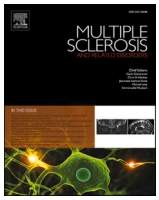
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 63 (2022) 103856

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Correspondence

Antibody response to SARS-CoV-2 vaccination following typical and three-dose dosing schedules in multiple sclerosis patients treated with disease modifying therapies

ARTICLE INFO

Keywords
Covid-19
Vaccine
Immunization
MS
Disease modifying treatment

ABSTRACT

Background: Immunizations against SARS-CoV-2 virus are now available and recommended, but the effect of additional dosing of the vaccine in immunocompromised MS patients is unknown.
Methods: *Part I* - A retrospective chart review of MS patients who were vaccinated against SARS-CoV-2 and tested commercially for Sars Covid Spike Protein Antibody between March 1 – June 30, 2021. *Part II* - Patients on treatment with anti-CD20 infusion medications who received a SARS-CoV-2 third mRNA vaccination dose August 13, 2021 – October 31, 2021 and were subsequently commercially tested for Sars Covid Spike Protein Antibody.
Results: *Part I* - A total of $N = 208$ MS patients, age range 23–76 were tested, with 49% (102/208) demonstrating a humoral response. Stratified by DMT type, patients treated with interferon, teriflunomide, or a remote history of alemtuzumab (>2 years since last DMT) yielded 100% measurable antibodies; >90% amongst patients treated with natalizumab, fumarates and glatiramer acetate; <50% measurable antibodies following vaccination in S1P modulators and anti-CD20 treated patients. Subsequently, in *Part II* – $N = 40$ patients on anti-CD20 treatments (33 ocrelizumab, 7 rituximab) who received 3 mRNA vaccinations yielded 20% humoral response.
Conclusions: MS patients are able to mount a humoral vaccine response to SARS-CoV-2, irrespective of the vaccine type administered; patients treated with S1P modulators and anti-CD20 agents are least likely to mount such a response with a typical dosing schedule. Patients treated with ocrelizumab/rituximab show a similar modest humoral immune system benefit following three doses as with standard dosing.

1. Introduction

In the United States, we currently have three vaccines approved by the FDA against the Sars-CoV-2 virus, with an additional vaccine dose recommended for all adults at least 6-months after the initial series. Previously published work has demonstrated that multiple sclerosis (MS) patients on treatment with anti-CD20 medications are at a disadvantage with respect to mounting a humoral immune response following Sars-CoV-2 vaccination (Achiron et al., 2021; Brill et al., 2021; Apostolidis et al., 2021), as are sphingosine-1-phosphate receptor modulator (S1P) treated patients (Achiron et al., 2021), while other disease modifying treatments (DMTs), do not interfere with the vaccine response (Capuano et al., 2021; MP Sormani et al., 2021). Certain immunocompromised patient groups, including organ transplant recipients (Kamar et al., 2021), and patients with systemic autoimmune disease (Connolly et al., 2021) have been shown to benefit from a third mRNA vaccine dose. Questions remain about the precise benefit of additional vaccination doses in immunocompromised MS patients. Here, we set out to document our single center experience related to the humoral responses following completion of SARS-CoV-2 regular vaccination series and the effect of an additional vaccination dose.

2. Methods

Part I: Patients of the Holy Name MS Center who were at least 3 weeks post completion of SARS-CoV-2 vaccination were offered commercial serum testing for Covid Spike Protein IgG Antibodies. We obtained IRB approval to retrospectively review the clinical and demographic data for patients whose serum was collected between March 1, 2021 and June 30, 2021.

Part II: Patients of the Holy Name MS Center who were on treatment with an anti-CD20 infusion medication (and initially vaccinated with an mRNA vaccine) were encouraged to receive a third dose as per CDC guidelines; afterwards, commercial serum testing for Covid Spike Protein IgG Ab was offered (Achiron et al., 2021) at least 3 weeks following the final vaccine dose. We obtained IRB approval to retrospectively review the clinical and demographic data for those on anti-CD20 infusions who received a 3rd vaccine dose August 13, 2021 – October 31, 2021. Testing was performed by Quest, Abbot Architect, DiaSorin Liaison (LabCorp), and Roche Eclysis. Quantitative analyses were performed in Excel 2016 and https://www.socscistatistics.com/.

3. Results

3.1. Part I

A total of 208 patients were tested in Part I, 67% (140/208) female, age range 23–76y, average ± SD 49.1y ±12.6. Ninety five percent of the tests (198/208) were performed by Quest (SARS COV2 Ab (IgG) Spike, Semiquantitative) with values greater than 1 Index interpreted as positive; 2% of tests (4/208) were performed by Abbot Architect which reported 50 AU/mL as positive; 2% (4/208) Roche Elecsys anti-SARS Cov2 S Reagent Assay (greater than 0.8 U/mL considered positive), 1% (2/208) DiaSorin Liaison SARS CoV2 S1/S2 IgG Assay with qualitative

https://doi.org/10.1016/j.msard.2022.103856
Received 14 December 2021; Received in revised form 27 April 2022; Accepted 4 May 2022
Available online 6 May 2022

result only.

In total, 49% (n = 102) of patients formed a detectable humoral antibody response. Antibodies were tested on average, 52.3 ± SD 12.0 days (range 13–165 days) following vaccination. Table 1 outlines the humoral response following vaccination in each DMT group. Patients least likely to make a humoral response were on S1P modulators 46% (6/13), and monoclonal anti-CD20 medications (rituximab, ocrelizumab, ofatumumab) 19% (21/116).

Evaluating anti-CD20 patients (92 ocrelizumab, 23 rituximab, 1 ofatumumab), 19% (21/116) made a measurable humoral response following vaccination. With respect to the infusion anti-CD20 treatments, patients who developed a positive vaccine antibody result were more likely to have waited longer (as demonstrated in Fig. 1) after their last infusion prior to vaccinating (average ± SD; range) 197.8d ± 144.0; 73–598 days vs 133.5d ± 55.0; 39–403 days as would be expected, t(11)=3.4, p<.001 (one-tailed t-test of 2 independent means). Patients who developed a positive humoral response were more likely to have had fewer treatment cycles of ocrelizumab/rituximab (average ± SD; range) 3.6 ± 1.7; 1–7 vs. 5.5 ± 2.5; 1–16, t(11)=−3.4, p<.001 (one-tailed t-test). A chi-square test of independence showed that there was no significant association between humoral response to vaccination and vaccine type (mRNA vaccine vs adenovector vaccine) amongst anti-CD20 treated patients. Of note, one patient receiving infusion treatment also required concomitant high dose steroids for five days, and another transitioned from infusion to injectable ofatumumab three months prior to vaccination (neither formed a humoral response).

3.2. Part II

A total of 40 patients (39 with MS, 1 with NMO) were tested following three mRNA SARS-CoV-2 vaccination doses, 26/40 (65%) female, age range 28–73yo, average ± SD 53.2y ±12.2. These patients were on treatment with ocrelizumab (n = 33), or rituximab (n = 7). Twenty percent (n = 8/40) tested positive for Covid Spike Protein Ab following the 3rd mRNA dose, of which three were not tested for antibodies prior to the third dose, and one was on treatment with natalizumab at the time of her initial mRNA series – her response was >20 (maximum reportable value for Quest testing) following dose 2 and 8.47 (on the same test) following dose 3. None of these patients are known to our center as having had Sars-CoV-2. Of the total group, three anti-CD20 treated patients had Sars-CoV-2, 1 with mild symptomatic disease prior to vaccination (had a low positive Spike Protein Ab result following mRNA dose #2 and negative following mRNA dose #3), and two asymptomatic, but lab positive. Patients who made a positive vs negative Spike Protein Ab result following mRNA dose #3 had similar delays between the antecedent infusion cycle and subsequent vaccination, t(38) = 0.26, p= .40, although there was a significant effect of the number of cycles of anti-CD20 infusion medication administered, t(38) = −1.7, p < .05.

4. Discussion

We have confirmed that MS patients are able to mount a humoral immune response following vaccination against SARS-CoV-2, with 49% of tested patients mounting a detectable response following the initial CDC recommended vaccination series. Patients least likely to mount a humoral response included, as expected (Achiron et al., 2021; MP Sormani et al., 2021; Novak et al., 2021; Disanto et al., 2021; Sabatino et al., 2022), anti-CD20 treated patients (19%) and S1P treated patients (46%). Although of note, the experience with fingolimod treated patients has been quite variable in the literature, 3.6%−96.9% humoral responses depending on the study (Achiron et al., 2021; MP Sormani et al., 2021; Disanto et al., 2021). We focused on ocrelizumab and rituximab treated patients with respect to antibody response following a third dose of SARS-CoV-2 mRNA vaccination, and found 20% (n = 8/40) made a humoral response (but cannot exclude that one patient was a

Table 1
Demographics and clinical characteristics of treated and covid-19 vaccinated MS patients who did and did not make Sars Covid Spike Protein Antibody Responses following typical vaccination schedule (2 doses of mRNA vaccination or 1 dose of adenovector vaccine).

	Sars Covid Spike Protein Ab+	Sars Covid Spike Protein Ab-
Alemtuzumab (n = 2, both infused >2yrs prior)	100% (n = 2/2)	–
• Age (y)	39–45	
• ALC (n = 2)	893–1504	
• Vaccine type (mRNA; adenovector)	1; 1	
Anti-CD20 (ocrelizumab, n = 92; rituximab, n = 23, ofatumumab, n = 1)	19% (n = 21/116)	81% (n = 96/116)
	24–68	24–76
	700–2586 (n = 21)	ALC 700–2900 (n = 83): 39–403; 133.5 ± 55.0
• Age (y)	73–598; 197.8 ± 144.00–2.5; 236	0–0; 103 (n = 84)
• ALC (n = 104)	(n = 13)	63; 32
• Time between prior infusion and vaccination (n = 116) (d) Range; Average ± SD; range)	18; 3	
• CD19 Absolute (IQR; maximum)		
• Vaccine type (mRNA; adenovector)		
Fumarates (n = 16)	94% (n = 15/16)	6% (n = 1/16)
	26–63	38yo received adenovector vaccine 3-months prior to testing, ALC 1728
• Age (y)	500–2597	
• ALC (n = 15)	13; 2	0; 1
• Vaccine type (mRNA; adenovector)		
Glatiramer Acetate (n = 11)	91% (n = 10/11)	9% (n = 1/11)
• Age (y)	37–71	66yo received adenovector vaccine 25-days prior to testing, ALC 2000
ALC (n = 5)	1379–2616 (n = 4)	
• Vaccine type (mRNA; adenovector)	10; 0	0; 1
Interferons (n = 6)	100% (n = 6/6)	–
	45–70	
• Age (y)	1281–3008	
• ALC (n = 4)	6; 0	
• Vaccine type (mRNA; adenovector)		
Methylprednisolone (treatment of first relapse, n = 1)	–	100% (n = 1/1)
		0; 1
• Vaccine type (mRNA; adenovector)		
Natalizumab (n = 30)	93% (n = 28/30)	7% (n = 2/30)
	23–59	51–53
• Age (y)	1337–5382 (n = 23)	3989–4190 (n = 2)
• ALC (n = 25)	1–64	16–22
• Time between prior infusion and vaccination (d)	20; 8	0; 2
• Vaccine type (mRNA; adenovector)		
S1P Modulators (fingolimod, n = 11; ozanimod, n = 1, siponimod, n = 1)	46% (n = 6/13)	54% (n = 7/13)
	30–51	39–53
	274–1200 (n = 4)	219–918 (n = 7)
	5; 1	4; 3
• Age (y)		
• ALC (n = 11)		
• Vaccine type (mRNA; adenovector)		
Teriflunomide (n = 13)	100% (n = 13/13)	–
	44–75	
• Age (y)	956–2588	
• ALC (n = 10)	12; 1	
• Vaccine type (mRNA; adenovector)		

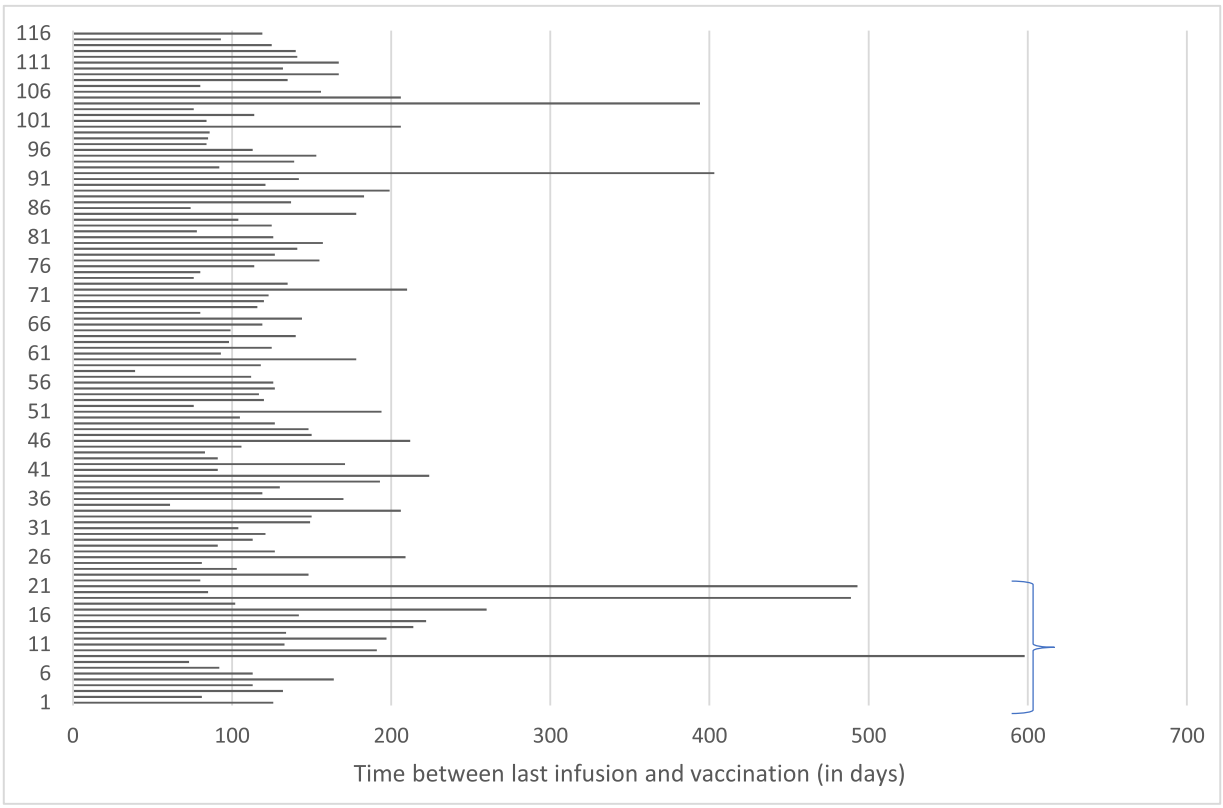


Fig. 1. Time between last ocrelizumab or rituximab infusion and covid-19 vaccination completion.
Each horizontal line represents an individual on treatment with an infusion anti-CD20 medication. The lower 21 patients, indicated by the bracket, are the only individuals who mounted a non-negative Sars Covid Spike Protein Ab response following a typical vaccination schedule (2 doses of mRNA vaccination or 1 dose of adenovector vaccine).

'carry-over' as her initial vaccination series preceded her initiation of ocrelizumab). There were too few subjects with measured antibody levels following both the second and the third vaccination to permit a within-patient longitudinal assessment. None of these 'responders' are known to our center to have had prior Sars-CoV-2 infection, although we did not routinely check for Covid IgG and it is possible that some may have had asymptomatic infection. In replication of Sabatino et al. (Sabatino et al., 2022) but in contrast to Brill et al. (Brill et al., 2021) we did find an association between the number of anti-CD20 infusions and likelihood of forming a serological response post-vaccination in both our 'typical vaccination' dosage group, and 'three time vaccination group'. We were able to show a benefit of a longer wait time between infusion and vaccination in our 'typical vaccination' group, in replication of previous work[23,] (Disanto et al., 2021), but not seen by Sabatino et al. (Sabatino et al., 2022) and not seen by us in our '3 dose' vaccination group.

There are several limitations to this observational study, including our modest number of subjects. We did not systematically perform serological assessments for asymptomatic infection, although we did routinely query patients regarding any infections at clinical encounters. Finally, this study is limited to commercially available tests which were performed with different laboratories thus we cannot make comparisons about antibody levels beyond positive and negative.

5. Conclusion

In summary, treated MS patients are able to mount a humoral vaccine response to SARS-CoV-2. The likelihood of attaining a humoral response is dependent on the DMT; we did not find evidence that it is dependent on the specific vaccine administered, although others have found differences in antibody levels following mRNA vaccinations (MP Sormani et al., 2021). Patients on treatment with S1P modulators and anti-CD 20 monoclonal antibodies are least likely to make a humoral response to vaccination following a typical vaccine schedule, and in the case of anti-CD20 infusions, following a 3-dose mRNA vaccine regiment as well. This study provides support for MS clinicians to consider complementary strategies to protect their patients against SARS-CoV-2 in case a blunted humoral response is expected to vaccination, for example, by recommending the recently FDA emergency use authorized, tixagevimab/cilgavimab intramuscular injection for pre-covid-19 exposure prophylaxis. Questions for future research include: what is the optimal dosing schedule for anti-CD20 infusion patients in terms of interval between vaccine doses, timing following infusion, and number of vaccine administrations, especially in light of reassuring data related to cellular immunity in these patients.

Conflict of Interest

AIW: Has received fellowship funding from the NMSS and consulting fees from Biogen, Genentech, and Horizon Therapeutics. These funding sources were unrelated to the present work.

MS: None.

MAP: Has received speaker and consulting fees from Biogen, Genentech, EMD Serono, Sanofi-Genzyme, Viela Bio, BMS. These funding sources were unrelated to the present work.

Funding

None.

References

Achiron, A., Mandel, M., Dreyer-Alster, S., et al., 2021. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord 14. https://doi.org/10.1177/17562864211012835.

Apostolidis, S.A., Kakara, M., Painter, M.M., et al., 2021. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat. Med. 27 (11), 1990–2001. https://doi.org/10.1038/s41591-021-01507-2.

Brill, L., Rechtman, A., Zveik, O., et al., 2021. Humoral and T-Cell Response to SARS-CoV-2 Vaccination in Patients With Multiple Sclerosis Treated With Ocrelizumab. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2021.3599.

Capuano, R., Donnarumma, G., Bisecco, A., et al., 2021. Humoral response to SARS-CoV-2 mRNA vaccine in patients with multiple sclerosis treated with natalizumab. Ther Adv Neurol Disord 14. https://doi.org/10.1177/17562864211038111.

Connolly, C.M., Teles, M., Frey, S., et al., 2021. Booster-dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series. Ann. Rheum. Dis. https://doi.org/10.1136/annrheumdis-2021-221206.

Disanto, G., Sacco, R., Bernasconi, E., et al., 2021. 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. 78 (12), 1529–1531. https://doi.org/10.1001/jamaneurol.2021.3609.

Kamar, N., Abravanel, F., Marion, O., Couat, C., Izopet, J., Del Bello, A, 2021. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N. Engl. J. Med. 385 (7), 661–662. https://doi.org/10.1056/NEJMc2108861.

Novak, F., Nilsson, A.C., Nielsen, C., et al., 2021. Humoral immune response following SARS-CoV-2 mRNA vaccination concomitant to anti-CD20 therapy in multiple sclerosis. Mult Scler Relat Disord 56, 103251. https://doi.org/10.1016/j.msard.2021.103251.

Sabatino Jr., J.J., Mittl, K., Rowles, W.M., et al., 2022. Multiple sclerosis therapies differentially affect SARS-CoV-2 vaccine-induced antibody and T cell immunity and function. JCI Insight 7 (4). https://doi.org/10.1172/jci.insight.156978.

Sormani M.P., Inglese M., Schiavetti I., et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *EBioMedicine*. Oct 2021; 72: 103581. 10.1016/j.ebiom.2021.103581.

Sormani, M.P., Inglese, M., Schiavetti, I., et al., 2021b. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. EBioMedicine 72, 103581. https://doi.org/10.1016/j.ebiom.2021.103581.

Asya I. Wallach*, Matthew Schiebel, Mary Ann Picone

Alfiero and Lucia Palestroni MS Comprehensive Care Center at Holy Name Medical Center, Teaneck, NJ, USA

* Corresponding author at: Holy Name Medical Center, 718 Teaneck Rd. Teaneck NJ 07666.

E-mail address: AsyaWallach@gmail.com (A.I. Wallach).