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Humoral response to SARS-CoV-2 mRNA vaccine in patients with multiple sclerosis treated with natalizumab

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Since the worldwide launch of the SARS-CoV-2 vaccine campaign, there have been many uncertainties regarding the immune response to vaccination in patients with multiple sclerosis (pwMS), particularly those on high-efficacy disease-modifying therapies (DMTs).[1] Achiron and colleagues[2] for the first time investigated the short-term humoral response to COVID-19 mRNA vaccine in pwMS treated with high-efficacy DMTs, in particular ocrelizumab (OCR), fingolimod (FNG), and cladribine (CLD). The study results showed that pwMS on OCR and FNG have a blunted humoral response to mRNA vaccine; contrariwise, CLD-treated pwMS have an efficient humoral response. The study from Achiron and colleagues did not focus on the humoral response to BNT162b2 mRNA Covid-19 vaccine in pwMS treated with natalizumab (NTZ), another high-efficacy DMT largely used in multiple sclerosis (MS). NTZ binds to α4β1-integrin, inhibiting leukocyte migration into the central nervous system and thus reducing the MS-related inflammatory activity.[3] Since studies on humoral response to vaccines in NTZ-treated pwMS reported contrasting results,[4–8] two recent consensus have stated that there are no sufficient data to draw any definitive and generalizable conclusion regarding the efficacy of vaccines during treatment with NTZ.[9,10] Therefore, it is of paramount importance to assess the response to SARS-CoV-2 vaccines in NTZ-treated pwMS, especially in the presence of new vaccine platforms. On this background, we decided to investigate the humoral response to BNT162b2 mRNA Covid-19 vaccine in pwMS treated with NTZ and to compare it to age- and sex-matched healthy controls (HCs).

We collected serum samples before the first dose and 7 days after the second dose of the BNT162b2 mRNA Covid-19 vaccine from HCs and pwMS on NTZ with: (1) no history of Covid-19, (2) no positive SARS-CoV-2 IgG antibodies at baseline, (3) no steroid administration within the month before the first dose of vaccine. Sera were tested at virology laboratory of our University Hospital, using the LIAISON® SARS-CoV-2 TrimericS-IgG assay (DiaSorin-S.p.A.), for the detection of IgG antibodies to SARS-CoV-2 spike protein, including neutralizing antibodies.[11] The IgG titers were expressed in binding antibody units (BAU), with 33.8 BAU/mL as negative/positive cut-off.[12]

The local Ethics Committee (named 'Comitato Etico Università degli Studi della Campania Luigi Vanvitelli – Azienda Ospedaliera Universitaria Luigi Vanvitelli – AORN Ospedali dei Colli') approved the study that was performed in accordance with the principles of Helsinki Declaration (approval code: 0015914).

Statistical analysis was performed with Stata version 14.0 (StataCorp, College Station, TX).

Mild to moderate vaccine adverse reactions were commonly reported in HCs and pwMS, with rates expected in general population;[13] no serious or unexpected local and systemic side effects were observed in both groups. We did not observe post-vaccination MS worsening or relapses within 1 month after the second dose administration.

We screened 31 pwMS, and 26 were finally included in the analysis: 3 were excluded because

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of a history of Covid-19 and 2 for steroid administration within the month before the first dose of vaccine. We selected 31 HCs age- and sex-matched from a larger dataset of HCs enrolled in a surveillance program at our clinic.

NTZ-treated pwMS (14 females, 53.8%) showed a median age of 31.4 years (P25–75: 24.5–37.6), an Expanded Disability Status Scale (EDSS) of 1.5 (P25–75: 1–2.5), a disease duration of 55.9 months (P25–75: 33.3–117.5), median treatment duration of 27.03 months (P25–75: 8.23–45.1), and median time elapsed since last NTZ infusion of 17.5 days (P25–75: 5–23). Seven days after the second dose of the vaccine, SARS-CoV-2 IgG antibodies were detectable in all HCs and pwMS on NTZ. pwMS on NTZ mounted a humoral response (median, 3170 BAU/mL; P25–75: 1510–4960) similar to HCs (median, 1900 BAU/mL; P25–6: 1315–5142) ($p = 0.35$). No correlations were found between IgG titers measured 7 days after the second vaccine dose and (1) age, (2) disease duration, (3) body mass index (BMI), (4) EDSS, (5) treatment duration, and (6) days elapsed since last NTZ administration. No differences were found in IgG titers ($p = 0.59$) between pwMS on standard interval dose (every 4 weeks: 10 pwMS) and those on extended interval dose (every 6 weeks: 16 pwMS).

We observed an efficient short-term humoral response to BNT162b2 mRNA Covid-19 vaccine in pwMS treated with NTZ. These results are in line with studies showing an efficient humoral immune response to influenza and tetanus toxoid vaccines in pwMS on NTZ.[4,5] These findings are particularly relevant because humoral response to NTZ seems to be variable and dependent on the type of vaccine,[9,10] making it particularly important to test a vaccine developed on a new platform, such as the new Covid-19 mRNA-based vaccine.[14]

As for similar studies, the main limitations of this study were (1) the lack of assessment of the cell-mediated immune response, known to be essential in vaccine immunogenicity, and (2) the short-term follow-up.

In conclusion, this is the first report on the immunogenicity of BNT162b2 mRNA Covid-19 vaccine in pwMS treated with NTZ and integrates the study by Achiron and colleagues on OCR, FNG, and CLD.[2]

Our findings indicate that BNT162b2 mRNA Covid-19 vaccine in patients treated with NTZ is safe and yields a short-term humoral immune response comparable to that achieved in HCs, independent of demographic, clinical, and drug-related variables.

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Conflict of interest statement

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