# Preserved T cell but attenuated antibody response in MS patients on Fingolimod and Ocrelizumab following 2nd and 3rd SARS-CoV-2 mRNA vaccine

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## Background & Objective

Immunosuppressed patients may not mount an adequate immune response to 2 doses of SARS-CoV-2 mRNA vaccines and are eligible to receive a 3rd dose. There is limited knowledge about T cell responses specifically in patients with multiple sclerosis (MS) who receive 3 doses of vaccine.

***Our objective is*** to assess the SARS-CoV-2 spike antibody responses and T cell responses in MS patients on high efficacy immunotherapies and healthy controls (HC) who received 2 (2-vax) and 3 (3-vax) doses of SARS-CoV-2 mRNA vaccines.

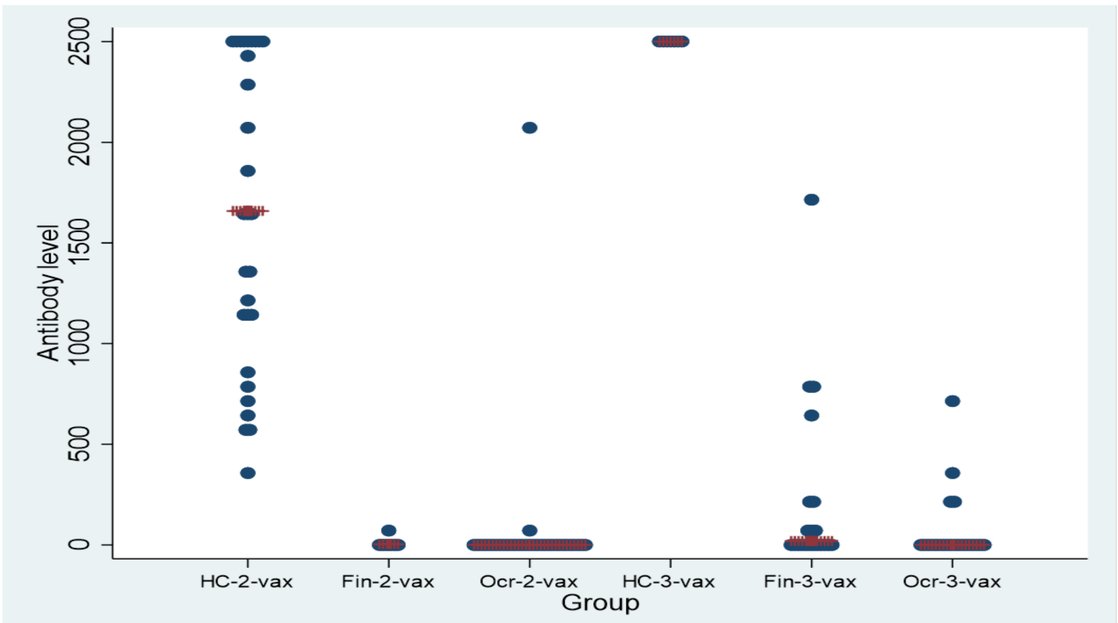
## Methods

We studied patients with MS, aged 18-65, on fingolimod (FIN) or ocrelizumab (OCR) for at least 3 months prior to their 1st mRNA SARS-CoV-2 vaccine dose (BNT162b2 or mRNA-1273) followed at the Brigham MS Center. HC who received the mRNA vaccines were also enrolled. Blood samples were collected after 2nd (2-vax) and 3rd (3-vax) dose of mRNA vaccine. The proportion of patients and HC who exhibited seroconversion, demonstrating serum SARS-CoV-2 spike antibody levels >0.4 U/ml was determined. T cell responses were examined in a subgroup of patients with MS and HC after 2-vax and 3-vax by flow cytometry.

## Results

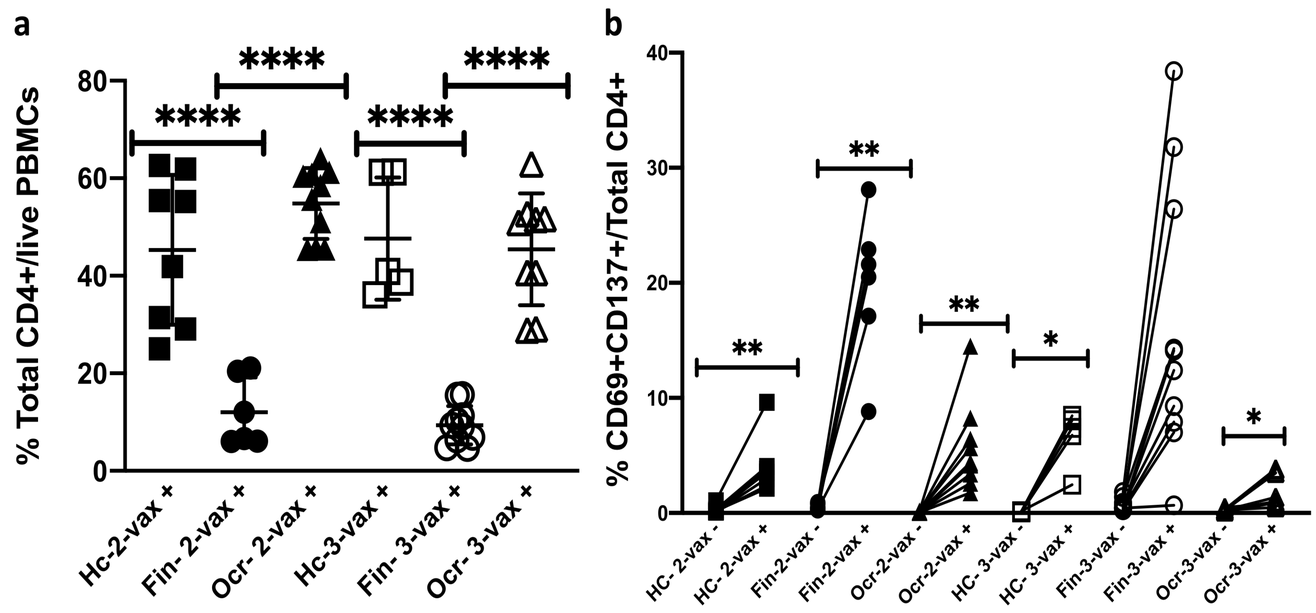
### Result 1: Attenuated anti-SARS-CoV-2 antibody response in MS patients as compared to HCs.

The proportion of patients who seroconverted after 2-vax was 8/33 (24.2%) in the OCR group, 5/7 (71.4%) in the FIN group, and 29/29 (100%) in the HC group (Fisher's exact test, $P = 5.7*10^{-11}$). After 3-vax, 9/21 (40.9%) patients in the OCR group seroconverted as compared to 19/21 (90.5%) in the FIN group, and 7/7 (100%) in the HC group (Fisher's exact test for difference, $P$=0.0003).



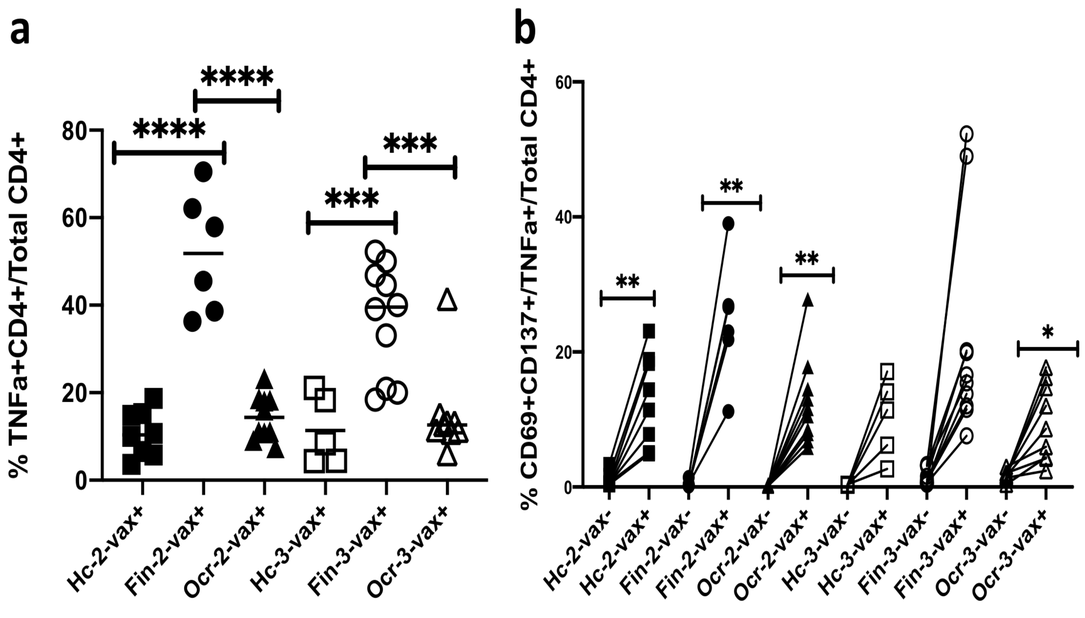

### Result 2: Increased percentage of SARS-CoV-2 peptide reactive total CD4+ T cells in HCs and ocrelizumab patients.

There was an increase in the percentage of SARS-CoV-2 peptide reactive total CD4+ T cells in HC and OCR group but not in FIN group after 2-vax and 3-vax (Sidak's multiple comparisons test , $P$<0.0001). There was an increased activation (CD69/CD137++) of total CD4+ T cells after stimulating with SARS-CoV-2 Prot_S peptide (+) as compared to the unstimulated condition (-) across all 3 groups after 2-vax and 3-vax.



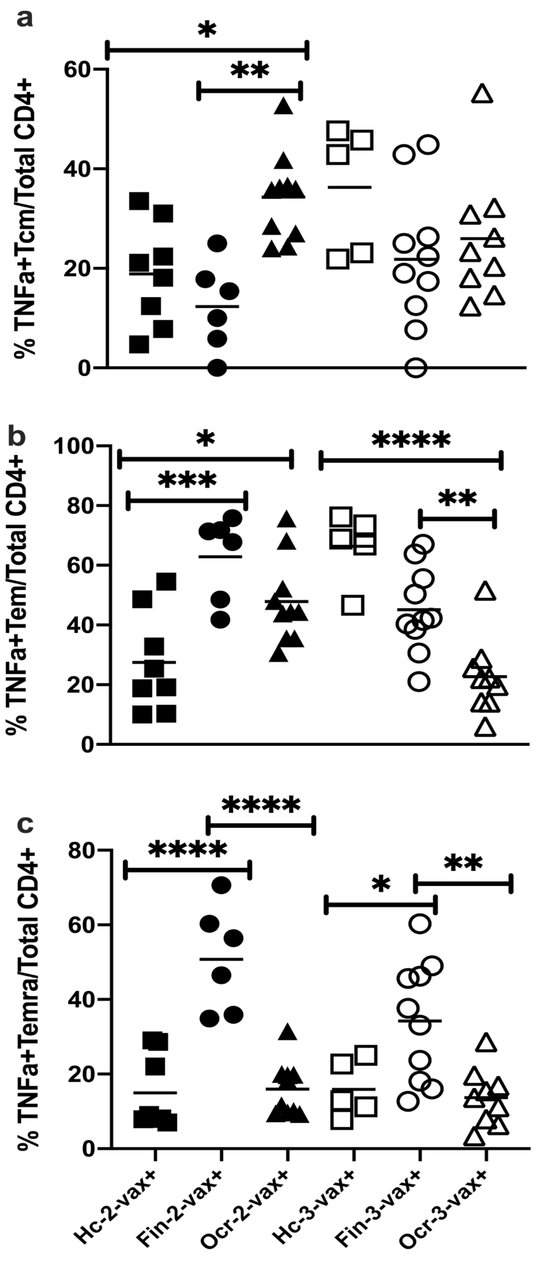

### Result 3: Increased percentage of SARS-CoV-2 peptide reactive TNFα producing total CD4+ T cells in fingolimod patients.

There was a significant increase in the percentage of IFNγ and TNFα producing CD4+ T cells in the fingolimod group as compared to HC and the ocrelizumab group after 2-vax and 3-vax ($P$<0.0001, Sidak's multiple comparisons test). There was an increased activation (CD69/CD137++) of TNFα producing CD4+ T cells after stimulating with SARS-CoV-2 Prot_S peptide (+) as compared to the unstimulated condition (-) across all 3 groups after 2-vax and 3-vax.




### Result 4: Increased percentage of SARS-CoV-2 peptide reactive TNFα producing central memory CD4+ T cells in ocrelizumab patients, TNFα producing effector memory CD4+ T cells in both patient groups and terminally differentiated effector memory CD4+ T cells in fingolimod patients.

There was a significant increase in the percentage of SARS-CoV-2 Prot_S peptide reactive TNFα producing central memory (Tcm) CD4+ T cells in ocrelizumab group as compared to fingolimod group ($P$=0.004) and HC ($P$=0.04) after 2-vax. The percentage of TNFα producing effector memory (Tem) CD4+ T cells was significantly higher in both, ocrelizumab ($P$=0.0252) and fingolimod groups ($P$=0.0002) as compared to HC after 2-vax. The percentage of TNFα producing terminally differentiated effector memory (Temra) CD4+ T cells was significantly higher in the fingolimod group as compared to ocrelizumab group and HC after 2-vax ($P$<0.0001) as well as 3-vax.




## Conclusion

MS patients on ocrelizumab and fingolimod had attenuated spike antibody responses, but preserved cytokine producing T cell responses to SARS-CoV-2 peptides compared to healthy controls after second and third SARS-CoV-2 mRNA vaccination.

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