Journal of Family Medicine

Open Access

Austin Publishing Group

Research Article

Multiple Sclerosis Disease-Modifying Therapies and Immunological Responses to COVID-19 Vaccination in Puerto Rican Patients

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Received: August 27, 2025
Accepted: September 11, 2025
Published: September 15, 2025

Abstract

Background: Patients with multiple sclerosis (MS) are commonly treated with disease-modifying therapies (DMTs) that modulate the immune system. However, concerns have been raised regarding how these therapies may influence the immunological response to COVID-19 vaccination, particularly in Hispanic Puerto Rican patients. Certain DMTs, particularly anti-CD20 therapies and S1P receptor modulators, have been associated with attenuated humoral responses.

Methods: This prospective, single-center study enrolled MS patients in Puerto Rico receiving various DMTs or no treatment (NoDMT). Participants received mRNA COVID-19 vaccines, with humoral and cellular immune responses assessed at multiple time points post-vaccination. Serum samples were analyzed for SARS-CoV-2 IgG antibodies against the spike protein, while cellular responses, including CD4 and CD8 T-cell activity, were also evaluated.

Results: Patients treated with anti-CD20 therapies (ocrelizumab, ofatumumab) and S1P receptor modulators (fingolimod, siponimod, ozanimod) demonstrated significantly reduced humoral responses compared to the NoDMT group. Other DMTs, including fumarates, teriflunomide, interferons, glatiramer acetate, alemtuzumab, natalizumab, and cladribine, did not show a marked impairment in antibody production. Cellular immune responses remained largely intact across all groups, with minor reductions in CD4 and CD8 T-cell counts observed in patients on S1P receptor modulators and cladribine.

Conclusion: These findings highlight the differential impact of DMTs on vaccine-induced immunity in Hispanic Puerto Rican MS patients. While most patients achieved adequate immune responses, those on anti-CD20 and S1P receptor modulators exhibited attenuated humoral immunity, underscoring the need for tailored vaccination strategies. Further studies are warranted to optimize COVID-19 vaccine efficacy in MS patient population.

Keywords: Multiple Sclerosis; COVID-19 vaccine; Humoral response; Cellular response; Puerto Rico; Hispanics

Abbreviations

DMT; Disease-modifying Therapies; DNA; Deoxyribonucleic Acid; IRB; Institutional Review Board; MS; Multiple Sclerosis; PR; Puerto Rico; RBD; Receptor Binding Domain; S1; Spike 1

Introduction

The vaccines against COVID-19, in an attempt to control the SARS-CoV-2 virus, are expected to promote an aggressive immunological response towards the virus. It has been suggested that immunomodulatory disease-modifying therapies (DMTs), which are used for the treatment of Multiple Sclerosis (MS), a chronic autoimmune disease that targets the central nervous system, could decrease the immunological response to vaccines [1]. Therefore, the clinical management of MS with DMTs could be a concern regarding the risk of COVID-19 complications in patients on this treatment approach [1].

Initial studies identified the potential risks for MS patients exposed to COVID-19, noting that those on certain DMTs might be more likely to have severe outcomes due to their immunosuppressive nature [1]. This prompted widespread interest in understanding how DMTs interact with COVID-19 and subsequent vaccines' immunological response. As vaccines became available, evaluating their safety and efficacy in this patient population became crucial.

Previous studies have demonstrated that while most MS patients developed robust antibody responses to mRNA vaccines, those on anti-CD20 therapies like ocrelizumab showed important attenuated

Citation: Chinea-Martínez AR, Martínez-Maldonado V, Sánchez-Real DE, Vega-Corteguera RJ, Carmona-Burgos DX, et al. Multiple Sclerosis Disease-Modifying Therapies and Immunological Responses to COVID-19 Vaccination in Puerto Rican Patients. J Fam Med. 2025; 12(2): 1382.

responses [2,3,4]. This raised concerns about the overall effectiveness of vaccination in these patients and underscored the need for tailored vaccination strategies for patients who are on autoimmune therapies. It has been suggested that there is variability in vaccine responses among different patient study populations and treatment regimens [5,6,7,8]. For instance, Rojas and colleagues evaluated the serological responses to the Sputnik V and AstraZeneca vaccines in Argentine MS patients [5]. This study found that patients on ocrelizumab and fingolimod had significantly lower antibody responses compared to those on other DMTs [5]. Similarly, studies focusing on long-term immune responses and the effects of booster vaccinations have found significant immune response variability depending on the DMT regimen [6,7]; and have identified early innate immune signatures that could predict effective humoral responses, providing a potential pathway for optimizing vaccination strategies in MS patients [8].

The objective of this study is to evaluate how the treatment of Puerto Rican (PR) MS patients with DMTs was associated with the immunological response that was expected to result after vaccinating these patients with the COVID-19 vaccine. Moreover, we compared how different DMTs, with their respective mechanisms of action depending on the medication, were related in any way to the immunological response to the COVID-19 vaccine.

Materials and Methods

This is a prospective, single-center study approved by the San Juan Bautista School of Medicine Institutional Review Board (IRB). Written informed consent approved by the IRB was obtained from all participants (IRB Approval EMSJBIRB-3-2021). The study population consisted of adults 18 to 65 years of age with any form of MS diagnosed according to the 2017 revised McDonald's criteria [9], patients of the San Juan MS Center clinic, and who were going to receive the mRNA-1273 or BNT162b2 COVID-19 mRNA vaccines. Participants meeting criteria for optic neuromyelitis, transverse myelitis, or who had any contraindications for the administration of the mRNA COVID-19 vaccines were excluded from this study.

Measurements

The main independent variable in this study was DMT exposure. The patient was categorized as exposed if they were treated with any of the following DMT including interferons (interferon beta-1a, interferon beta-1b, and peginterferon beta-1a), glatiramer acetate, fumarates (dimethyl fumarate, diroximel fumarate, and monomethyl fumarate), teriflunomide, anti-CD20s (ocrelizumab and ofatumumab), alemtuzumab, cladribine, S1P receptor modulators (fingolimod, siponimod, and ozanimod), or natalizumab. The patient was categorized as not exposed (comparison group) if there were PR MS patients 18 to 65 years old with any type of MS and not being treated with a DMT (NoDMT).

The main response variable for this study was humoral immune responses. All samples were collected onsite by study personnel and then sent to a local laboratory for processing. Safety and cellular responses were measured by standard testing. Humoral immune response of individuals was performed using the AdviseDx SARS-Cov-2 IgG II assay. This assay is used as an aid in identifying individuals with an adaptive immune response to COVID-19, indicating recent or prior infection, or in this case, the presence of antibodies following vaccination. According to the AdviseDx SARS-Cov-2 IgG II assay, the cutoff for determining if patients were able to develop immunity after COVID-19 vaccination was 50.0 AU/mL.

Study Logistics

After informed consent was obtained, baseline, demographic, and medical history data were collected, including history of previous infection with COVID-19. Furthermore, serum samples were obtained for safety and to assess cellular immune responses before vaccination. At Visit 1, a brief medical history questionnaire was completed along with serum samples to assess safety and humoral and cellular responses after the second dose of the COVID-19 vaccine. At a subsequent visit (Visit 2) participants who received either a third vaccine dose or booster, with a safety questionnaire and serum sample for humoral response assessment. The fourth and final visit (Visit 3), consisted of a follow-up questionnaire with serum samples for safety and long term humoral and cellular responses after COVID-19 vaccination (Figure 1). The first and second doses of COVID-19 vaccines that were taken before visit one were usually administered two to three weeks apart, which was the CDC guideline at the time of COVID-19 pandemic. The third dose of COVID-19 vaccine was usually administered 6 months to one year after the second dose of COVID-19 vaccine according to CDC guidelines.

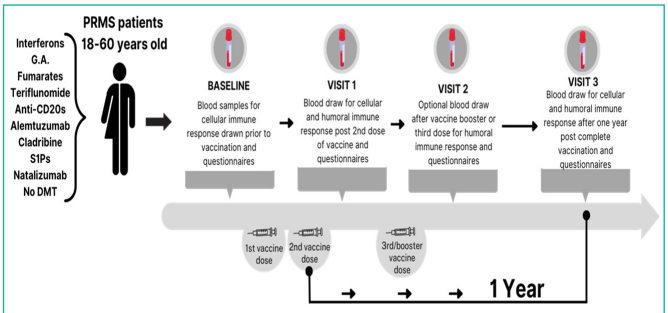

Figure 1: Experimental design for evaluating Immunological response in Hispanic Puerto Rican MS patients treated with a DMT or with no DMT after receiving COVID-19 vaccine and booster vaccines.

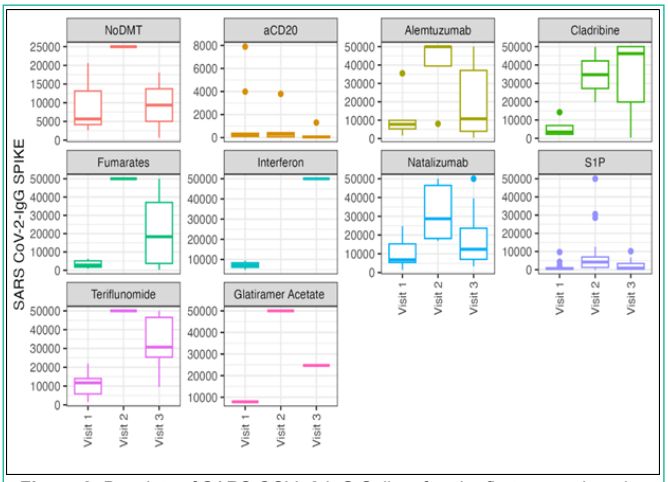

Figure 2: Boxplots of SARS COV -2 IgG Spike after the first, second, and third vaccines.
Note that "y" axis varies for each of the treatments. The thicker line in the boxes is the median, the lower and higher horizontal lines are the 25 and 75 percentiles, the whiskers are the 5 and 95 percentiles, while the points are outliers.
NoDMT = No disease modifying therapy.

Table 1: Demographic, disease, and vaccine history of patients in Disease Modifying Therapies.

DMTs	Sex, N (%) Males Females	Age at Baseline Mean ± SD	Baseline Disability EDSS Mean ± SD	DMT Duration Mean ± SD	DMT Line No. of DMTs 1 | 2 | ≥3	Vaccine, N (%) mRNA-1273 BNT162b2
aCD20s	5 (35.7)	47.6 ± 8.0	3.9 ± 2.2	2.5 ± 1.4	3 | 4 | 7	10 (71.4)
N=14	9 (64.3)					4 (28.6)
Nata	5 (55.6)	36.5 ± 10.2	2.2 ± 1.8	7.1 ± 4.7	3 | 3 | 2	9 (100)
N=9	4 (44.4)					0
Alem	1 (16.7)	40.9 ± 5.0	2.8 ± 2.5	3.8 ± 0.9	0 | 1 | 5	6 (100)
N=6	5 (83.3)					0
Clad	2 (33.3)	50.6 ± 11.5	5.8 ± 2.0	1.2 ± 0.6	0 | 0 | 6	3 (50)
N=6	4 (66.7)					3 (50)
S1Ps	2 (13.3)	39.7 ± 10.1	1.6 ± 1.5	3.4 ± 2.3	7 | 7 | 1	12 (80)
N=15	13 (86.7)					3 (20)
Fum N=6	3 (50) 3 (50)	42.8 ± 9.5	0.6 ± 0.6 (EDSS available for 4/6 patients)	3.2 ± 2.0 (Available for 5/6 patients)	2 | 2 | 2	6 (100) 0
Teriflu N=6	1 (16.7) 5 (83.3)	45.1 ± 10.4	1.8 ± 2.4	2.8 ± 1.3	1 | 1 | 4	6 (100) 0
Interf N=2	1 (50) 1 (50)	32.7 ± 6.6	Unknown for both patients	5.5 ± 0.5	1 | 1 | 0	1 (50) 1 (50)
G.A. N=1	0 1 (100)	58.1	0	7 ± 0	0 | 1 | 0	1 (100) 0
No DMT N=3	1 (33.3) 2 (66.7)	47.2 ± 5.8	2 ± 0 (EDSS available for 2/3 patients)	N/A	0 | 0 | 2	2 (100) 0

Abbreviations: aCD20s (ocrelizumab, ofatumumab), Nata (natalizumab), Alem (alemtuzumab), Clad (cladribine), S1Ps (fingolimod, Siponimod, ozanimod), Fum (fumarates: dimethyl fumarate, diroximel fumarate, and monomethyl fumarate), Teriflu (teriflunomide), Interf (Interferons: interferon beta-1a, interferon beta-1b, and peginterferon beta-1a), G.A. (glatiramer acetate).

Statistical Analysis

All statistical analyses were performed with R Statistical Software (v.4.4.0;R Core Team) [10]. The main packages used were tidyverse [11] for data wrangling, janitor [12] and ggplot2 for visualization [13]. Descriptive statistics (mean, standard deviation, median and quantiles) were calculated for each continuous variable. Frequencies and percentages were used for categorical variables. To compare the association of types of DTM treatments and the response variable, individuals who were not administered any treatment are identified as NoDMT. Sample sizes vary among survey periods and treatments, as shown in the figures.

Results

A total of 68 MS patients were included in the study sample. Table 1 presents demographic, treatment, and clinical characteristics of the patients included in this study.

DMTs such as anti-CD20s (ocrelizumab and ofatumumab) and S1P receptor modulators (fingolimod, siponimod, and ozanimod) had lower humoral response in production of SARS COV-2-IgG SPIKE protein after administration of COVID-19 vaccine and subsequent booster vaccines (Figure 2 and Figure 3). The other types of medications used in this study (alemtuzumab, cladribine, fumarates, interferons, natalizumab, teriflunomide, and glatiramer acetate) had no significant effect on the humoral response and the patients treated with these medications were able to successfully produce immunoglobulins against the SARS COV-2 spike protein comparable to the comparison group (NoDMT). Evaluation of boxplots comparing the effect of different medications on the production of lymphocytes (Figure 4), showed no significant effect on the absolute lymphocyte count after administration of the COVID-19 vaccine on DMTs treated patients. However, S1P receptor modulators

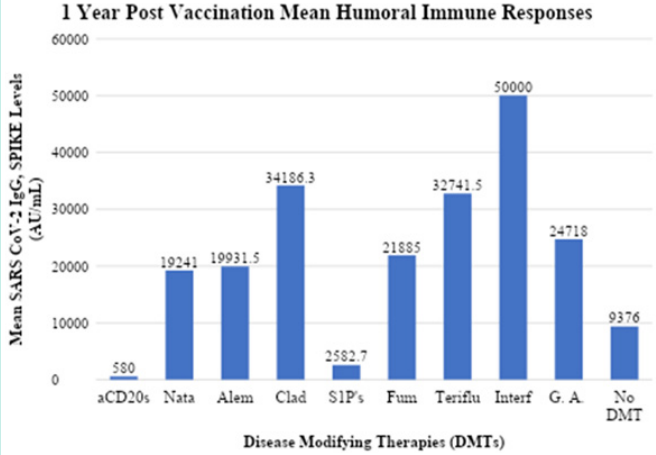

Figure 3: Differences between humoral immune response between different DMTs one year post COVID-19 vaccination.

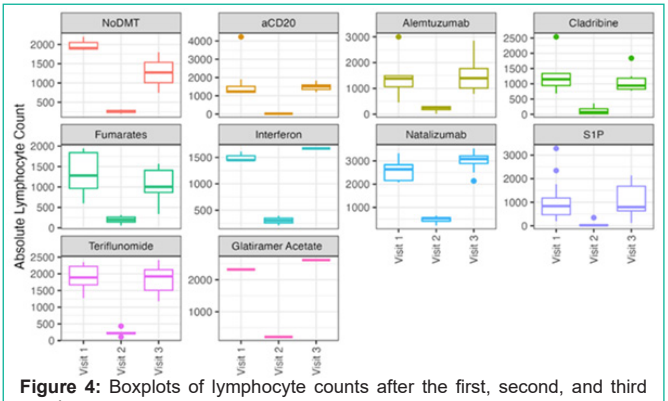

Figure 4: Boxplots of lymphocyte counts after the first, second, and third vaccines.
Note. The "y" axis varies for each of the treatments (see Figure 2 for boxplot legends).

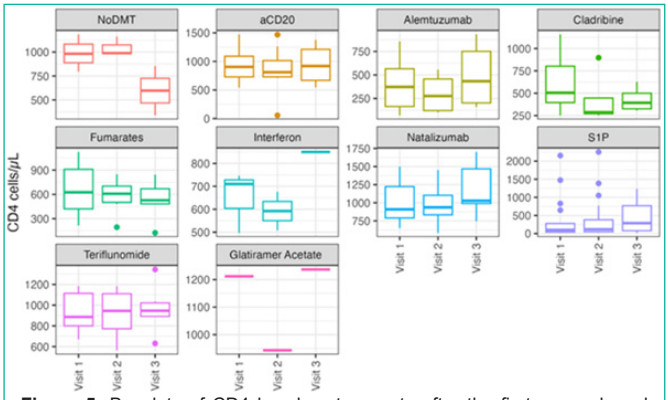

Figure 5: Boxplots of CD4 lymphocyte counts after the first, second, and third vaccines.
Note that the "y" axis varies for each of the treatments (see Figure 2 for boxplot legends).

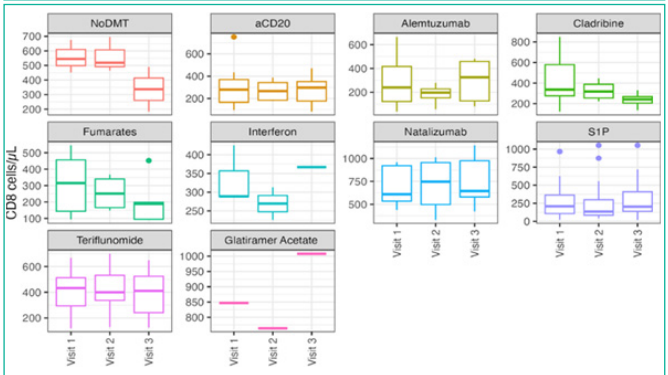

Figure 6: CD8 lymphocyte counts after the first, second, and third vaccines.
Note that the "y" axis varies for each of the treatments (see Figure 2 for boxplot legends).

did affect the expression of CD4 cells and CD8 cells as seen in Figure 5 and Figure 6, respectively. There is a slight decrease in the expression of CD4 cells and CD8 cells as evidenced by their comparison with the comparison group (NoDMT).

Discussion

In evaluating the immune response of COVID-19 vaccine and its booster vaccines, as expected, this effect is due to the mechanism of action of anti-CD20s and SP1 receptor modulators on preventing the activation of B-cells and, thus, the production of immunoglobulins, SARS COV-2-IgG in this case, and the sequestration of lymphocytes in the lymph nodes and reduction of lymphocytes in the bloodstream, respectively. This replicated the results of a previous study where the effects of anti-CD20s (ocrelizumab) and a S1P receptor modulator (fingolimod) were evaluated after administering patients with the COVID-19 vaccine and found that these two impaired the humoral response, and, therefore, the impairment of immunoglobulin production [14]. Similarly, Tortorella and colleagues discussed that a significantly lower anti-RBD antibody response rate was found in patients treated with ocrelizumab and fingolimod when compared to HCWs and patients treated with cladribine or IFN-β. Anti-RBD antibody median titer was also significantly lower in patients treated with ocrelizumab, fingolimod, and cladribine compared to HCWs and IFN-β-treated patients [6]. Even though S1P receptor modulators were able to decrease the absolute lymphocyte count due to their mechanism of blockage of migration of lymphocytes from secondary lymphoid organs, and thus, depletion of absolute lymphocyte count in the bloodstream [15]; the relationship was similar when compared with the comparison group (No DMT). This demonstrates that S1P receptor modulators do not completely deplete absolute lymphocytes in the bloodstream nor greatly affect lymphocyte production after receiving the COVID-19 vaccine. Similar value results were obtained from patients treated with cladribine where there was a small decrease in the number of absolute lymphocyte counts due to its mechanism of action.

The modulation of S1P receptors, the CD4 T-cells (T-helper cells) and CD8 T-cells (cytotoxic T-cells) would not be stimulated, and the activation and recruitment of other CD4 cells and CD8 cells would not occur. A similar effect was seen with the medication cladribine, as previously mentioned, where there was a reduction of CD4 cells and CD8 cells due to its ability to cause apoptosis in T-cells by creating breaks in DNA strands [16] by inserting itself into the DNA.

Since the anti-SARS COV-2 IgG SPIKE is determined as the humoral response to the COVID-19 vaccine, we used this parameter to verify if patients treated with a DMT were able to produce an immune response comparable to the non-MS population. We compared our results with a study performed in non-MS population in Germany [17]. Patients who presented with the least humoral response were patients treated with anti-CD20s and S1P receptor modulators. Our comparison group (NoDMT) also was able to mount an immune response after one year post third dose of COVID-19 vaccine, but lower than the anti-CD20s and S1P treated groups. Comparing MS patients treated with these two medications (anti-CD20s and S1P) with the non-MS population[17], we can conclude that these patients were still able to generate an immune response after receiving the third dose of COVID-19 vaccine, comparable to the general (non-MS) population and this immune response was preserved after one year of receiving said third dose of COVID-19 vaccine.

The mRNA vaccines induce both humoral and cell-mediated specific immune responses against spike peptides in all HCWs and in most patients with MS. These results carry relevant implications for managing vaccinations, suggesting promoting vaccination in all treated patients with MS [6]. Our study was a single-arm study with a small sample size, and we did not assess the causal relationship between the measured humoral immune response and protection from COVID-19 infection or a lower likelihood of hospitalization. Considering multiple variants of SARS-CoV-2 that have been documented globally during and after the COVID-19 pandemic, future research is needed. It remains important to continually assess the ability of currently available vaccines to confer protection against newly emerging variants

Conclusion

Overall, the evolution of research from 2020 to 2023 has significantly advanced our understanding of the interplay between MS treatments and COVID-19 vaccination. This body of work highlights the need for ongoing vigilance and tailored approaches to ensure that MS patients, particularly those from specific ethnic and regional backgrounds such as Hispanic Puerto Ricans, receive optimal protection against COVID-19. In regard to vaccination of MS patients, a proper plan is important to be designed for DMT-treated

patients. As shown in this study, certain DMTs, depending on their mechanism of action, can affect the humoral and cellular response to vaccines. For this reason, depending on the specific DMT the patient is currently being treated with, a plan must be outlined to ensure proper development of humoral response and develop immunity to the disease the vaccine is tailored for.

Acknowledgements/Funding

We would like to acknowledge the contribution of Fundación de Esclerosis Múltiple de Puerto Rico, International Radiology; Margarita Suárez and Eric Godreau from the San Juan Bautista School of Medicine, and Olga J Santiago Rivera, PhD, for their review and editing of the manuscript.

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