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Longitudinal humoral response in MS patients treated with cladribine tablets after receiving the second and third doses of SARS-CoV-2 mRNA vaccine☆

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ABSTRACT

Background: Multiple sclerosis (MS) patients receive immunomodulatory treatments which can influence their ability to maintain vaccine specific serological response overtime. MS patients treated with cladribine tablets developed a positive serology response following two doses of mRNA COVID-19 vaccine. However, there is only limited data regarding the effect of cladribine tablets on long-term humoral response after the second and the third booster.

Methods: Serology response to SARS-CoV-2 was tested in healthy controls (HCs) and MS patients treated with cladribine tablets 6 and 9–12 months after the second dose, and 1 and 3–6 months following the third booster-dose of the BTN162b2 mRNA vaccine.

Results: Thirty-five out of 36 MS patients treated with cladribine tablets and 100% (46/46) of HCs had a positive serology response up to 10 months after the second vaccine dose. In addition, all cladribine tablets -treated MS patients (22/22) and HCs (24/24) had a positive robust serology response following the third vaccine with a positive humoral response sustain up to 6 months. One month after the third vaccine dose IgG levels were significantly lower in patients treated with cladribine tablets compared to HCs (15,598+11,313 vs 26,394+11,335, $p<0.01$). Six-month post second vaccine and 3–6 months post third vaccine there was no difference in IgG levels between the groups (1088.0 ± 1072.0 vs 1153.0 ± 997.1, $p = 0.79$; 5234+4097 vs 11,198+14,679, $p = 0.4$).

Conclusion and relevance: MS patients treated with cladribine tablets have sustained positive vaccine specific serology response following the second and third SARS-CoV-2 vaccine dose.

1. Introduction

The resurgence of corona virus disease (COVID-19) worldwide despite the fact that high percentages of the population have been vaccinated with two doses of mRNA vaccine, along with increase data of waning vaccine immunity of the mRNA vaccines over time, has led to the recommendation of a third vaccine dose (Mizrahi et al., 2021; Goldberg et al., 2021). The third dose of mRNA vaccines has been shown to elicit a strong humoral response (Patalon et al., 2022; Gilboa et al., 2021; Eliakim-Raz et al., 2021).

COVID-19 vaccines have been reported to be safe for multiple sclerosis (MS) patients, with no evidence of increased risk of relapse (Achiron et al., February 2021; Dreyer-Alster et al., 2022; König et al., 2022). Patients with MS are treated with various disease-modifying treatments (DMTs) that affect different levels of the immune system and may affect the humoral immune response to COVID-19 vaccines

Abbreviations: COVID-19, Coronavirus disease; MS, Multiple Sclerosis; DMTs, disease-modifying treatments; RBD, Receptor Binding Domain; EDSS, Expanded Disability Status Scale.

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(Kalincik et al., 2021).

Cladribine tablets (Mavenclad), a purine analogue selectively target lymphocytes and causes marked reduction of B cells and a modest reduction in T and NK cells (Beutler, 1992; Baker et al., 2017; Stuve et al., 2019). We and others have shown that MS patients treated with cladribine tablets develop a humoral response to two doses of the mRNA SARS-CoV-2 vaccines (Capone et al., 2021; Brill et al., 2021; Tortorella et al., 2022). However, only a few studies have examined the effect of cladribine tablets on a long-term humoral response after the second vaccination and data on the response following the third booster vaccine dose is limited (Achiron et al., 2021).

In the current work, we present a study assessing the serology response of MS patients treated with cladribine tablets, 6 and 9–12 months after the second vaccine dose as well as following the third vaccine dose.

2. Methods

2.1. Ethical considerations

The Hadassah and Rambam Medical Organization Ethics Committees approved this study. All patients provided written informed consent (975-20-HMO, 0188-21-RMB).

2.2. Patients

Patients with MS treated with cladribine tablets who received two or three doses of COVID-19 mRNA vaccine (BTN162b2 Pfizer/BioNTech) were included. None of the patients were infected with COVID-19 until 30.11.2021 (Before the omicron variant outbreak in Israel). Patients who were pregnant, breastfeeding, or diagnosed with another autoimmune disease were excluded from the study.

The study cohort include 44 MS patients treated with cladribine tablets (Female:Male = 33:11, average age 39.45±12.88 years, EDSS 2.88±1.98, average disease duration 8.24±7.44 years, and lymphocytes count 1.35±0.86) and forty-six HCs. Thirty-six patients with MS treated with cladribine tablets and 46 HCs provided blood samples 6 months following the second vaccine dose, 5 cladribine tablets treated MS patients gave blood 9–12 months following the second vaccine. Blood samples were analyzed 1 month following the third vaccine in 17 cladribine treated MS patients and 24 HCs, and from 5 cladribine tablets treated patients and 8 HCs, 3–6 months following the third vaccine dose.

2.3. Study design and serology

Enrolled patients provided a blood sample 6 and/or 9–12 months after the second COVID-19 mRNA vaccine, and 1 and 3–6 months after the third vaccine. Serology response to SARS-CoV-2 Spike Receptor Binding Domain (RBD) was measured using the Architect SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics). A positive response was defined by an IgG titer of ≥50 arbitrary units (AU/ml).

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of all parameters considered in this study. A student *t*-test was performed to measure differences in serology response between the HCs and MS patients treated with cladribine tablets. Correlations between demographic and clinical variables and serology response were assessed by Pearson's correlation. Differences were considered significant when $P < 0.05$.

3. Results

3.1. Long-term serology response after the second vaccine dose

In order to find the long-term vaccine specific serology response in MS patients treated with cladribine tablets we analyzed blood samples 6 and 9–12 months following the second vaccine dose. This study follows our recent report on serology responses 2–3 weeks following second vaccine in patients treated with cladribine tablets (Brill et al., 2021). Thirty-five out of 36 MS patients treated with cladribine tablets and 100% (46/46) of HCs had a positive serology response 6 months after the second vaccine dose. No difference was found between SARS-CoV-2-IgG titer of HCs and cladribine tablets-treated MS patients 6 months following the second vaccine (1153.0 ± 997.1 vs 1088.0 ± 1072.0, $p = 0.79$). All additional 5 samples from cladribine tablets treated patients obtained 9–12 months following the second vaccine had positive serology response (612.40±316.82) (Fig. 1). In both HCs and MS patients treated with cladribine tablets, IgG titers significantly decreased 6 months following the second vaccine dose (compared to 1 month following second dose), however between the groups, the decline was not significantly different (Δ 13,552±8573 vs Δ 12,029±12,260, $p = 0.62$, supplement figure 1).

No correlation was found between SARS-CoV-2 IgG levels 6 months following the second vaccine and lymphocytes count ($r = 0.03$, $p = 0.86$), EDSS ($r=-0.11$, $p = 0.51$), age ($r=-0.03$, $p = 0.88$), disease duration ($r=-0.15$, $p = 0.4$), and the time between last cladribine dose and vaccination ($r = 0.15$, $p = 0.49$). In addition, no difference was found between patients who received one or two courses of cladribine tablets prior to vaccination (835 ± 825.5 vs 1275 ± 1285, $p = 0.4$).

3.2. Serology response following the third vaccine dose

Following the third vaccine dose all participants, 22 MS patients treated with cladribine tablets and 24 HCs, had positive serology response. IgG levels of cladribine tablets-treated MS patients were significantly lower compared to HCs in samples obtained 1 month after the third vaccine dose (15,598±11,313 vs 26,394±11,335, $p<0.01$), but not 3 to 6 months following the third vaccine (11,198±14,679 vs 5234 ±4097, $p = 0.4$). All study participants had significantly increased IgG titers 1 month after the third vaccine compared to the IgG levels 6 months after the second vaccine (Δ 26,095.28±10,973.84 vs Δ 11,903.88±11,741, $p = 0.001$ Supplementary figure 2).

All HCs were vaccinated with the third dose 5–6 months after the second dose. Out of 17 MS patients treated with cladribine tablets, 6 were vaccinated 5–6 month following the second dose and 11 were vaccinated 7–12 months following the second dose. Average IgG titer in patients that were vaccinated more than 7 months after the second dose were lower, but the difference was not statistically significant (19,079 ±10,461 vs 13,699±11,782, $p = 0.37$, supplementary figure 3).

No correlation was found between IgG titers 1 months following the third vaccine dose and lymphocytes count ($r=-0.27$,$p = 0.35$), EDSS ($r = 0.22$,$p = 0.40$) age ($r = 0.09$, $p = 0.74$), disease duration ($r = 0.13$, $p = 0.63$), duration between last cladribine tablets dose and third vaccine ($r=-0.21$, $p = 0.44$), time between the second vaccine and third vaccine ($r=-0.16$, $p = 0.61$) and between patients who received two courses of cladribine tablets before the third vaccine to patients with only one course of cladribine tablets (12,804±11,443 vs 15,986±11,658, $p = 0.56$).

4. Discussion

A national third-dose vaccination campaign was initiated in Israel on August 1, 2021. To date, a third vaccine is recommended in many countries. Several groups have demonstrated a reduction in the odds of SARS-CoV-2 infection and hospitalization within a few weeks of receiving the third vaccine compared with receiving the 2 primary doses

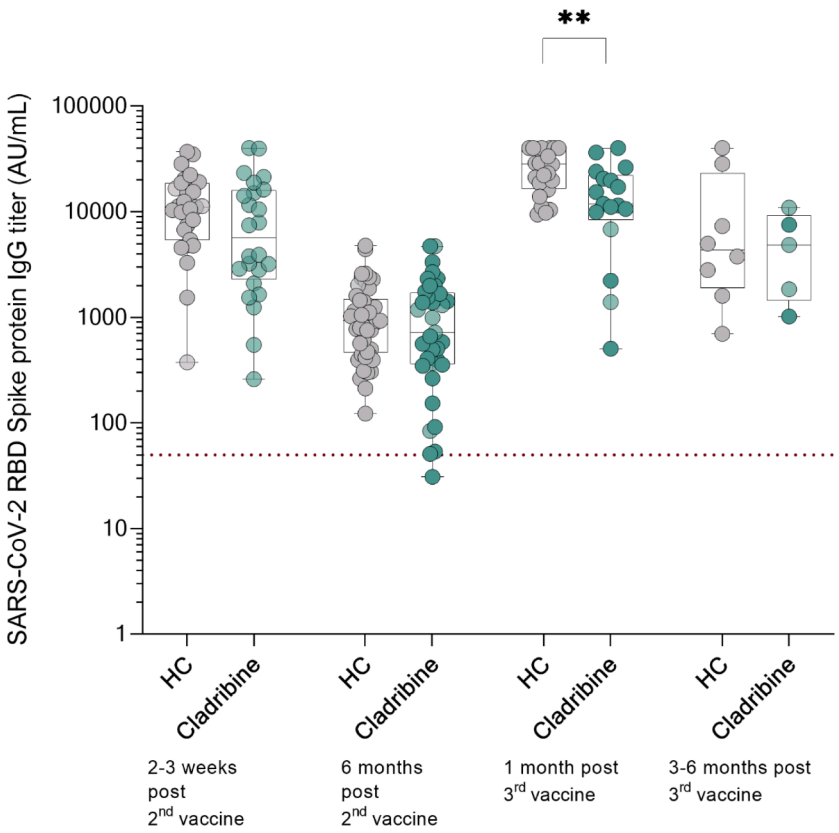

Fig. 1. Longitudinal serology response to SARS-CoV-2 mRNA vaccine of cladribine treated MS patients and HCs. Fig. 1 Serology response of HCs and cladribine tablets-treated MS patients following the 2nd and 3rd mRNA vaccine dose on logarithmic amplitude scale. 2–3 weeks (n = 31, 13,003 ±8893AU/ml vs n = 21, 11,135±12,029, p = 0.52), and 6 months (n = 46, 1153.0 ± 997.1 vs n = 36, 1088.0 ± 1072.0, p = 0.79) following the 2nd vaccine, and 1 month (n = 24, 26,394±11,335 vs n = 17, 15,598±11,313, p = 0.40) and 3–6 months (n = 8, 11,198±14,679 vs n = 5, 5234±4097, p = 0.40) following the 3rd vaccine. Data presented as mean±SD. Dotted line indicates positive threshold (≥50 AU/ml).

(Patalon et al., 2022; Barda et al., 2021; Thompson et al., 2022). According to a number of studies, serology response of healthy individuals following the third vaccine is greater compared to the second vaccine booster (Gilboa et al., 2021; Eliakim-Raz et al., 2021).

In the current study, we describe longitudinal serology response in MS patients treated with cladribine tablets at 6 and 9–12 months after the second dose as well as at 1 and 3–6 months after the third dose of the BNT162b2 mRNA vaccine. Our results show that 97% of MS patients treated with cladribine tablets have a positive serology response following 6 months and up to 12 months after the second dose. In addition, in all participants, the third vaccine results in a robust increased serological response; however, the average response in MS patients treated with cladribine tablets is lower than that of HCs. We did not find a correlation between IgG levels and age, EDSS, lymphocytes count, disease duration, and duration between last cladribine dose and vaccination. Also, no difference was found between patients who received one or two courses of cladribine tablets before the third vaccine dose.

To date, several reports show that the majority of MS patients treated with cladribine tablets have positive serology response after receiving two doses of the mRNA vaccine. Nevertheless, it is still unclear whether IgG levels are comparable to HCs (Capone et al., 2021; Brill et al., 2021; Tortorella et al., 2022; Grothe et al., 2021; Maniscalco et al., 2022).

The protection of the mRNA vaccines against COVID-19 fades after several months (Mizrahi et al., 2021; Goldberg et al., 2021). Goldberg et al., showed that the risk for infection was significantly higher for participants that were vaccinated 6 months before the study, compared to those who were vaccinated later (Goldberg et al., 2021). This parallels the known decrease in IgG levels 6 months following a second vaccination and infection (Zhong et al., 2021; Shrotri et al., 2021; Seow et al., 2020). In addition, 5–6 months following the second vaccine there is a significant overall decrease at memory B-cells and neutralizing antibodies, however T cell responses are preserved (Tarke et al., 2022). Of note is that it is still unclear what is cutoff IgG level that would provide protection against infection or from severe COVID-19 disease course (Islamoglu et al., 2021). In addition, the cross-sectional natures of the vaccine response studies to date do not reach consensus about the best timing of vaccines and effects of boosters or third doses to maximize humoral and cellular responses (Rieckmann et al., 2021).

Data on the long-term durability of the serology response of MS patients treated with cladribine tablets is scarce. We found that up to 12 months following the second and up to 6 months after the third vaccine dose, both HCs and MS patients treated with cladribine tablets have a positive serology response.

The humoral response of patients treated with cladribine tablets was significantly lower 1 month following the third vaccine dose but not 6 months post second vaccine dose and 3–6 months after the third vaccination. Timing of the vaccine is known to affect humoral response (Moghadas et al., 2021). While all HCs were vaccinated with the third dose 5–6 months after the second dose, in the group of MS patients treated with cladribine tablets there was a wider range between the two doses. Patients that were vaccinated with the third dose more than 7 month after the second, had lower IgG titers in average. Further, larger MS cohort studies may provide insight on the cause of the difference between HCs and cladribine tablets treated patients.

5. Conclusion

In conclusion, we found that MS patients treated with cladribine tablets have sustained positive vaccine specific serology response following the second and third vaccine dose of the BNT162b2 mRNA vaccine.

Conflict of Interest

A. Vaknin-Dembinsky has served on scientific advisory boards for F. Hoffmann-La Roche, Biogen, Sanofi- Aventis and the healthcare business of Merck KGaA, Darmstadt, Germany and has received grants from F.

Hoffmann-La Roche, Biogen and the healthcare business of Merck KGaA, Darmstadt, Germany.

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CRediT authorship contribution statement

Livnat Brill: Conceptualization, Validation, Investigation, Writing – original draft. **Ariel Rechtman:** Conceptualization, Validation, Investigation, Writing – original draft. **Alla Shifrin:** Resources, Writing – review & editing. **Ayal Rozenberg:** Resources, Writing – review & editing. **Svetlana Afanasiev:** Resources, Writing – review & editing. **Omri Zveik:** Investigation, Writing – review & editing. **Nitzan Haham:** Investigation, Writing – review & editing. **Neta Levin:** Resources, Writing – review & editing. **Adi Vaknin-Dembinsky:** Conceptualization, Validation, Resources, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A. Vaknin-Dembinsky has served on scientific advisory boards for F. Hoffmann-La Roche, Biogen, Sanofi- Aventis and the healthcare business of Merck KGaA, Darmstadt, Germany and; has received grants from F. Hoffmann-La Roche, Biogen and the healthcare business of Merck KGaA, Darmstadt, Germany.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103863.

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