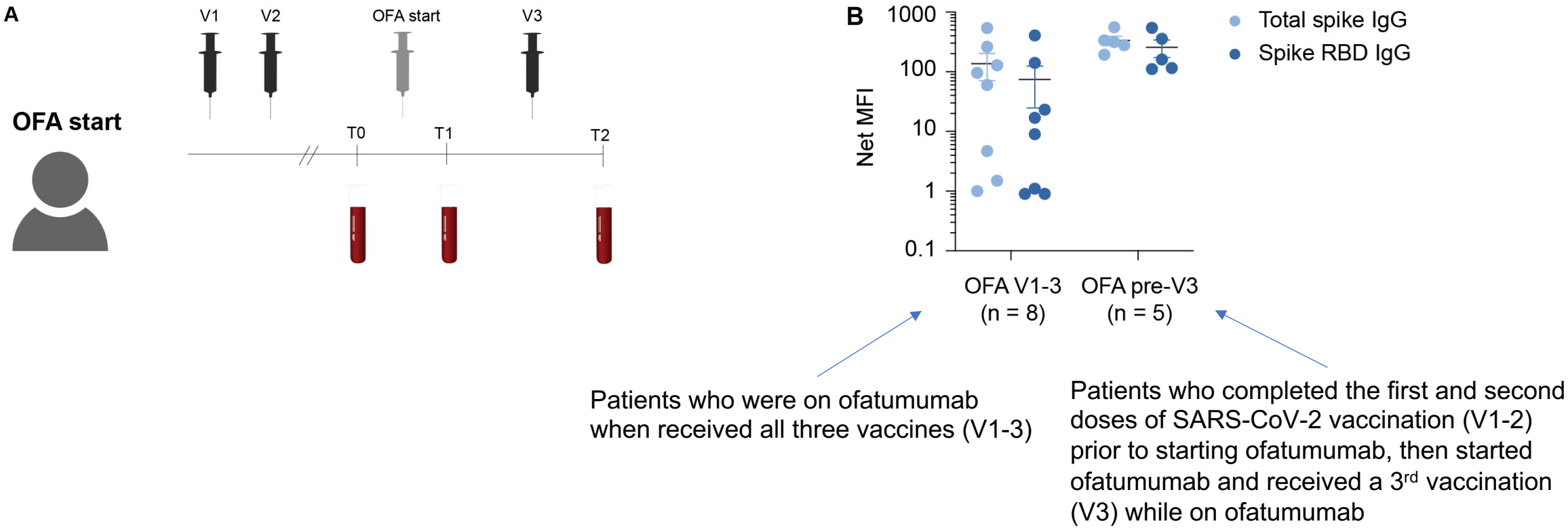
Figure 4. T-cell response – Proportion of CD4+ T cells (A) and CD8+ T cells (B) that are spike-reactive are shown for the different treatment groups at each time point.



- At T3, all participants appeared to have both a CD4 and CD8 T-cell response.

Results (6/6)

Figure 5. Impact of ofatumumab start on pre-existing and de novo SARS-CoV-2 vaccine-induced immunity



- Patients who started ofatumumab after having received 1st and 2nd vaccines had high antibody titers following 3rd vaccine.

Limitations

- Sample size is limited, thus results should be interpreted with caution.
- Due to limited sample size, it is not possible to account for differences between groups, therefore, it is not feasible to compare groups.
- This study measured immune outcomes only and did not explore clinical outcomes.

Conclusions

- **Humoral immunity**
  - In this interim analysis of adult MS patients on S1Ps and anti-CD20s, while immune response was overall attenuated, a majority of patients in all DMT groups (> 70% S1P and > 50% anti-CD20) mounted an antibody response to 3rd vaccination (booster)
    - Assessing immune response to different epitopes (e.g., total vs. RBD protein) may differ in correlation to neutralizing antibodies
  - Additional clinical insights include:
    - Length of treatment may impact immune response
    - Understanding previous treatment history is important when assessing immune response
      - This interim analysis suggests that prior ocrelizumab, rituximab or S1P treatment may impact immune response after switch to another DMT
    - Vaccination prior to DMT initiation may improve antibody responses compared to vaccination following DMT initiation
    - Patients who responded to 2nd vaccine retained response following 3rd (booster) vaccine
    - Some patients who did not initially seroconvert after the 2nd vaccine did appear to seroconvert after the 3rd (booster) vaccine
- **Cellular immunity**
  - In this interim analysis, all adult MS patients on S1Ps and anti-CD20s mounted a T-cell response to 3rd (booster) vaccine in all DMT groups
  - T-cells are thought to be clinically important for clearance and recovery from COVID-19 infection

Disclosures

- This study was sponsored by Novartis Pharmaceuticals Corporation
- CD, EMM and KW are employees of Novartis. JJS has received research funding from Novartis. MRW has received research grant funding from Roche/Genentech and speaking honoraria from Novartis, Takeda and Genentech. SSZ has received consulting honoraria from Alexion, Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc and has served on Data Safety Monitoring Boards for Lilly, BioMS, Teva and Therapeutics. RB has received research grant funding from Novartis, Roche Genentech and Biogen, and consulting honoraria from Alexion, Biogen, EMD Serono, Genzyme Sanofi, Novartis, and Roche Genentech.

Thank you