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Humoral response to SARS-CoV-2 COVID-19 vaccines in patients with multiple sclerosis treated with immune reconstitution therapies

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ABSTRACT

Background: It has been generally accepted that people with MS (PwMS) should be vaccinated against COVID-19. The aim of our investigation was to evaluate the humoral response to natural SARS-CoV-2 infection and to two COVID-19 vaccines (BNT162b2 Pfizer-BioNTech and Beijing/Sinopharm BBIBP-CorV) in our cohort of PwMS under high efficacy disease modifying therapies (DMTs), cladribine and alemtuzumab.

Methods: Twenty two PwMS treated at the Clinic of Neurology, in Belgrade, who developed COVID-19 and/or were vaccinated against SARS-CoV-2, during treatment with cladribine and alemtuzumab, were included. Out of 18 patients treated with cladribine, 11 developed COVID-19, and 11 were vaccinated against SARS-CoV-2 (four with mRNA vaccine, 7 with Sinopharm). Four MS patients under alemtuzumab were vaccinated against SARS-CoV-2; three with mRNA, and one with Sinopharm vaccine. SARS-Cov-2 IgG response was measured using ELISA anti-spike protein-based serology (INEP, Belgrade, Serbia).

Results: All 7 patients under cladribine treatment who suffered from COVID-19, developed IgG antibodies, 2.0-5.5 months after last symptoms. All four (100%) patients under cladribine who were vaccinated with Pfizer-BioNTech vaccine, and three out of seven (42.9%) vaccinated with Sinopharm, developed antibodies. All 4 patients under alemtuzumab developed antibodies after vaccination. In all cases, seroprotection occurred, irrespective of timing of vaccination and absolute lymphocyte count.

Conclusion: Our findings in a small number of highly active PwMS in whom, lymphodepleting, immune reconstitution therapies, were applied in order to successfully manage MS, indicate that in a number of these patients it was possible to develop at the same time seroprotection in these patients after COVID-19 vaccination in these complex circumstances.

INTRODUCTION

The COVID-19 is an ongoing pandemic of coronavirus disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the appearance of COVID-19, clinicians were especially concerned about its possible effects in people with multiple sclerosis (PwMS) treated with a disease modifying therapy (DMT). One of the crucial questions is whether MS patients treated with DMT are able to produce adequate immune response to SARS-CoV-2 infection and to the vaccines. At the moment, this issue has not been clarified yet (Sellner and Rommer 2021).

It is well known that infections are more common in PwMS on DMTs and, additionally, even more frequent in those on high efficacy drugs (Willis and Robertson 2020; Luna et al., 2020). Furthermore, it has to be emphasized that the majority of DMTs have immunosuppressive activities. However, there is limited evidence that immunosuppressed people have an increased risk to COVID-19 for most MS-related treatments (D'Antiga et al., 2020; Reder et al., 2021; Simpson-Yap et al. 2021). Anyhow, it has been generally accepted that the risk of COVID-19 infection has to be balanced against the consequences of poorly

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Table 1
Demographic and clinical characteristics of investigated RRMS patients treated with cladribine tablets and alemtuzumab

Study population	RRMS patients N = 22 Cladribine N = 18	Alemtuzumab N = 4
Gender, n (%)		
Males	5 (27.8%)	0 (0%)
Females	13 (72.2%)	4 (100%)
Age, years		
Mean±SD	42.4±9.4	34.8±13.6
Disease duration, years		
Mean±SD	14.4±7.8	11.5±5.8
Disability by EDSS score		
Median	3.0	3.5
IQR	3.0	3.5

RRMS-relapsing-remitting multiple sclerosis, EDSS-Expanded Disability Status Scale,SD-standard deviation, IQR-interquartile range

controlled MS. In order to understand the risks posed to PwMS using DMTs, it is crucial to understand the impact of the treatment on infection-risk, vaccination responses and the mechanisms of immunity to SARS-CoV-2.

Pulsed lymphodepleting or immune reconstitution therapies, alemtuzumab and cladribine tablets, are new highly effective DMDs which show prolonged treatment effects after a brief treatment course (Giovannoni 2016). Although both cladribine and alemtuzumab are immune depleters, their mechanism of action is significantly different (Baker et al., 2020). Alemtuzumab, a humanized monoclonal IgG1-antibody that targets CD52 antigen, leads to a rapid and long-lasting depletion of CD52-positive cells (Thompson et al., 2010). Thus, it induces significant depletion of CD4, CD8 T cells and memory B cells (Baker et al., 2017a; Akgun et al., 2020). However, it also affects innate immunity and leads to early deletion of monocytes (Thomas et al., 2016; Baker et al., 2017b; Gross et al., 2016). Therefore, infection risk is significant after drug infusion and decreases over time since lymphocytes repopulation occurs (Buonomo et al., 2018; Wray et al., 2019). Thus, it can be expected that with time PwMS are likely to be able to generate a SARS-CoV-2 response and respond to vaccination.

Cladribine can induce comparable long-term memory B cell depletion similar to that observed with alemtuzumab, but without the innate cell and the severe lymphopenia associated with alemtuzumab (Ceronie et al., 2018; Ruggieri et al., 2019). Cladribine is more a selective B-cell depleting agent which depletes B-cells by about 85-90%, affecting both naïve and memory B-cells, where naïve B cells rapidly repopulate (Baker et al., 2017a; Baker et al., 2019; Moser et al., 2020). T-cell depletion is more modest (50%) (Baker et al., 2017a).

As of June 2021, four COVID-19 vaccines have been approved in Serbia. One is mRNA-vaccines encoding protein S (Pfizer-BioNTech vaccine), the other two are adenoviral vector-based vaccines (AstraZeneca and Gam-COVID-Vac–Sputnik V), and finally, the fourth is inactivated vaccine developed from 2 SARS-CoV-2 strains (WIV04 and HB02), Beijing/Sinopharm BBIBP-CorV (Al Kaabi et al., 2021).

The aim of our investigation is to evaluate the humoral response to natural SARS-CoV-2 infection and to two COVID-19 vaccines (BNT162b2 Pfizer-BioNTech and Beijing/Sinopharm BBIBP-CorV) in our cohort of PwMS under cladribine and alemtuzumab treatment. To the best of our knowledge, these are the first data related to the development of IgG antibodies to SARS-CoV-2 in PwMS under alemtuzumab after vaccination.

MATERIAL AND METHOD

In this case series study, all MS patients treated at the Clinic of Neurology, UCCS, in Belgrade, with cladribine tablets (N=22) and alemtuzumab (N=4) who developed COVID-19 and/or were vaccinated against SARS-CoV-2, during treatment, were invited to participate. Out of these 22 patients treated with cladribine tablets, 18 accepted to participate, and the remaining four rejected to be enrolled in the study. All 4 patients treated with alemtuzumab accepted to be recruited. Demographic and clinical characteristics of all enrolled relapsing-remitting (RR) MS patients treated with cladribine tablets and alemtuzumab are presented in Table 1.

According to the recommendations for COVID-19 vaccination for MS patients established by the Medical Advisory Board of the Serbian MS Society on January 21, 2021, patients were suggested to be vaccinated without stopping their current disease modifying therapies (DMTs). At that moment, it has been suggested that patients treated with cladribine tablets and alemtuzumab should be vaccinated at least three months after the last treatment dose.

Out of 18 investigated patients treated with cladribine tablets, 11 (61.1%) developed

Table 2
RRMS patients treated in Belgrade with cladribine tablets and alemtuzumab who developed COVID-19 and/or were vaccinated against COVID-19

Study population	RRMS patients N = 22 Cladribine N = 18	Alemtuzumab N = 4
COVID-19 disease, n (%)		
Yes	11* (61.1%)	0 (0%)
No	7 (38.9%)	4 (100%)
Patients with positive SARS-CoV-19 IgG after COVID-19 disease, n (%)		
Yes	7/7 (100%)	NA
No	0/7 (0%)	
Time from the last dose of the drug to the first symptoms of COVID-19 disease, months		
Mean±SD (range)	3.7±2.2 (1.0-6.5)	NA
Time from last symptoms of COVID-19 disease to testing, months		
Mean±SD (range)	3.9±1.8 (2.0-5.5)	NA
SARS-CoV-2 IgG titer after COVID-19 disease		
Mean±SD (range)	66.4±26.1 (33-119)	NA
Patients with positive SARS-CoV-19 IgG after vaccination, n (%)	7/11 (63.6%)	4/4 (100%)
Patients with positive SARS-CoV-19 IgG after Sinopharm vaccine, n (%)	3/7 (42.9%)	1/1 (100%)
Patients with positive SARS-CoV-19 IgG after Pfizer-BioNTech vaccine, n (%)	4/4 (100%)	3/3 (100%)
SARS-CoV-2 IgG titer after vaccination		
Mean±SD (range)	57.4±37.1 (25-115)	74.0±28.5 (37-106)
SARS-CoV-2 IgG titer after Sinopharm vaccination		
Mean±SD (range)	35.0±7.2 (29-43)	**
SARS-CoV-2 IgG titer after Pfizer-BioNTech vaccination		
Mean±SD (range)	74.3±42.9 (25-115)	74.3±34.8 (37-106)
Time from the last dose of the drug to vaccination, months		
Mean±SD (range)	5.9±1.7 (3-8)	7.1±3.6 (2-10)
Time from the last dose of vaccination to testing, months		
Mean±SD (range)	1.3±1.0 (0.1-3)	1.5±1.0 (1-3)
Absolute lymphocyte count (ALC) (10^9/L)		
Mean±SD (range)	1.3±0.7 (0.6-3.1)	0.8±0.5 (0.2-1.4)
Absolute lymphocyte count		
Normal	11 (61.1%)	1 (25%)
Abnormal	7 (38.9%)	3 (75%)

Seroprotection was defined as INEP ELISA titre >15; Normal ALC≥1.0 × 10^9/L
* 4/11 patients had COVID-19 before vaccination
** Only one patient vaccinated by Sinopharm vaccine developed SARS-CoV-2 IgG titer 73.

COVID-19, confirmed by the polymerase chain reaction (PCR) from nasopharyngeal swab. Additionally, in total, 11 (61.1%) patients treated with cladribine tablets were vaccinated against SARS-CoV-2, and out of them four, developed COVID-19 prior to vaccination.

Four of these patients received 2 intramuscular injections, which contained 30 μg of BNT162b2 (0.3 ml per dose) (Pfizer-BioNTech vaccine), 21 days apart. Seven subjects received 2 intramuscular injections, which contained 6.5 U inactivated antigen SARS-CoV-2 with adjuvant, Beijing/Sinopharm BBIBP-CorV, 21 days apart.

Four MS patients under alemtuzumab were vaccinated against SARS-CoV-2, three with two doses of Pfizer-BioNTech vaccine, and one with two doses, of Beijing/Sinopharm BBIBP-CorV, 21 days apart. None of the patients under alemtuzumab developed COVID-19.

Blood samples were taken between 7 and 9 AM, after overnight fasting, in serum vacutainer tubes with clot activator. Serum was separated by centrifugation at 3000 g for 10 minutes. The levels of IgG class antibodies against SARS-CoV-2 virus in sera samples were measured using ELISA SARS-CoV-2 IgG (INEP, Belgrade, Serbia). The specificity of the test is based on recombinant SARS-CoV-2 proteins, immobilized on ELISA microtiter plate, including Spike subunit covering the complete sequence of receptor binding domain (RBD). All samples were tested in a single run, in order to minimize intra assay variability. The results are evaluated semiquantitatively, and reported as index. Results with index < 15 are considered negative.

Blood samples were evaluated for the presence of IgG antibodies to SARS-CoV-2 during treatment with cladribine tablets and alemtuzumab. At the same time, absolute lymphocyte count (ALC) in the blood samples was assessed.

The study was approved by the Clinic of Neurology, UCCS, in Belgrade Institutional Review Board. All patients signed inform consent.

Statistical analysis

Categorical variables are described as frequency and percentage. Continues variables, depending of type of distribution, were reported as mean ± standard deviation (SD) or median with interquartile ranges (IQR). Spearman correlation coefficient was used to assess correlation between IgG antibody titers and ALC in MS patients.

RESULTS

In Table 2, data related to the frequency of seropositivity, titers of IgG antibodies against SARS-CoV-2 and their detection time and ALC detected at the same time, in MS patients under treatment with cladribine tablets and alemtuzumab, after COVID-19 and/or vaccination, are presented.

All seven patients who suffered from COVID-19, without being vaccinated afterwards, had IgG antibodies under cladribine treatment, which were detected after mean time from the last symptoms of COVID-19 of 3.7±1.8 months (range 2.0-5.5 months). Mean SARS-CoV-2 IgG titer at that time was 66.4±26.1 (range 33-119) (seroprotection was defined as INEP ELISA titre >15). None of the patients included in the study who were under alemtuzumab developed COVID-19.

Eleven patients under cladribine treatment were vaccinated. Mean time from the last dose of the cladribine to vaccination was 5.9±1.7 (range, 3-8) months. In three out of seven patients (42.9%) vaccinated with Sinopharm vaccine, protective humoral immunity was demonstrated. In these patients, antibodies were detected in blood samples which were taken after the mean time of 1.3±1.0 months after completing immunization with two doses of vaccine. All the remaining four (100%) patients under cladribine who were vaccinated with Pfizer-BioNTech vaccine demonstrated SARS-CoV-2 IgG antibodies; mean time from the last dose of vaccination to the detection of protective titer of antibodies was 1.3±1.0 (range, 0.1-3) months. These antibodies were detected in blood samples which were taken after the mean time of 1.3±1.0 months after complete immunization with two doses of vaccine. SARS-CoV-2 IgG titer after vaccination was 35.0±7.2 in average for Sinopharm vaccine, and 74.3±42.9 for Pfizer-BioNTech vaccine. There is no correlation between seropositivity and time of vaccination after the last dose of the drug (ρ=0.092, p=0.789).

It should be emphasized that in the subgroup of our four patients under cladribine who had COVID-19 prior to vaccination, antibodies were demonstrated in three of them (two after Sinopharm vaccine and one after Pfizer) and one patient did not have antibodies (after Sinopharm vaccine).

Four patients under alemtuzumab treatment were vaccinated. Mean time from the last dose of the alemtuzumab to vaccination was 7.1±3.6 (range, 2-10) months. All patients developed protective humoral immunity after vaccination. In these patients, antibodies were detected in blood samples which were taken after the mean time of 1.5±1.0 months after completing immunization with two doses of vaccine. Mean time from the last dose of vaccination to the detection of protective titer of antibodies was 1.5±1.0 (range, 1-3) months. SARS-CoV-2 IgG titer after vaccination was 74.3±34.8 for Pfizer-BioNTech vaccine, and 73 in one patient who received Sinopharm vaccine.

ALC detected in patients under cladribine and alemtuzumab treatment are presented in Table 2. Normal ALC was detected in 61.1% of patients under cladribine and in one out of four (25%) patients under alemtuzumab. Patient with the lowest ALC (0.2×10^9) also developed seroprotection with SARS-CoV-2 antibody titer of 80. Based on Spearman correlation coefficient which determine relationship between SARS-CoV-2 antibody presence and ALC, it was concluded that seroprotection had occurred irrespective of lymphocyte count (ρ=-0.114, p=0.652).

ALC in relation with post-vaccination seropositivity and time of vaccination are presented for each patient under cladribine treatment in Picture 1 and under alemtuzumab treatment in Picture 2. Seroprotection in SARS-CoV-2 titers occurred in patients treated with cladribine tablets who were vaccinated early (M 5–6 in Year 1 and M in Year 2) or late (M 8 in Year 1). In this group, patients had normal ALC, and also grade 1 and grade 2 lymphopenia. Seroconversion occurred in all patients treated with alemtuzumab, irrespective of timing of vaccination and ALC. It also developed in the patient who was vaccinated 2 months after the last dose of alemtuzumab. This patient did not follow national recommendation regarding the timing of vaccination, due to the fear that delayed vaccination may lead to the potential development of severe COVID-19.

DISCUSSION

In our study, all seven patients under cladribine treatment, who suffered from COVID-19 developed IgG antibodies, which were detected after 2.0-5.5 months, from the last symptoms of COVID-19. Until January 2021, COVID-19 has been reported in 53 patients treated with cladribine (Gelibter et al., 2021; Dersch et al., 2020; Jack et al., 2020; Celius, 2020; Preziosa et al., 2020; De Angelis et al., 2020), and soon after based on the data extracted from the Merck KGaA Global Patient Safety Database, 272 cases of COVID-19 among cladribine recipient were reported (Jack et al., 2021). Serological data were presented only for nine patients under cladribine, until now. In line with our results, majority developed antibody response after infection. Only two of these PwMS under cladribine did not develop antibody response (Gelibter et al., 2021). None of our four patients enrolled in the survey who were under alemtuzumab developed COVID-19. Until now, there are 15 reported cases of COVID-19 with alemtuzumab (Iovino et al., 2021). In a number of cases, antibody response was detected after infection (Zabalza et al., 2020).

We have demonstrated that out of our eleven patients under cladribine treatment who were vaccinated 3-8 months 7 developed protective humoral immunity. Four of them were vaccinated with the Pfizer-BioNTech vaccine 5-8 months, after the last dose of the drug and all of them developed normal antibody response (100%). The remaining 7 PwMS received Sinopharm vaccine, after 3-8 months after

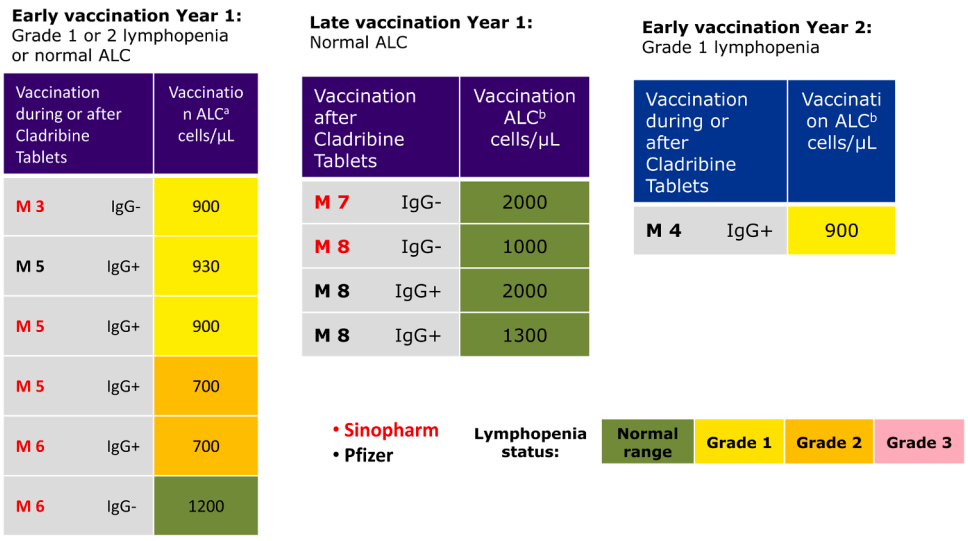

Fig. 1. SARS-CoV2 vaccine after initiation of Cladribine Tablets treatment.

the last dose of the drug, and 3 of them (42.9%) developed antibody response. In these patients, who did not develop antibodies, ALC varied from normal to grade 2 lymphopenia status. Three out of four remaining PwMS who did not develop seroprotection had normal ALC and were vaccinated 6-8 months after the last dose of the drug; the last one had grade 1 lymphopenia and time from the last dose of cladribine to vaccination was three months. Four patients under alemtuzumab treatment were vaccinated 2-10 months after the last dose of the drug (one with Sinopharm vaccine and three Pfizer-BioNTech). All patients developed protective humoral immunity after vaccination. ALC in these patients ranged from normal to grade 3 lymphopenia status and antibodies were also detected in a patient with extremely low lymphocytes (210/μL). Protective humoral immunity was also demonstrated in the patient who was vaccinated 2 months after the last dose of alemtuzumab. This person did not follow Recommendations for COVID-19 vaccination for MS patients established by the Medical Advisory Board of the Serbian MS Society regarding the timing of vaccination, and she did not want to delay available vaccination because she was afraid of the potential development of the severe COVID-19 which she wanted to prevent. Additionally, it has to be mentioned that, similarly, a case has been already described, where the first month after alemtuzumab administration, the patient was able to produce a sufficient adaptative response to natural infection, including antibody production against SARS-CoV-2 (Fernández-Díaz et al., 2020). Thus, it has to be emphasized that both time of vaccination after the last dose of the drug and ALC had no impact on the development of seroprotection either in PwMS treated with cladribine or in those under alemtuzumab. The explanation of the influence of cladribine tablets and alemtuzumab, lymphocyte-lowering agents, on the immune system's ability to develop antibodies in response to a vaccine in patients with low lymphocyte count has not been fully clarified yet and warrants further investigation.

Recently, the MAGNIFY-MS study was started in order to determine the onset of action of cladribine tablets over two years in patients with highly active relapsing MS (Roy and Boschert, 2021). Since some patients enrolled in this study received Varicella Zoster virus (VZV) and seasonal influenza vaccines, vaccinations during the course of the trial as standard of care, it has been decided to investigate the vaccine response. In line with our results, in this small retrospective investigation performed in 15 patients, seroprotective antibody levels against VZV and seasonal influenza were maintained or increased, for at least 6 months, independent of lymphocyte count, measured at the time of vaccination in year 1 or 2 of cladribine treatment, in all patients.

Until now, only one study investigated humoral immune response to COVID-19 vaccine in PwMS treated with high efficacy DMTs (Achiron et al., 2021). Patients were vaccinated exclusively with Pfizer-BioNTech vaccine. Protective humoral immunity was analyzed and detected in 100% of PwMS treated with cladribine, 22.7% of those treated with ocrelizumab, and for only 3.8% of PwMS treated with fingolimod. Findings related to the development of antibodies after vaccination with Pfizer-BioNTech vaccine in PwMS under cladribine are identical as those obtained in our investigation. Authors stated that low rate of PwMS who developed IgG response was irrespective to normal ALC. Finally, it has been found that time from the last dosing (shortest duration 4.4 months) also did not affect humoral response to COVID-19 vaccination, which is again in line with our findings. Additionally, very recently experience in four patients, under cladribine (two) or under ocrelizumab (two) treatment, all with low lymphocyte count, three of them vaccinated after 3 months from the last dose with good immune response, one (under ocrelizumab) after 2 months, without developing an appropriate titer of antibodies, has been reported (Buttari et al., 2021). Patients under cladribine were vaccinated with adenoviral vector-based vaccine (AstraZeneca) and mRNA vaccine (Pfizer-BioNTech).

It has to be emphasized that the limitation of a small number of participants in our survey, does not allow to obtain a general conclusion but may rather indicate a general trend. Our findings in a small number of highly active PwMS in whom lymphodepleting, immune reconstitution therapies, cladribine and alemtuzumab, were applied in order to successfully manage MS, indicate that in a number of these patients it was possible to develop at the same time seroconversion after COVID-19 vaccination in the complex circumstances in the post-COVID-19 era. Out of our 7 cladribine treated patients who received Sinopharm vaccine, 4 did not develop protective humoral immunity, and all 4 cladribine patients who received Pfizer vaccine developed humoral immunity; additionally, all four patients treated with alemtuzumab developed seroconversion, 3 with Pfizer and one with Sinofarm vaccine. It is well known that any vaccine may not fully protect everyone who gets it. According to the data from the clinical trials, there is difference in vaccine efficacy between mRNA and inactivated vaccines. According to manufacturers' data, Pfizer vaccine induces protective immunity in 95% of fully vaccinated persons and Sinofarm in 79.3% (Baden et al., 2021, Xia et al., 2021). It could be expected that COVID-19 vaccines with a high efficacy should be highly effective in the real-world but this data are not available yet. Further investigations are warranted to define guidelines for the vaccination protocols for PwMS, especially those treated with high efficacy DMTs.

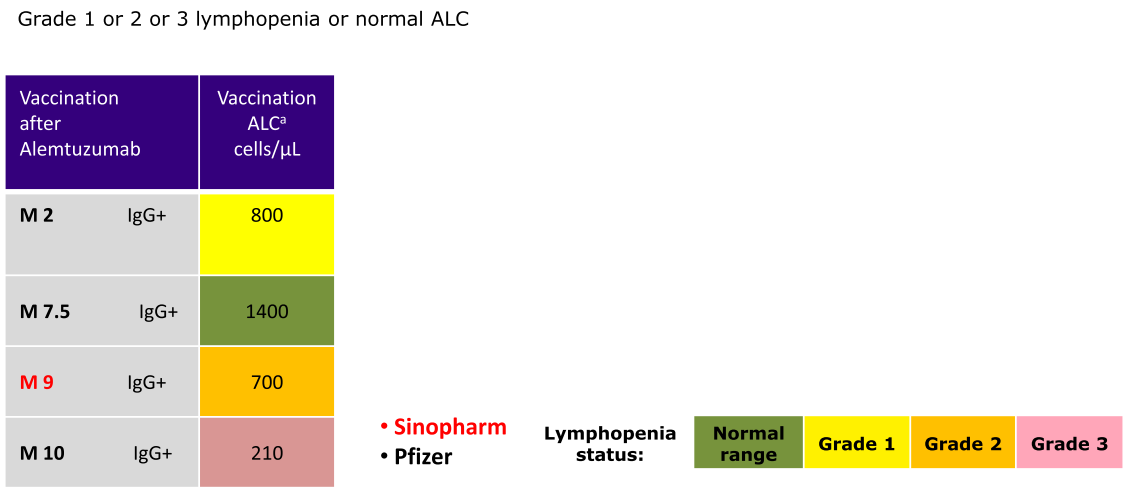

Fig. 2. SARS-CoV2 vaccine after initiation of Alemtuzumab treatment.

Declaration of Competing Interest

None

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Authors contribution

Jelena Drulovic, Tatjana Pekmezovic and Sarlota mesaros contributed to the study concept methodological approach.

Jovana Ivanovic, Vanja Martinovic, Olivera Tamas, Nikola Veselinovic, Danica Cujic, and Marija Gnjatovic contributed to the study conduct, data collection.

All authors participated in the evaluation and interpretation of the data. All authors reviewed the manuscript drafts and approved the final version of the manuscript.

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