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The story of protective humoral immunity against COVID-19 in a chilean cohort of multiple sclerosis patients: Vaccines are necessary

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ABSTRACT

Background: There is scarce data in Latin America about how the protective humoral immunity behaves in patients that received an inactivated COVID-19 or mRNA vaccine or boosters in people with Multiple Sclerosis (pwMS).

Objective: To evaluate humoral response to COVID-19 vaccines in a cohort of Chilean pwMS treated with high efficacy therapies (HET) and the effect of a booster.

Methods: Observational cohort study of pwMS receiving mRNA or inactivated (CoronaVac) COVID-19 vaccines and a booster with mRNA vaccine 5 months after. IgG anti spike was determined in 4 groups: cladribine, anti-20 (rituximab or ocrelizumab), alemtuzumab and reference group.

Results: Hundred and thirty-two patients: 24.7% on cladribine and 13% on ocrelizumab, 84.9% received CoronaVac. No significant differences between time from last dose of HET and IgG production. Significant differences on absolute lymphocyte count between cladribine and antiCD20 ($p<0.01$). Anti-CD20 produced the lowest 4weeks post-vaccine IgG titers. 72.5% pwMS had Protective humoral immunity (PHI) at 4weeks but only 18.5% of the antiCD20 group did have it. The 5 months post-vaccine IgG titers were evaluated in 69 patients; all kept PHI; 26.6% of the antiCD20 group with no previous PHI, received a booster with mRNA vaccine and did produce PHI after it.

Conclusions: CoronaVac produce PHI in pwMS treated with HET in the analyzed cohort, except for Anti-CD20 therapies in our cohort. The booster in the anti CD20 therapy with no PHI after 2 doses of the COVID-19 vaccine had a small impact in the IgG anti spike production. Further studies are needed in our cohort to understand the kinetics of the PHI with inactivated vaccines and the boosters.

Keywords: inactivated vaccine, mRNA vaccine, cladribine, anti-CD20, alemtuzumab, booster

Introduction

COVID-19 pandemic has challenged neurologists and multiple sclerosis patients regarding the proper care of their disease but also the correct timing to receive a COVID-19 vaccine. Different countries have approved different COVID-19 vaccines (messenger RNA vaccine, inactivated virus, viral vector vaccine) but in Latin America there is scarce information regarding the humoral levels through time in people with multiple sclerosis (pwMS) that received inactivated or mRNA COVID-19 vaccines. This information becomes of special interest in patients receiving high efficacy disease modifying therapies (DMT). The knowledge we have about non-COVID-19 vaccines and pwMS came from different publications [1,2] and it was used as a reference parameter to guide patients through their vaccination process. Some reports of adverse events with COVID-19 vaccines in some pwMS were published all around the world, giving a warning call on which vaccine should we recommend to pwMS[3,4] depending on the treatment in current use. The first results of safety and efficacy of one COVID-19 vaccine, the mRNA vaccine BNT162b2 COVID-19, came from the Israeli group led by Achiron A et al[5,6]. They found that the vaccine proved to be safe, with no increase in the relapse rate. Interestingly, this study showed that pwMS treated with fingolimod or anti CD20 showed low humoral response to the vaccine[5,6], opening a debate regarding the question should we vaccinate this special group of patients?

In Chile, the vaccination program was approved by February 2021, starting a massive process among the population, receiving BNT162b2 COVID-19 or CoronaVac (an inactivated vaccine) depending on the availability of the vaccines and a booster program in august 2021 for all the population with BNT162b2 COVID-19[7]. This booster program in Latin America was pioneer at its time in the region, especially because little data was available at that time about the real impact of a booster with homologous or heterologous vaccines, and more interestingly in patients using HET[8].

Our objective was to evaluate the humoral response after 2 doses of covid-19 vaccines (BNT162b2 COVID-19 or CoronaVac) in pwMS on platform treatments and high efficacy therapies (HET) and follow its levels after 5 months and report the effect of a booster in pwMS, especially in patients using anti CD20 therapies.

Material and Methods

People with multiple sclerosis from two tertiary referral hospitals in Chile (Clínica Alemana and Clínica Dávila) were invited to participate in an observational cohort study on immune responses after COVID-19 vaccine. Potential participants were approached between January 1st 2021 and February 28th 2022. Patients included fulfilled the 2017 McDonald criteria[9] who were not vaccinated prior to study entry. Exclusion criteria were patients with vaccine contraindication, pregnancy, and ongoing acute infection. Being an observational study, the researchers did not influence the vaccination schedule. Patients followed the vaccination recommendations issued by the Ministry of Public Health of Chile[7] and the Chilean society of demyelinating diseases[10]. Patients were vaccinated with BNT162b2-COVID-19 or CoronaVac vaccines according to availability at the time of vaccination. The first and second doses were administered with the same type of vaccine, no patient had a heterologous vaccination schedule. The interval between both doses was 4 weeks. Patients were vaccinated regardless of the lymphocyte count and without stopping their current immunomodulatory treatment. Those patients treated with depletion therapies such as alemtuzumab, rituximab, ocrelizumab and cladribine were vaccinated at any time after the last treatment dose. All patients are scheduled to receive a booster with BNT162b2-COVID-19, 6 months after completing the original vaccination schedule.

Information on clinical aspects was extracted from the electronic medical record of each patient, being the following: demographic data, characteristics of MS (MS duration, phenotype, EDSS), DMT during vaccination and time from last DMT dose. Information regarding adverse effects was collected at one month after vaccination. Blood samples were evaluated for the absolute lymphocyte count and presence of SARS-CoV-2 spike IgG[11]. The absolute lymphocyte count was determined at baseline. It was classified arbitrary in three grades (>1000 cells/mm^3, between 500 and 1000 cells/mm^3, and <500 cells/mm^3). SARS-CoV-2 spike IgG was determined at baseline (prior vaccination), one month (4w) and five months (5m) after the second vaccine dose. In addition, patients who received a third dose were tested after 4 weeks after the booster. Protective humoral immunity (PHI) was defined as post-vaccine titers > 1.0 [11] or 50% increased titers compared to baseline in those patients with baseline titers > 1.0.

The response to the vaccines was evaluated in 4 groups according to the baseline treatment. Patients treated with depletion therapies were selected: cladribine, anti-CD20 (rituximab or ocrelizumab) and alemtuzumab. Considering previous publications[1], naïve patients and patients treated with dimethyl fumarate, teriflunomide and injectable therapies were used as "reference group". For comparative analysis we do not include patients treated with fingolimod (n 9) and natalizumab (n 4) due to the small sample in this cohort. Patients signed informed consent as part of the ongoing observational MS study database approved by the local Ethics Committee. Clinical record was coded anonymously to ensure confidentiality during statistical analyses.

Statistical analysis

Categorical variables are described as frequency, and percentage and continuous variables were reported by their median and interquartile range. Chi square test was applied to analyze categorical variables. Considering previous publications[5], protective humoral immunity was compared among anti-CD20 with each group of treatment. Shapiro–Wilk test, Kolmogorov–Smirnov test, skewness, kurtosis, and histogram were used to test normality in continuous variables. The time from last DMT dose and IgG titers presented a non-normal distribution, therefore non-parametric tests (Wilcoxon and Kruskal-Wallis test) were used. Independent samples tests were used for comparison between groups and paired tests were used to compare IgG titers (baseline - 4w and 4 w-5m) within the same group. Absolute lymphocyte count presented a normal distribution, therefore parametric

tests (T test and ANOVA test) were used. Spearman's correlation was used to measure the strength and direction of monotonic association between IgG titers and absolute lymphocyte count. P-value cutoffs of 0.05 indicated significance. Data analyses were performed using R Study version 3 and GraphPad Prism version 8.0.0.

Results

One hundred and thirty-two participants were included, the demographic and clinical variables are presented in Table 1. Most patients received CoronaVac (84.9 %). The most frequent DMT was cladribine (24.7 %) followed by ocrelizumab (13 %). After grouping the patients according to their treatment, the reference group was the most representative group (37.1 %). Median time from last DMT dose before vaccination was: 9 months for cladribine (IQR 4), 5.5 months for antiCD20 (IQR 5.5) and 3 months for alemtuzumab (IQR 9). No significant differences were found between the time from last DMT dose and the vaccine for each treatment. Mean absolute lymphocytes counts were reference group 1662.65 cells/mm^3 ± 1015.33, cladribine 1014.92 cells/mm^3 ± 506.52, alemtuzumab 1210.09 cells/mm^3 ± 542.66 and antiCD20 1970.41 cells/mm^3 ± 818.39 (Figure 1), significant differences were only found between cladribine and antiCD20 ($p<0.01$).

Vaccine humoral response

Post-vaccine SARS-CoV-2 spike IgG titers were evaluated in each treatment group (see Table 1). Patients under treatment with anti-CD20 presented the lowest 4w post-vaccine IgG titers (mean 10 U/mL IQR 76) followed by the reference group (mean 32.5 U/mL IQR 97). When comparing the basal IgG titers (pre-vaccination) with 4w post-vaccine IgG titers, a significant increase was found in all groups ($p<0.01$) except in patients under treatment with anti-CD20. Significant differences were found when comparing the anti-CD20 group 4w IgG titers with cladribine ($p<0.01$) and alemtuzumab ($p<0.01$). Although no significant differences were found when compared to the reference group ($p=0.03$). Protective humoral immunity (PHI) at 4w was demonstrated in 90/124 patients (72.5 %).

Most patients under treatment with anti-CD20 failed to develop a protective antibody titer, only 5/27 (18.5 %) had PHI. Likewise, it was found that patients under treatment with anti-CD20 showed a lower level of protective humoral immunity than patients with cladribine ($p<0.01$), alemtuzumab ($p<0.01$) and the reference group ($p<0.01$). A weak correlation was found between the absolute lymphocyte counts with 4w post-vaccine IgG titers (rho: 0.21, p 0.32). Figure 2 shows the relationship between absolute lymphocyte counts with 4w post-vaccine IgG titers by grouped baseline treatments.

Although the humoral responses of fingolimod and natalizumab were not included in the comparative analyzes (see methods), we found that all pwMS (9/9 with fingolimod and 4/4 with natalizumab) presented PHI at 4 weeks and maintained protective titers at 5 months.

Figure 1

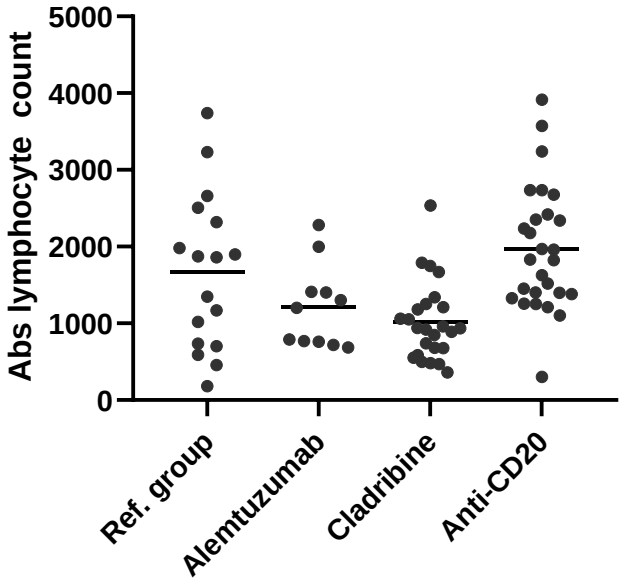

Figure 1. Absolute lymphocyte counts with 4w post-vaccine IgG titers by grouped baseline treatments. The horizontal black lines represent the mean of each group.

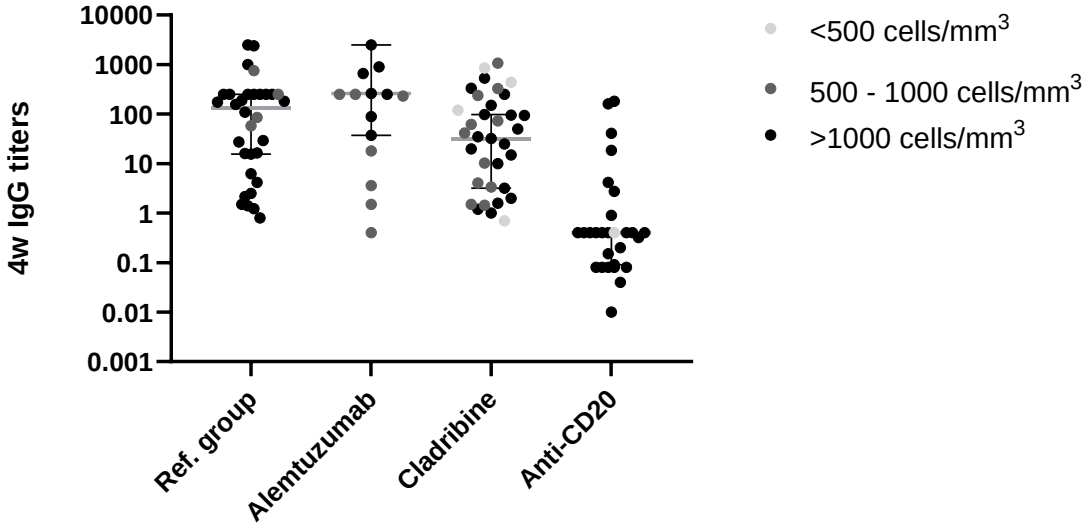

Figure 2. 4w post-vaccine IgG titers by grouped baseline treatments DMT in relation to absolute lymphocyte count presented as grading (>1000 cells/mm³, between 500 and 1000/cells mm³ and <500 cells/mm³). Antibody titer values are adjusted to a log 10 scale. The horizontal grey lines represent the median IgG titers and IC 95% of each group.

Long-term protective humoral immunity

The persistence of IgG titers at 5 months among those patients, as PHI, was analyzed (n 34). When comparing the 4w IgG titers with 5m IgG titers post-vaccine (paired test), no significant decrease was found among alemtuzumab (n 4; p=0.22), antiCD20 (n 6; p=0.39), reference group (n 7; p=0.16) and cladribine (n 17; p=0.06). All patients kept PHI.

The response to the booster vaccine (BNT162b2) was evaluated in 15 patients under treatment with ocrelizumab and without humoral response at 5th month (IgG titers < 1.0). PHI was found in 4/15 (26.6%) patients after booster vaccination. When comparing the 5m IgG titers with post booster vaccine IgG titers (paired test), no significant increase was found (p=0.06).

Table 1. Clinical and demographic variables of study population.

Study population (N= 132)	Ref. group (n= 52)	Alemtuzumab (n= 14)	Cladribine (n= 36)	Anti-CD20 (n= 30)
Age (SD)	38.08 (11.22)	32.36 (5.3)	35.11 (8)	40.4 (14.33)
Female, %	78.8	42.9	75	70
MS duration, mean (SD)	3.56 (5.1)	4.93 (5.33)	5.53 (4.31)	5.9 (6.2)
RRMS, %	88.5	85.7	88.9	70
EDSS	1.8 (1.26)	1.61 (1.27)	2.19 (1.7)	2.92 (2.18)
ALC, mean (SD)	1662.65 (1015.33)	1210.09 (542.66)	1014.92 (506.52)	1970.41 (818.39)
4w IgG titers, median (IQR)	32,50 (97)	55,50 (83)	53,50 (96)	10,00 (76)
4w PHI,%	85.7	92.9	85.7	18.5

ALC: absolute lymphocyte counts (cells/mm³). EDSS: Expanded Disability Status Scale RRMS: Relapsing-remitting multiple sclerosis. SPMS: Secondary progressive multiple sclerosis. PPMS: Primary progressive multiple sclerosis. 4w IgG titers: 4w post-vaccine IgG titers. PHI: Protective humoral immunity at 4w (U/mL)

Discussion

The immunogenicity of COVID-19 vaccines in people with multiple sclerosis (PwMS) is influenced by both the disease and disease-modifying therapies (DMTs). MS itself does not appear to impair vaccine responses, as studies show that PwMS not on DMTs have similar antibody levels to healthy individuals[6,9,10,11,12]. Research on DMTs reveals that treatments like interferon, dimethyl fumarate, glatiramer acetate, and teriflunomide generally produce adequate antibody responses[6,9,10,11,12,13]. Interferon may even enhance immune responses due to its mechanism of action[14]. However, some DMTs impact vaccine efficacy. Sphingosine l-phosphate receptor modulators (e.g., fingolimod) and anti-CD20 therapies (e.g., ocrelizumab) often result in reduced antibody responses [6,9,10,11,15,16,17,18]. Fingolimod and similar drugs hinder antibody production, while ocrelizumab significantly lowers antibody levels but preserves cellular immunity, including CD8 T-cells[19,20]. Although cellular responses are robust, the humoral response is less reliable in patients on these therapies.

Most of our cohort in on highly effective treatments (HET) that can cause lymphopenia and immunosuppression. This makes it a population of risk of severe COVID-19, especially the antiCD20[26] so it is of most of our interest to foresee that our cohort will follow the vaccination schedule and to follow the production of PHI with the vaccines.

The question regarding time of the last dose of the HET was other important matter because the cohort was vaccinated as soon as the vaccines were available, so it was not possible to follow the international recommendations according to the last infusion or tablet[27]. Different publications suggest that the timing is very important for the PHI in pwMS treated with antiCD20[12,18]. We did not find a significant different

between the timing of the last dose of the HET and the development of PHI.

Regarding to lymphocyte count, Achiron et al[6] described that 22.7% of the ocrelizumab group developed PHI irrespective to normal absolute lymphocyte count and that fingolimod treated patients with low lymphocyte count failed to develop PHI. Even though one of the limitations of our study is the number of patients, all our fingolimod patients had PHI despite their lymphocyte count and they kept the PHI after 5 months of vaccination. The only significant difference in the lymphocyte count was between cladribine and antiCD20, with a lower count for cladribine. The weak correlation found between the absolute lymphocyte counts with 4w post-vaccine IgG titers must be considered in the timing of the vaccine, and maybe the relation between last dose of the medication – absolute lymphocyte count – vaccination time does influence the IgG titers but not the capacity to produce PHI.

There has been a lot of discussion regarding the effect of the COVD-19 vaccines in pwMS treated with fingolimod or anti CD20 therapies. Recent studies on booster doses show increased antibody levels in PwMS, though those on fingolimod or anti-CD20 therapies still have lower seroconversion rates. König et al[17] reported a significant increase in IgG titers after the third vaccine dose, but only 24.8% of anti-CD20-treated patients and 6.9% of fingolimod-treated patients developed protective humoral immunity. Dreyer-Alster et al[27] also observed substantial increases in IgG titers with the third dose, although their cohort did not include patients on ocrelizumab or fingolimod.

Our data shows that anti-CD20 presented the lowest 4w post-vaccine IgG titers and that it was significant compared to cladribine and alemtuzumab. No direct comparison was done to the IgG levels with fingolimod or natalizumab. Surprisingly, only 18.5% of the antiCD20 had PHI, like Achiron's publication[6], being the most important difference the type of vaccine. This data can raise the question if it really matters which type of vaccine if used in pwMS treated with B cell depleting therapies. Apostolidis S. et al.[19] showed that even though no humoral response was detected in anti CD20 pwMS, there is still a cellular response that will give protection to the patients: a more robust CD8 T cell response that is kept in time.

We were able to follow the IgG titers during 5 months after receiving the 2 doses of the vaccines. Reconstitution therapies did not decrease their IgG titers in a significant manner but also this was observed in the antiCD20 patients that had PHI. So, the questions are: do patients need a booster? When will they need it? A booster will induce humoral response in those who failed? Booster with the same vaccine or another type? Measuring IgG titers is not done on a routine basis and some publications suggest that a booster with heterologous vaccine may elicit stronger antibody and T-cell responses[12] but there is no longitudinal data in pwMS that demonstrate a persistent PHI or a switch in the non-responder group with the booster[22], so the schedule for the booster is done only on theoretical basis. Our data in the non-respondent group 5m after vaccination showed that the booster with a heterologous vaccine only shifted 26.6% to a positive PHI and that the IgG titers were not different to the ones that responded to the first vaccine regime. The number of patients with the long-term data in the antiCD20 group is small, but it seems that every new dose of a COVID-19 vaccine, homologous or heterologous after the first vaccine schedule, will increase the chances of having PHI in a 20-30%.

Although post-vaccination infections have been reported, particularly in patients on anti-CD20 therapies and fingolimod, but most cases have been mild[28,29,30]

Based on our results and data published by other groups[2,3,4,12] recommend covid-19 vaccination to all pwMS under treatment, trying to respect the schedule suggested by different societies or investigators[2].

Our study has several limitations. The sample size for some treatment groups, particularly those with anti-CD20 therapies, was small, which could affect the generalizability of the results. Variations in vaccine types and timing of vaccination relative to the last DMT dose could also influence the results. Furthermore, the study focused primarily on IgG antibody levels and did not comprehensively assess cellular immune responses. Long-term follow-up was limited to 5 months, highlighting the need for further research to assess the durability of immunity and the efficacy of booster doses. Finally, individual variability in vaccine response may not have been fully captured. However, despite our limitations, our study underscores the variable efficacy of COVID-19 vaccines in people with multiple sclerosis (PwMS), especially those receiving disease-modifying therapies (DMTs). While MS itself does not appear to hamper vaccine efficacy, specific DMTs may affect immune responses. Given the widespread use of highly effective therapies (HET), ensuring adherence to vaccination schedules, and monitoring protective humoral immunity (PHI) is crucial. Although we did not observe a significant effect of the timing of the last HET dose on PHI, this remains an area of interest. Anti-CD20 therapies showed the lowest antibody titers following vaccination, with a limited percentage achieving PHI. This highlights the need for continued evaluation of vaccination strategies, including the potential benefits of booster doses. Despite some limitations, our findings support COVID-19 vaccination for all people with MS receiving treatment and advocate for further research to optimize vaccination protocols for this high-risk group.

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Conflict of interest

Galleguillos L has received honorary fees for educative talks from MERCK SA., Biogen Idec, Roche Chile, Sanofi-Genzyme, TEVA, Novartis and BMS

Alonso A has received honorary fees for educative talks from MERCK SA., Biogen Idec, Roche Argentina, Sanofi-Genzyme, TEVA, Novartis and BMS

The other authors have nothing to declare.

References

1.- Galleguillos L, Alonso R. Key points to keep in mind related to COVID-19 vaccines in people with multiple sclerosis. Mult Scler Relat Disord. 2021 Sep;54:103142. doi: 10.1016/j.msard.2021.103142. Epub 2021 Jul 16.

2.- Coyle PK, Gocke A, Vignos M et al. Vaccine Considerations for Multiple Sclerosis in the COVID-19 Era. Adv Ther. 2021 Jul;38(7):3550-3588. doi: 10.1007/s12325-021-01761-3. Epub 2021 Jun 1. Erratum in: Adv Ther. 2022 Jan;39(1):822-830.

3.- Alonso R, Chertcoff A, Leguizamón FDV, Galleguillos Goiry L et al. Evaluation of short-term safety of COVID-19 vaccines in patients with multiple sclerosis from Latin America. Mult Scler J Exp Transl Clin. 2021 Nov 29;7(4):20552173211061543.

4.- Kelly H, Sokola B, Abboud H. Safety and efficacy of COVID-19 vaccines in multiple sclerosis patients. J Neuroimmunol. 2021 Jul 15;356:577599. doi: 10.1016/j.jneuroim.2021.577599. Epub 2021 May 4.

5.- Achiron A, Dolev M, Menascu S et al. COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by February 2021. Mult Scler. 2021 May;27(6):864-870. doi: 10.1177/13524585211003476. Epub 2021 Apr 15.

6.- Achiron A, Mandel M, Dreyer-Alster S et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord. 2021 Apr 22;14:17562864211012835.

7.- Ministerio de Salud de Chile. Plan nacional de vacunación COVID19. https://www.gob.cl/yomevacuno/ (accessed on April 4th 2022).

8.- Beard K, Sriwastava S. Insight in booster COVID-19 vaccine and disease modifying therapy in multiple sclerosis. J Neurol Sci. 2021 Nov 15;430:120034. doi: 10.1016/j.jns.2021.120034. Epub 2021 Oct 19.

9.- Capone F, Rossi M, Cruciani A, Motolese F, Pilato F, Di Lazzaro V. Safety, immunogenicity, efficacy, and acceptability of COVID-19 vaccination in people with multiple sclerosis: a narrative review. Neural Regen Res. 2023 Feb;18(2):284-288. doi: 10.4103/1673-5374.346539. PMID: 35900404; PMCID: PMC9396498.

10.- Pitzalis M, Idda M.L, Lodde V, Loizedda A, Lobina M, Zoledziewska M, Virdis F, Delogu G, Pirinu F, Marini MG, Mingoia M, Frau J, Lorefice L, Fronza M, Carmagnini D, Carta E, Orrù V, Uzzau S, Solla P, et al. (2021) Effect of different disease-modifying therapies on humoral response to BNT162b2 vaccine in sardinian multiple sclerosis patients. Front Immunol 12:781843.

11.- Sormani MP, Schiavetti I, Landi D, Carmisciano L, De Rossi N, Cordioli C, Moiola L, Radaelli M, Immovilli P, Capobianco M, Brescia Morra V, Trojano M, Tedeschi G, Comi G, Battaglia MA, Patti F, Fragoso YD, Sen S, Siva A, Furlan R, et al. (2021b) SARS-CoV-2 serology after COVID-19 in multiple sclerosis: an international cohort study. Mult Scler J doi: 10.1177/13524585211035318.

12.- Tallantyre EC, Vickaryous N, Anderson V, Asardag AN, Baker D, Bestwick J, Bramhall K, Chance R, Evangelou N, George K, Giovannoni G, Godkin A, Grant L, Harding KE, Hibbert A, Ingram G, Jones M, Kang AS, Loveless S, Moat SJ, et al. (2022) COVID-19 vaccine response in people with multiple sclerosis. Ann Neurol 91:89-100.

13.- Georgieva ZG, Döffinger R, Kumararatne D, Coles AJ, McCarthy C (2021) Diminished seroconversion following a single SARS-COV-2 vaccine in ocrelizumab-treated relapsingremitting multiple sclerosis patients. Mult Scler doi: 10.1177/13524585211046786.

14.- Maniscalco GT, Manzo V, Ferrara AL, Perrella A, Di Battista M, Salvatore S, Graziano D, Viola A, Amato G, Moreggia O, Di Giulio Cesare D, Barbato S, Servillo G, Longo K, Di Giovanni M, Scarpati B, Muggianu SM, Longo G, Russo G, et al. (2021) Interferon beta-1a treatment promotes SARS-CoV-2 mRNA vaccine response in multiple sclerosis subjects. Mult Scler Relat Disord 58:103455.

15.- Achtnichts L, Jakopp B, Oberle M, Nedeltchev K, Fux CA, Sellner J, Findling O (2021) Humoral immune response after the third SARS-CoV-2 mRNA vaccination in CD20 depleted people with multiple sclerosis. Vaccines 9:1470

16.- Ciotti JR, Valtcheva MV, Cross AH (2020) Effects of MS disease-modifying therapies on responses to vaccinations: a review. Mult Scler Relat Disord 45:102439.

17.- König M, Torgauten HM, Tran TT, Holmøy T, Vaage JT, Lund-Johansen F, Nygaard GO (2022) Immunogenicity and safety of a third SARS-CoV-2 vaccine dose in patients with multiple sclerosis and weak immune response after COVID-19 vaccination. JAMA Neurol 79:307-309.

18.- Skorić MK, Rogić D, Lapić I, Šegulja D, Habek M (2022) Humoral immune response to COVID-19 vaccines in people with secondary progressive multiple sclerosis treated with siponimod. Mult Scler Relat Disord 57:103435.

19.- Apostolidis SA, Kakara M, Painter MM et al. 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.

20.- Brill L, Rechtman A, Zveik O, Haham N, Oiknine-Djian E, Wolf DG, Levin N, Raposo C, VakninDembinsky A (2021) Humoral and T-cell response to SARS-CoV-2 vaccination in patients with multiple sclerosis treated with ocrelizumab. JAMA Neurol 78:1510-1514.

21.- Thompson AJ, Banwell BL, Barkhof F et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-173. doi: 10.1016/S1474-4422(17)30470-2. Epub 2017 Dec 21.

22.- Sociedad chilena enfermedades desmielinizantes. https://sochedem.cl/. (accessed on April 4th, 2022)

23.- Elecsys® Anti-SARS-CoV-2. https://diagnostics.roche.com/global/en/products/params/elecsys-anti-sars-cov-2.html. (accessed on April 4th, 2022).

24.- Schiavetti I, Ponzano M, Signori A et al. Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: A systematic review and meta-analysis. Mult Scler Relat Disord. 2022 Jan;57:103358. doi: 10.1016/j.msard.2021.103358. Epub 2021 Nov 5.

25.- National Multiple Sclerosis Society. Timing MS Medication with COVID-19 vaccines. https://www.nationalmssociety.org/coronavirus-covid-19-information/covid-19-vaccine-guidance/Timing-MS-Medications-with-COVID-19-Vaccines. Accessed on April 4th, 2022.

26.- Disanto G, Sacco R, Bernasconi E et al. Association of Disease-Modifying Treatment and Anti-CD20 Infusion Timing With Humoral Response to 2 SARS-CoV-2 Vaccines in Patients With Multiple Sclerosis. JAMA Neurol. 2021 Dec 1;78(12):1529-1531.

27.- Dreyer-Alster S, Menascu S, Mandel M, Shirbint E, Magalashvili D, Dolev M, Flechter S, Givon U, Guber D, Stern Y, Miron S, Polliack M, Falb R, Sonis P, Gurevich M, Achiron A (2022) COVID-19 vaccination in patients with multiple sclerosis: Safety and humoral efficacy of the third booster dose. J Neurol Sci 434:120155.

28.- Chilimuri S, Mantri N, Gongati S, Zahid M, Sun H (2021) COVID-19 vaccine failure in a patient with multiple sclerosis on ocrelizumab. Vaccines 9:219.

29.- Januel E, De Seze J, Vermersch P, Maillart E, Bourre B, Pique J, Moisset X, Bensa C, Maarouf A, Pelletier J, Vukusic S, Audoin B, Louapre C; COVISEP Investigators (2021) Post-vaccine COVID-19 in patients with multiple sclerosis or neuromyelitis optica. Mult Scler doi: 10.1177/13524585211049737.

30.- Rose DR, Mahadeen AZ, Carlson AK, Planchon SM, Sedlak J, Husak S, Bermel RA, Cohen JA, Moss BP (2021) Clinical features and outcomes of COVID-19 despite SARS-CoV-2 vaccination in people with multiple sclerosis. Mult Scler J Exp Transl Clin 7:20552173211057110.

