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COVID-19

Six-month humoral response to BNT162b2 mRNA COVID-19 vaccine in people with multiple sclerosis treated with natalizumab

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Abstract

Background Few studies investigated the immune response to SARS-CoV-2 vaccine in patients with multiple sclerosis (pwMS) treated with natalizumab (NTZ) and found a short-term efficient humoral response; however, there are no studies assessing the levels of SARS-CoV-2 IgG antibodies in pwMS treated with NTZ over time.

Methods Humoral immune response to BNT162b2 mRNA COVID-19 vaccine was assessed in a group of 26 pwMS on NTZ up to 6 months after a full COVID-19 vaccination cycle and compared it with 43 age- and sex-matched group of HC. Serum samples were collected before the first dose (T0), and 4 weeks (T1) and 6 months (T2) after the first dose of BNT162b2 mRNA COVID-19 vaccine. The LIAISON® SARS-CoV-2 TrimericS-IgG assay (DiaSorin-S.p.A.) was employed for the detection of IgG antibodies to SARS-CoV-2 spike protein (cutoff for positive IgG antibodies: 33.8 BAU/mL).

Results At T1 and T2, both groups showed an efficient humoral response to BNT162b2 mRNA COVID-19 vaccine. A significant reduction of IgG antibodies to SARS-CoV-2 spike protein was detected at T2 both in pwMS and in HC, but SARS-CoV-2 IgG antibodies were still above the cutoff limit in all participants.

Conclusions pwMS on NTZ develop and maintain a long-term humoral response after a full COVID-19 vaccination cycle comparable to their healthy peers, and these findings are relevant for clinicians called to counsel about COVID-19 mRNA vaccine timing and booster doses in pwMS treated with NTZ.

Keywords COVID-19 · Humoral response · Multiple sclerosis · Natalizumab · BNT162b2 mRNA COVID-19 vaccine · Vaccine

Introduction

Few studies investigated the immune response to SARS-CoV-2 vaccine in patients with multiple sclerosis (pwMS) on natalizumab (NTZ) [1–3], a high-efficacy disease-modifying therapy (DMT) that binds to α4β1-integrin and inhibits migration of leukocytes into the central nervous system, thus halting inflammatory activity typical of MS [4, 5]. In the first short-term study on pwMS on NTZ [1], in which levels of IgG antibodies to SARS-CoV-2 spike protein (anti-TSP IgG) were evaluated in 31 pwMS 7 days after the second dose of the BNT162b2 mRNA vaccine, the authors reported an efficient humoral response, with values comparable to those of age- and sex-matched healthy controls (HCs). In another cross-sectional study evaluating the humoral response ~ 3 months after the second BNT162b2 mRNA vaccine dose in 32 pwMS treated with NTZ, a positive humoral response was measured in all pwMS, with no significant differences on levels of anti-TSP IgG between the NTZ and HC groups [2]. A third study on a larger population of 100 pwMS on NTZ confirmed that 4 weeks after the second dose of a mRNA vaccine (BNT162b2 or mRNA-1273), all participants mounted a full humoral response [3].

To date, there are no studies assessing anti-TSP IgG levels in pwMS treated with NTZ over time; thus, it is important to explore the humoral response evolution in this population

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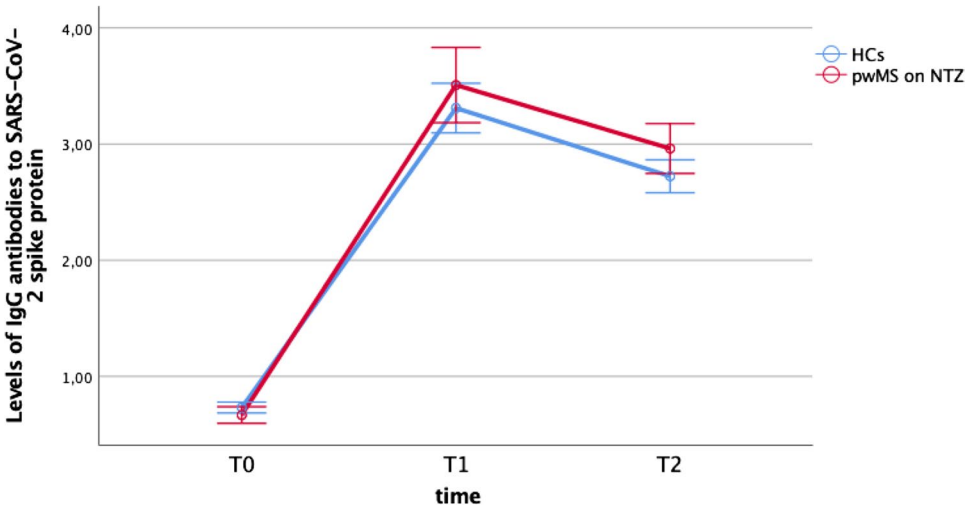

Fig. 1 Log-transformed values of levels of antibodies to SARS-CoV-2 spike protein in people with multiple sclerosis (pwMS) and healthy controls (HC) at T0 (before the vaccination cycle), T1 (4 weeks after the first dose), and T2 (6 months after the first dose)

also in view of a booster dose. To address this question, we measured the humoral immune response to BNT162b2 mRNA COVID-19 vaccine in pwMS on NTZ up to 6 months after the first dose of a full COVID-19 vaccination cycle and compared it with age- and sex-matched HCs.

Materials and methods

Serum samples were collected before the first dose (T0), and 4 weeks (T1) and 6 months (T2) after the first dose of BNT162b2 mRNA COVID-19 vaccine. To be included in the study, both HCs and pwMS on NTZ did not have to have (a) a history of COVID-19, (b) positive anti-TSP IgG at T0, and (c) treatment with corticosteroids within 1 month before the first dose of vaccine. The LIAISON® SARS-CoV-2 TrimericS-IgG assay (DiaSorin-S.p.A.) was employed for the detection of anti-TSP IgG, including neutralizing antibodies [6]. The IgG titers were expressed in binding antibody units (BAU), whereas the cutoff for positive IgG antibodies was set at 33.8 BAU/mL [7]. Sera analysis was conducted at the virology laboratory of our University Hospital. The study was approved by the local Ethics Committee, in accordance with the Helsinki Declaration (approval code: 0015914). Each participant was informed on the aim of the study and was asked to sign an informed consent form.

Statistical analysis was performed with SPSS, version 25.0. Mean, standard deviation, median, and P25-75 were calculated to describe variables, whereas normality of distribution was assessed with Komolgorov-Smirnov test; due to the non-normality of distributions, a logarithmic transformation was performed for anti-TSP IgG values. The comparison between pwMS on NTZ and HCs on sociodemographic variables was performed with chi-square (χ^2) and Mann–Whitney U test, as appropriate, whereas the comparison on levels of anti-TSP IgG over time was performed with a multivariate analysis of covariance (MANCOVA), with anti-TSP at T0, T1, and T2 as dependent variables, and the group of participants (pwMS on NTZ vs HCs) as independent variable, controlling fox sex, age, EDSS and DMT duration. Multiple regression analyses were performed to assess predictors (age, sex, EDSS, disease duration, DMT duration) of change in levels of anti-TSP IgG over time in both groups.

Results

Thirty-two pwMS on NTZ and forty-three HC-matched from a larger dataset of HCs enrolled in a surveillance program at our institution were screened; 6 pwMS were excluded from the study due to IgG titers above the cutoff at T0, suggesting a history of COVID-19. The final sample included 26 pwMS on NTZ and 43 HC. The sample of pwMS on NTZ (females: 69.2%) had a median: age of 31.3 years (P25-75 = 24.3–41.9), EDSS of 1.5 (P25-75 = 1.0–2.5), disease duration of 4.3 years (P25-75 = 2.7–9.5), and DMT duration of 1.8 years (P25-75 = 0.008–7.4). No differences were found between pwMS on NTZ and HC on age ($U = 411.00$, $Z = -1.833$, $p = 0.067$) and sex ($\chi^2(1) = 0.123$, $p = 0.725$). At T1 and T2, both groups showed an efficient humoral response to BNT162b2 mRNA COVID-19 vaccine; the MANCOVA revealed a significant main effect of time ($\Lambda = 0.151$, $F(2,62) = 174.364$; $p < 0.001$) on Anti-TSP levels; the time * group interaction was not significant ($\Lambda = 0.952$, $F(2,62) = 1.570$; $p = 0.216$; see Fig. 1): levels of anti-TSP at T0 were significantly lower than those at T1 (I-J = −2.709, SE = 0.061) and T2 (I-J = −2.142, SE = 0.043), and levels of anti-TSP at T2 were significantly lower than those at T1 (I-J = −0.567, SE = 0.055). Regression analysis showed that

EDSS significantly predicted changes in anti-TSP IgG levels over time (beta = −0.515, $t = -2.943$, $p = 0.007$) in pwMS on the NTZ groups; in the HCs group, no significant predictors of change in anti-TSP IgG levels over time were found.

Discussion

The results of this study confirm and expand previous studies [1–3] by showing that pwMS on NTZ develop and maintain a 6-month humoral response after the first dose of a full COVID-19 vaccination cycle comparable to their healthy peers; moreover, we found that, in pwMS on NTZ, higher physical disability is associated with a lower humoral response over time. These findings are relevant for clinicians called to counsel about COVID-19 mRNA vaccine timing and booster doses in pwMS treated with NTZ. Of course, our study is not exempt from limitations: (a) B- and T-cell immunity was not assessed; (b) humoral response was assessed just to BNT162b2 mRNA COVID-19 vaccine; therefore, our results are not generalizable to other mRNA or viral vector vaccines; (c) our MS sample included mostly young patients with a relatively low physical disability and a short disease duration. Taken together our results provide evidence on the long-term humoral response to BNT162b2 mRNA COVID-19 vaccine in pwMS treated with NTZ, indicating that this high-efficacy DMT might not interfere with the ability to mount and maintain an efficient IgG response for at least 6 months.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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