


# Humoral immune response and lymphocyte levels after complete vaccination against COVID-19 in a cohort of multiple sclerosis patients treated with cladribine tablets

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## ABSTRACT

**BACKGROUND:** Patients with multiple sclerosis (MS) receiving immunomodulatory drugs were excluded from clinical trials on COVID-19 vaccines. Therefore, data regarding the efficacy of COVID-19 vaccines to induce humoral immunity in MS patients treated with B- and T-cell depleting agents is urgently warranted. Cladribine tablets are a high-efficacy disease-modifying treatment that exerts its therapeutic effect via sustained but transient lymphocyte depletion.

**AIM:** We report humoral responses in a German cohort of MS patients treated with cladribine tablets.

**METHODS:** This retrospective analysis included patients  $\geq 18$  years who were treated with cladribine tablets for relapsing MS in the first or second year and were fully vaccinated against COVID-19. Two weeks after the second vaccination at the earliest, blood samples were obtained for the assessment of anti-SARS-CoV-2 IgG antibodies, lymphocyte counts, B-cells, CD4<sup>+</sup> T-cells, and CD8<sup>+</sup> T-cells. Anti-SARS-CoV-2 IgG antibodies were quantified with the LIAISON<sup>®</sup> SARS-CoV-2 TrimericS IgG assay. Positivity was defined at a cutoff value of 33.8 BAU/mL.

**RESULTS:** In total, 38 patients (73.7% female, aged 23–66 years) were included in the analysis. Ten patients (26.3%) were treatment-naïve before initiating treatment with cladribine tablets. Most patients (84.2%) received mRNA vaccines. The time between the last dose of cladribine tablets and vaccination ranged between 2 and 96 weeks. Six patients (15.8%) were vaccinated within 4 weeks of their last cladribine dose. All patients achieved positive anti-SARS-CoV-2 IgG antibody levels. Humoral immune response was independent of age, time of vaccination in relation to the last cladribine dose, lymphocyte counts as well as B- and T-cell counts.

**CONCLUSIONS:** Treatment with cladribine tablets did not impair humoral response to COVID-19 vaccination. Time since last cladribine dose, age, prior therapy, lymphocyte count as well as B- and T-cell counts had no effect on seropositivity of anti-SARS-CoV-2 IgG antibodies.

**KEYWORDS:** Cladribine tablets, COVID-19, multiple sclerosis, SARS-CoV-2, lymphopenia, humoral immune response

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## Introduction

Since its initial emergence in the Chinese province of Wuhan, more than 180 million cases of coronavirus disease 2019 (COVID-19) have been reported as of July 2021, including more than 3.9 million deaths worldwide.<sup>1</sup> The approval and use of several effective vaccines against COVID-19 is the most promising approach to rein in the current pandemic. In an unprecedented brief period of time, four effective vaccines against the causative agent severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) have been licensed to date by the European Medicines Agency (EMA).

As many effective immunomodulatory therapies for multiple sclerosis (MS) act by suppressing B- and T-cells, there is insecurity about the effectiveness of vaccines in MS patients receiving immunomodulatory drugs. Patients with MS were

excluded from clinical vaccination trials,<sup>2,3</sup> leaving the MS community to rely on emerging case reports while vaccines were rolled out in order to assess vaccine effectiveness in this population.<sup>4–7</sup> In a pilot cohort from Israel, humoral COVID-19 vaccination responses in MS patients receiving high-efficacy disease modifying treatments (DMTs) indicated various degrees of effectiveness, depending on the DMT.<sup>8</sup> Specifically, a positive SARS-CoV-2 IgG antibody response was achieved in all patients receiving cladribine tablets, whereas positivity was limited to 3.8% and 22.7% in patients treated with fingolimod and ocrelizumab, respectively.<sup>8</sup> However, a low number of patients and methodological concerns about the low sensitivity of the used antibody test (sensitivity reported as 90.0%)<sup>9</sup> are just two issues potentially limiting the validity of these findings.<sup>10,11</sup>



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Additional data regarding the efficacy of the COVID-19 vaccine to induce humoral immunity in MS patients treated with B- and T-cell depleting agents is urgently warranted. Therefore, we here report humoral responses in a cohort of MS patients treated with cladribine tablets, which exert their therapeutic effect via sustained but transient lymphocyte depletion.<sup>12</sup> Specifically, we took a closer look at lymphocyte subsets in a German cohort of cladribine-treated MS patients and measured the numbers of B-cells as well as CD4<sup>+</sup> and CD8<sup>+</sup> T-cells in addition to absolute lymphocyte count and SARS-Cov-2 IgG antibody response.

## Methods/patients

### Study design and patients

This retrospective analysis was conducted at a single center in Germany. Due to the retrospective nature of the study, ethics approval was not required according to local law. Patients signed informed consent regarding publishing this data. Male and female patients aged 18 years or older who were treated with cladribine tablets for RMS in the first or second year and were fully vaccinated against COVID-19 were included. Patients received 1 of 3 vaccines approved in Germany (BNT162b2 [BioNTech/Pfizer], mRNA-1273 [Moderna], and ChAdOx1 nCoV-19 [AstraZeneca]). Demographic data and prior treatment were retrieved from patient records. Two weeks after the second vaccination at the earliest, blood samples were obtained for the assessment of anti-SARS-CoV-2 IgG antibodies, lymphocyte counts, B-cells, CD4<sup>+</sup> T-cells, and CD8<sup>+</sup> T-cells.

### Outcomes

The primary outcome parameter was the amount of anti-SARS-CoV-2 IgG antibodies. The CE certified LIAISON<sup>®</sup> SARS-CoV-2 TrimericS IgG assay (DiaSorin; sensitivity was reported as 98.7% and specificity as 99.5%) was used for the quantitative determination of anti-trimeric spike protein specific IgG antibodies to SARS-CoV-2. The antigen of the test, the trimeric spike glycoprotein, is a stabilized trimer offering an improved detection of IgG neutralizing antibodies. The maximum response that could be measured was 2080 BAU/mL, with a cutoff of 33.8 BAU/mL for seropositivity.<sup>13</sup> As secondary outcome parameters, lymphocyte counts, B-cell counts, and CD4<sup>+</sup> and CD8<sup>+</sup> T-cell counts were determined at the time of antibody testing.

### Statistical analysis

Descriptive statistical analysis of all collected data was performed using the SPSS (IBM Deutschland GmbH, Ehningen, Germany) for Windows program package (Version 22.0). For continuous variables, statistical parameters including arithmetic mean, standard deviation, and range were calculated. Frequency distributions for discrete variables were provided as percentage in relation to the total sample. Correlations between age, time of vaccination, lymphocyte, B-cell, CD4<sup>+</sup>, CD8<sup>+</sup> counts, and anti-SARS-CoV-2 IgG antibodies were assessed using Spearman

**Table 1.** Patient demographics and vaccination-related data.

PARAMETER	N = 38
Gender, n (%)	
Female	28 (73.7)
Male	10 (26.3)
Age (mean ± SD), years	
Mean ± SD	43.8 ± 11.9
Median (range)	43 (23–66)
Treatment with cladribine tablets	
1st year	12 (31.6)
2nd year	26 (68.4)
Prior treatment	
Treatment-naïve	10 (26.3)
Fingolimod	11 (28.9)
Dimethyl formamide	8 (21.1)
Interferon/glatiramer acetate	7 (18.4)
Natalizumab	1 (2.6)
Alemtumumab	1 (2.6)
Vaccine type	
mRNA <sup>a</sup>	32 (84.2)
Vector <sup>b</sup>	5 (13.2)
Heterotropic	1 (2.6)
Time between last dose of cladribine tablets and vaccination, weeks	
Mean ± SD	33.1 ± 26.1
Median (range)	30 (2–96)
Lymphopenia at the time of antibody determination	
Grade 0	11 (28.9)
Grade 1	10 (26.3)
Grade 2	13 (34.2)
Grade 3	4 (10.5)

SD, standard deviation.

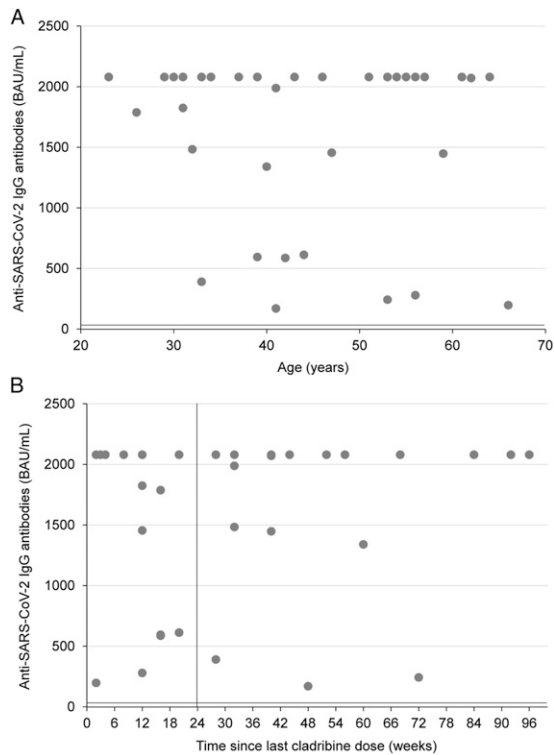
<sup>a</sup>BNT162b2 (BioNTech/Pfizer) or mRNA-1273 (Moderna).

<sup>b</sup>ChAdOx1 nCoV-19 (AstraZeneca).

correlation. Due to the observational nature of the study, no confirmatory hypothesis testing was performed, and all statistical tests were considered exploratory.

## Results

In total, 38 patients were included in the analysis. Of those, 26 (68.4%) patients were in the second year of treatment with cladribine tablets and 12 (31.6%) were in the first year. The mean age was 43.8 ± 11.9 years; patients were predominantly female (73.7%). Baseline demographics are summarized in Table 1. Ten patients (26.3%) were treatment-naïve before initiating treatment with cladribine tablets. The majority of patients (84.2%) received mRNA vaccines (78.9% BNT162b2, 5.3% mRNA-1273, and 13.2% ChAdOx1 nCoV-19). The time between the last dose of cladribine tablets and vaccination ranged between 2 and 96 weeks. Six patients (15.8%) were



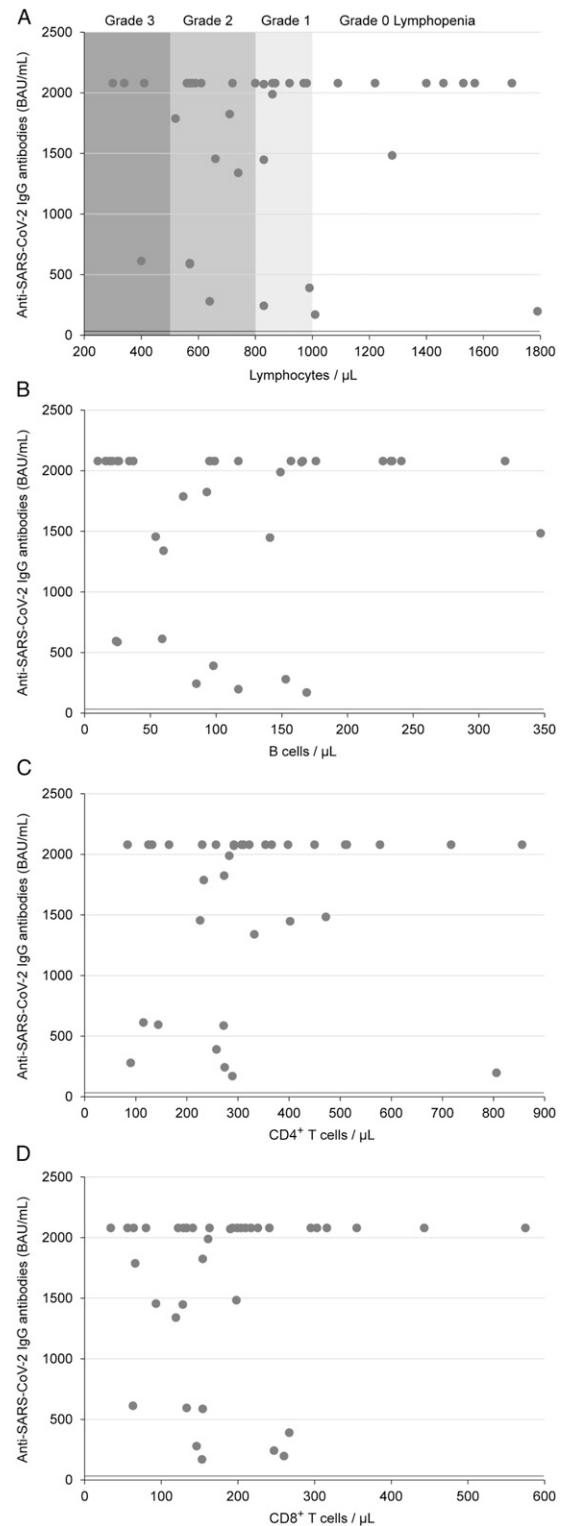
**Figure 1.** Immune response (anti-SARS-COV-2 IgG antibody levels) stratified by age (A) and time since last dose of cladribine tablets (B). The horizontal line denotes the cutoff value for seropositivity (33.8 BAU/mL). The vertical line marks the 6-month gap recommended by the KKNMS before starting vaccinations.

vaccinated within 4 weeks, 17 patients (44.7%) within 26 weeks, and 12 patients (31.6%) within 52 weeks of their last cladribine dose. Blood samples for antibody testing were obtained between 14 and 62 days (mean 21 days) after the second vaccination.

### Outcome

Overall, all patients achieved positive anti-SARS-CoV-2 IgG antibody levels. Immune response was independent of age in the majority of patients (Figure 1A). Although not reaching statistical significance, younger patients (<40 years) had a trend toward higher levels of anti-SARS-CoV-2 IgG antibodies; the majority of patients >40 years also had high levels of anti-SARS-CoV-2 IgG antibodies. Those with lower levels were still above the cutoff value of 33.8 BAU/mL.

In all patients, anti-SARS-CoV-2 IgG antibody levels were independent of the time of vaccination in relation to the last cladribine dose (Figure 1B). Vaccination occurred at different grades of lymphopenia. Immune response was sufficient despite low lymphocyte counts in all patients (Figure 2A). Positive anti-SARS-CoV-2 IgG antibody levels were achieved even in patients with lower B-cell counts (Figure 2B). Stratification by T-cell subsets showed that immune response was also independent of CD4<sup>+</sup> ( $r_s = .12, P = .47$ , Figure 2C) and CD8<sup>+</sup> T-cell



**Figure 2.** Immune response (anti-SARS-COV-2 IgG antibody levels) stratified by grade of lymphopenia (A), B-cell count (B), CD4<sup>+</sup>T-cells (C), and CD8<sup>+</sup>T-cells (D). The horizontal line denotes the cutoff value for seropositivity (33.8 BAU/mL).

counts ( $r_s = .15, P = .36$ , Figure 2D). When only focusing on patients with suboptimal antibody responses (excluding maximum values), we found similar results ( $n = 16$ ; CD4<sup>+</sup>:  $r_s = .08, P = .77$ ; CD8<sup>+</sup>:  $r_s = -.21, P = .44$ ). Figure 2

## Discussion

Vaccination against COVID-19 led to positive anti-SARS-CoV-2 IgG antibody levels in cladribine-treated MS patients, confirming and extending recently published real-world data from Israel and Serbia.<sup>6,8</sup> Development of positive anti-SARS-CoV-2 IgG antibody levels occurred largely independent of age, time since last dose of cladribine tablets, prior therapy, lymphocyte count, as well as numbers of B- and T-cells. Low but sufficient antibody levels were found more frequently in elderly patients. This can be considered to be caused by the well-known phenomenon of immunosenescence.

In general, developing protective immunity requires mounting an adaptive immune response to the vaccine through B- and T-lymphocytes. Specific antigens stimulate B- and T-lymphocytes, causing them to expand into memory clones. After re-exposure to the same antigen, memory cells proliferate rapidly and transform into effector cells. Activated B-cells differentiate into plasma cells which produce IgM antibodies as primary response, followed by IgG antibodies.<sup>14</sup> However, treatment with cladribine tablets leads to a decrease in circulating B-cells and T-cells in the months following the treatment cycles.<sup>15,16</sup> As the efficacy of vaccinations may thus be impaired, the Competence Network Multiple Sclerosis (KKNMS), an interdisciplinary research network throughout Germany, recommends in case of cell-depleting treatment, that vaccinations be postponed until 4 to 6 months after the last dose, when the immune system has been at least partially reconstituted.<sup>17</sup> Patients from our cohort achieved seropositivity even when vaccinated prior to the recommended time frame with respect to the last dose of cladribine tablets. This observation rather supports the statement of the MS International Federation (MSIF) to get the vaccine when it becomes available. The limited data currently available does not suggest that timing the vaccine in relation to cladribine dosing is likely to make a significant difference in vaccine response.<sup>18</sup>

Likewise, a retrospective investigation showed maintenance or increase of seroprotective antibody levels against varicella zoster and seasonal influenza for at least 6 months irrespective of lymphocyte counts measured at the time of vaccination in year 1 or 2 of treatment with cladribine tablets.<sup>19</sup> In case of treatment with anti-CD20 monoclonal antibodies, however, the recommended time frame of delaying vaccination at least 4 months might be more important in order to achieve a sufficient humoral immune response as published data from France have shown.<sup>20</sup>

In order to understand why a humoral immune response develops independent of the time since the last cladribine dose, it is important to take a closer look at the B- and T-cell kinetics of cladribine tablets. Following treatment with cladribine tablets, B-cells show a fast and prominent decline compared with T-cells (approximately 70% vs 50% reduction from baseline at week 5). Recovery of B-cells was rapid after reaching the nadir (>80% reduction) at week 13, retaining reductions from baseline of 60% and 30% at weeks 24 and 48, respectively,

whereas CD4<sup>+</sup> and CD8<sup>+</sup> T-cells had a more gradual recovery.<sup>21</sup> Depending on BMI and other factors, repopulation kinetics are known to vary markedly between individuals, which may explain the heterogeneity observed in this cohort.<sup>22</sup>

For the humoral immune response, B-cells are required to produce immunoglobulin M and immunoglobulin G (IgG) antibodies against SARS-CoV-2, which have been shown to specifically neutralize the virus.<sup>23</sup> In addition, cell-mediated immune response occurs via helper T-cells (CD4<sup>+</sup>) and cytotoxic T-cells (CD8<sup>+</sup>).<sup>24</sup> Although B-cells were still depleted at the time of vaccination in some patients, our results indicate that the amount of remaining B-cells was sufficient to produce a humoral immune response with seropositive anti-SARS-CoV-2 IgG antibody levels. The characterization of peripheral immune cell subset dynamics and immunoglobulin levels in the first 12 months of cladribine tablets therapy revealed a pronounced effect on B-cells, especially memory B-cells in the first 2 months of cladribine tablet treatment, suggesting a contribution to early efficacy onset. The reduction in memory B-cells sustained over 12 months along with a moderate decrease across T-cell subtypes may contribute to the long-term effect of cladribine tablets. In contrast, regulatory B-cells known to play a role in vaccine response, recovered by month 3, and then increased over baseline levels.<sup>25</sup> Cellular immune response independent of B-cell response during B-cell depletion with anti-CD20 antibodies has been reported recently.<sup>26</sup> It might be worthwhile to speculate that T-cell responses will develop as well during lymphocyte depletion following treatment with cladribine tablets. However, additional investigations are required to confirm this. The same study showed a better correlation between the magnitude of vaccine-induced humoral responses and the extent of B-cell reconstitution at the time of vaccination than with the time window between vaccination and the last anti-CD20 infusion. The authors concluded that B-cell reconstitution might be the underlying mechanism for this effect, so that assessing re-emergence of peripheral B-cells may be a better marker for humoral immunity after vaccination than the time since the last cell depleting treatment dose.<sup>26</sup>

The absence of vaccine failures in the presence of low lymphocyte counts could be explained by preservation of CD4<sup>+</sup> and CD8<sup>+</sup> T-cell responses to vaccination. Reports on BNT162b1 have shown that the strength of CD4<sup>+</sup> T-cell responses correlates positively with both receptor-binding-domain-binding IgG and SARS-CoV-2-neutralizing antibody titers. The strength of receptor-binding-domain-specific CD8<sup>+</sup> T-cell responses correlated positively with vaccine-induced CD4<sup>+</sup> T-cell responses but did not significantly correlate with SARS-CoV-2 neutralizing antibody titers.<sup>27</sup>

Our study contributes additional information to the data obtained by Achiron and co-workers.<sup>8</sup> Seropositivity was not only achieved with mRNA vaccines but also with the vector vaccine that several patients received. In addition to anti-SARS-CoV-2 IgG antibodies and absolute lymphocyte counts, we determined lymphocyte subsets of B-cells, CD4<sup>+</sup> T-cells, and

CD8<sup>+</sup> T-cells. Furthermore, we offer more data of vaccinating closer to the last cladribine tablet dose prior to the 4.4 months recommended by Achiron and co-workers.<sup>8</sup> Patients vaccinated as early as 2 weeks after cladribine dosing were able to mount positive anti-SARS-CoV-2 IgG antibody levels.

### Limitations

Our study has some limitations. The small size of the cohort and the monocentric design limited the power of the study. T-cell responses were not obtained, and data analysis was impaired by an upper cutoff of the used assay at a plateau level. The antibody assay we used provides an indirect measure of neutralizing antibodies. The trimeric spike glycoprotein is the stabilized native form of the SARS-CoV-2 spike protein. A stabilized trimer may elicit an accurate detection of IgG neutralising antibodies.<sup>28</sup> Evaluation of concordance with neutralizing antibody titers yielded a positive and negative percent agreement of 100% and 96.9%, respectively.<sup>13</sup> Whether detection of antibodies is a sufficient indicator of immune response remains unclear. Absence of antibody detection does not preclude a protective T-cell response. Whether the amount of SARS-CoV-2 IgG antibodies is sufficient to prevent COVID-19 and protect against variants of the coronavirus remains subject of further research. Currently, the antibody titer required for protection against SARS-CoV-2 is unknown. How long positive antibody titers can be maintained in patients on cladribine tablets is also yet unknown and needs to be elucidated in future studies.

### Conclusions

In conclusion, treatment with cladribine tablets did not impair humoral response to COVID-19 vaccination. Time since last cladribine dose, age, prior therapy, lymphocyte count as well as B- and T-cell counts had no effect on seropositivity of anti-SARS-CoV-2 IgG antibodies.


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### Author contributions

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### REFERENCES

1. European Centre for Disease Prevention and Control. COVID-19 situation update worldwide, as of week 25. updated 1 July 2021. <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>. Accessed July 7, 2021.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416. 2020/12/31. doi:10.1056/NEJMoa2035389.
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615. 2020/12/11. doi:10.1056/NEJMoa2034577.
4. Buttari F, Bruno A, Dolcetti E, et al. COVID-19 vaccines in multiple sclerosis treated with cladribine or ocrelizumab. *Mult Scler Relat Disord*. 2021;52:102983. 2021/05/15. doi:10.1016/j.msard.2021.102983.
5. Khayat-Khoei M, Conway S, Rubinson DA, et al. Negative anti-SARS-CoV-2 S antibody response following Pfizer SARS-CoV-2 vaccination in a patient on ocrelizumab. *J Neurol*. 2021;268(10):3592-3594. 2021/02/28. doi:10.1007/s00415-021-10463-3.
6. Drulovic J, Ivanovic J, Martinovic V, et al. Humoral response to SARS-CoV-2 and COVID-19 vaccines in patients with multiple sclerosis treated with immune reconstitution therapies. *Mult Scler Relat Disord*. 2021;54:103150. 2021/07/24. doi:10.1016/j.msard.2021.103150.
7. Gallo A, Capuano R, Donnarumma G, et al. Preliminary evidence of blunted humoral response to SARS-CoV-2 mRNA vaccine in multiple sclerosis patients treated with ocrelizumab. *Neurol Sci*. 2021;42:3523-3526. 2021/06/16. doi:10.1007/s10072-021-05397-7.
8. 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;14:1-8. doi:10.1177/17562864211012835.
9. US Food & Drug Administration. EUA Authorized Serology Test Performance. <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance>. Accessed August 3, 2021.
10. Peteret HF, Tumani H, Zettl UK. Correspondence: 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;14:1-2. 2021/06/24. doi:10.1177/17562864211022581.
11. Piquet AL, Corboy JR, Vollmer TL. Correspondence to: 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;14:1-2. 2021/06/10. doi:10.1177/17562864211019567.
12. Leist TP, Weissert R. Cladribine: Mode of action and implications for treatment of multiple sclerosis. *Clin Neuropharmacol*. 2011;34:28-35. 2011/01/19. doi:10.1097/WNF.0b013e318204cd90.
13. DiaSorin. LIAISON® SARS-CoV-2 TrimericS IgG assay. [https://www.diasorin.com/sites/default/files/allegati\\_prodotti/liaisonr\\_sars-cov-2\\_trimerics\\_igg\\_assay\\_m0870004408\\_a\\_lr.pdf](https://www.diasorin.com/sites/default/files/allegati_prodotti/liaisonr_sars-cov-2_trimerics_igg_assay_m0870004408_a_lr.pdf). Accessed August 5, 2021.
14. Centonze D, Rocca MA, Gasperini C, et al. Disease-modifying therapies and SARS-CoV-2 vaccination in multiple sclerosis: an expert consensus. *J Neurol*. 2021;268:3961-3968. 2021/04/13. doi:10.1007/s00415-021-10545-2.
15. Ceronie B, Jacobs BM, Baker D, et al. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. *J Neurol*. 2018;265:1199-1209. 2018/03/20. doi:10.1007/s00415-018-8830-y.
16. Jacobs BM, Ammoscato F, Giovannoni G, et al. Cladribine: Mechanisms and mysteries in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018;89:1266-1271. 2018/07/12. doi:10.1136/jnnp-2017-317411.
17. KKNMS. Quality Handbook MS/NMOSD. Recommendations for the treatment of Multiple Sclerosis/Neuromyelitis-optica-diseases for physicians. [Qualitätshandbuch MS/NMOSD. Empfehlungen zur Therapie der Multiple Sklerose/Neuromyelitis-optica-Spektrum-Erkrankungen für Ärzte]; 5. revised and updated edition January 2020; 2020. <http://www.kompetenznetz-multiplesklerose.de>. Accessed May 3, 2021.
18. Multiple Sclerosis International Federation. Global COVID-19 advice for people with MS. <http://www.msif.org/wp-content/uploads/2021/06/June-2021-MSIF-Global-advice-on-COVID-19-for-people-with-MS-FINAL.pdf>. Accessed July 8, 2021.
19. Roy S, Boschert U. Analysis of influenza and varicella zoster virus vaccine antibody titers in patients with relapsing multiple sclerosis treated with cladribine tablets. *ACTRIMS 2021 Virtual Congress* 2021;P059.
20. Bigaut K, Kremer L, Fleury M, et al. Impact of disease-modifying treatments on humoral response after COVID-19 vaccination: A mirror of the response after

- SARS-CoV-2 infection. *Rev Neurol (Paris)*. 2021; online; 2021/06/27. doi:10.1016/j.neurol.2021.05.001.
21. Stuve O, Soelberg Soerensen P, Leist T, et al. Effects of cladribine tablets on lymphocyte subsets in patients with multiple sclerosis: an extended analysis of surface markers. *Ther Adv Neurol Disord* 2019; 12:1-16. 2019/06/28. doi:10.1177/1756286419854986.
  22. Otero-Romero S, Ascherio A, Lebrun-Fréney C. Vaccinations in multiple sclerosis patients receiving disease-modifying drugs. *Curr Opin Neurol*. 2021;34:322-328. 2021/03/13. doi:10.1097/wco.0000000000000929.
  23. Ju B, Zhang Q, Ge J, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 2020; 584: 115-119. 2020/05/27. doi:10.1038/s41586-020-2380-z.
  24. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020;38:1-9. 2020/02/28. doi:10.12932/ap-200220-0772.
  25. Wiendl H, Schmierer K, Hodgkinson S, et al. Characterization of peripheral immune cell dynamics and repopulation patterns in the first 12 months of cladribine tablets treatment: MAGNIFY-MS study (2235). *Neurology* 2021;96:2235.
  26. 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;online; 2021/09/16. doi:10.1038/s41591-021-01507-2.
  27. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T-cell responses. *Nature* 2020; 586: 594-599. 2020/10/01. doi:10.1038/s41586-020-2814-7.
  28. Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun* 2020;11:2251. 2020/05/06. doi:10.1038/s41467-020-16256-y.