Anti-Spike IgG in multiple sclerosis patients after BNT162b2 vaccine: An exploratory case-control study in Italy

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ARTICLE INFO

ABSTRACT

Background: Patients with neuroimmunological conditions such as multiple sclerosis (MS) often receive disease-modifying therapies (DMTs) or immunosuppressants which may reduce the response to vaccines. BNT162b2 (Pfizer-BioNTech) is the first COVID-19 vaccine authorized in Italy. Its clinical efficacy and serological response were not evaluated in MS patients receiving DMTs or immunosuppressants. This early multicenter study evaluated serological response to BNT162b2 and safety in these patients.
Methods: From February 2021 we enrolled consecutive MS patients, treated with at least one DMT and all healthcare workers (HCWs), having received or being scheduled to receive the first dose of BNT162b2. Blood samples were collected after the second vaccine dose and analyzed to quantitatively detect the presence of anti-Spike antibodies. Serological response was compared to the one from a control population of HCWs, with neither neuroimmunological conditions nor receiving immunosuppressants. Patients receiving treatments associated with a possible reduced response (Under-scrutiny treatment group) were also compared to those undergoing other treatments. Anti-Spike levels were described as median and interquartile range (IQR). Comparisons were performed with Wilcoxon-Mann-Whitney test. Solicited and unsolicited adverse events (AEs) were collected.
Results: 39 MS patients and a control population of 273 HCWs were included. One patient, under treatment with ocrelizumab, did not respond to BNT162b2, while all the remaining patients and all controls developed a serological response to the vaccine. Median anti-Spike levels were similar between patients (1471.0 BAU/ml; IQR 779.7 to 2357.0) and controls (1479.0 BAU/ml; IQR 813.1 to 2528.0) ($p = 0.53$). Patients included in the Under-scrutiny treatments group showed reduced anti-Spike levels (156.4 BAU/ml; IQR 33.4 to 559.1) compared to those receiving other treatments (1582.4 BAU/ml; IQR 1296.5 to 2219.0) ($p = 0.001$). Solicited AEs were all mild to moderate in severity, generally reported in the first days after vaccination, and resolved in the following days. Two MS patients reported a clinical relapse after the second vaccine dose.
Conclusion: BNT162b2 induced a serological response in MS patients treated with DMTs similar to controls not receiving DMTs or immunosuppressants. Some treatments were associated with reduced levels of anti-Spike antibodies in patients. These observations have relevant implications for treated patients receiving BNT162b2 and the community.

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1. Introduction

A new coronavirus (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19), became pandemic since December 2019, leading to more than 4.5 million deaths worldwide (Hopkins University and Medicine, 2021; World Health Organization, 2020; Wu et al., 2020). Novel vaccines against SARS-CoV-2 have been rapidly developed and authorized. BNT162b2 (Pfizer-BioNTech), was the first COVID-19 vaccine authorized in Italy in December 2020. BNT162b2 is an mRNA-based platform that induces the production of antibodies against the SARS-CoV-2 Spike protein (anti-Spike) and demonstrated high efficacy in preventing COVID-19 after two doses administered three weeks apart (Polack et al., 2020; Walsh et al., 2020). Vaccination against COVID-19 is currently recommended in patients with multiple sclerosis (MS) (| SIN | Società Italiana di Neurologia, 2021). Immunosuppressants or disease-modifying therapies (DMTs) used in MS and other immunological conditions may hamper the response to vaccines (Centonze et al., 2021; Ciotti et al., 2020). Clinical trials for BNT162b2 did not include subjects receiving DMTs or other immunosuppressants, and specifically, MS patients were not investigated (Polack et al., 2020; Walsh et al., 2020). An adequate response to vaccination against SARS-CoV-2 has relevant implications for patients and the whole community. The Italian COVID-19 vaccination campaign started on December 27th, 2020 and included subjects over the age of 80 years and healthcare workers (HCWs). We conducted a study to evaluate whether DMTs or immunosuppressants may reduce the serological response to BNT162b2 in treated MS patients, along with a safety analysis.

2. Methods

2.1. Study design and population

This is an exploratory, multicenter, case-control, prospective study to evaluate the ability of BNT162b2 to induce the production of anti-Spike IgG antibodies and its safety in MS patients receiving DMTs. From February 2nd to April 2nd, 2021, consecutive HCWs with MS followed at three participating centers in Italy (Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milano; I.R.C.C.S. Fondazione Mondino, Pavia; Azienda Ospedaliera Policlinico Umberto I, Roma) were enrolled in the study. Inclusion criteria were: having a diagnosis of MS; ongoing treatment with at least one DMT or immunosuppressant; having received or being scheduled to receive the first dose of BNT162b2. Participants were 18 years or older and provided written informed consent. The study duration was nine weeks starting from the first vaccine administration. We compared patients' serological response to that of a control population of HCWs employed by the Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta. Controls received BNT162b2 according to the same schedule; gave consent to the use of anonymized biological and clinical data for research purposes; had available data on comorbidities and current medications. Controls treated with any DMTs or immunosuppressants, affected by any autoimmune (except for immune hypothyroidism) or neuroimmunological condition, or without available clinical data were excluded. The study received approval from the institutional review boards of each center. The STROBE statement was followed in the drafting of this manuscript.

2.2. Collected variables and study outcomes

Sociodemographic and clinical data were collected, including age, sex, time of disease onset and diagnosis, Expanded Disability Status Scale (EDSS), comorbidities, concomitant medications, the current DMTs or immunosuppressants with starting date, the last administration date of depletant DMTs, and history of previous confirmed COVID-19 (by nasal swab polymerase chain reaction and/or serological test). Data on total lymphocytes counts were collected from the latest available total blood count before vaccine administration and the presence of

lymphopenia was coded according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). At the end of the study, all patients completed a questionnaire regarding adverse events (AE) after the first and the second dose of BNT162b2. Solicited AEs included site injection reactions (pain, erythema, swelling), dysesthesia in the injected arm, lymph nodes swelling, cutaneous rash, diffuse pruritus, headache, chills or malaise, fever, fatigue, anosmia/dysgeusia, diffuse muscular or articular pain, nausea, abdominal pain, diarrhea, insomnia, and sweating. Participants were asked about previous contacts with confirmed COVID-19 cases and the risk of exposure in the work setting. Spontaneously referred AEs, including MS relapses, were also collected.

The primary outcomes of the study were the serological response to BNT162b2 and the comparison of anti-Spike levels between patients and the control population. The serological response was also evaluated by distinguishing patients and controls on the basis of previous confirmed COVID-19. Secondary outcomes were the description of serum anti-Spike levels for each DMT and the comparison between patients receiving any DMT associated with a possible reduced response to BNT162b2 (Under-scrutiny treatments group), according to available literature and expert consensus (Centonze et al., 2021; Ciotti et al., 2020), and those receiving other DMTs (Other treatments group). Only patients without a history of COVID-19 were included in the analysis of secondary outcomes. Safety was evaluated by including all AEs reported by patients.

2.3. Biological analyses

Blood samples were collected once from the second to the sixth week after the second BNT162b2 dose (end of study). Blood was collected in serum tubes without anticoagulants, left to coagulate at room temperature for 30 minutes, and centrifuged at 4 °C 1800xG for 10 min. Sera were transferred to clean vials and stored at -20 °C pending analysis. Samples were analyzed with SARS-CoV-2 IgG II Quant (Abbott) on the Architect instrument (Abbott) to quantitatively and qualitatively detect IgG antibodies against the Spike protein S1 receptor-binding domain (RBD). Antibody Units per ml were converted into WHO binding antibody units (BAU/ml), according to the manufacturer's indications. A threshold of at least 7.1 BAU/ml was the cut-off for a positive response to immunization. Samples were also tested qualitatively for the presence of IgGs against the nucleocapsid antigen (anti-N) to verify a possible previous asymptomatic SARS-CoV-2 infection.

2.4. Statistical analyses

Continuous variables were reported as median and interquartile range (IQR) while categorical variables were reported as frequency and percentage. Normality of experimental data (anti-Spike) was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Anti-Spike levels between patients and controls and between subgroups were compared with the Wilcoxon-Mann-Whitney test. $P < 0.05$ was considered statistically significant. Analyses were performed using Stata 15.1 software and charts were created using Prism Graphpad.

3. Results

3.1. Serological response after BNT162b2 in patients and controls

A total of 39 MS patients were enrolled. All patients received two vaccine doses, as scheduled, had relapsing-remitting MS, and were treated with DMTs for MS. The control group consisted of 273 subjects. Patients and controls characteristics are detailed in **Table 1,** **Supplement S1,** and **Table S1**. Four patients reported a history of COVID-19. All of them tested negative for anti-N and reported having had confirmed SARS-CoV-2 infection in the period between March and July 2020.

38 MS patients showed a serological response to BNT162b2, with

anti-Spike levels ranging from 26.34 to > 5680.00 BAU/ml. One 29 years old female, treated with ocrelizumab from May 2019, did not respond to the vaccine and showed a serum anti-Spike level of 1.8 BAU/ml (**Fig. 1A** and **B**). She received the last ocrelizumab infusion in November 2020, three months before the first vaccine dose. Further characterization of patients receiving ocrelizumab is provided in **Supplement S2**. All controls achieved response to BNT162b2.

No significant difference in median anti-Spike levels was observed between patients and controls ($p = 0.53$) (**Table 2**). Patients and controls with a history of COVID-19 had higher median anti-Spike levels compared to those without previous COVID-19, albeit the difference was statistically non-significant among patients ($p = 0.12$ and $p < 0.001$ for patients and controls, respectively) (**Fig. 1A** and **Table 2**).

The description of anti-Spike levels for each different DMT in patients without a history of COVID-19 is provided in **Fig. 1B** and **Table 3**. The Under-scrutiny treatments subgroup included 8 patients treated with fingolimod, ocrelizumab, or natalizumab at the time of vaccination. The Other treatments group included 27 patients; among them, 3 patients (1 alemtuzumab and 2 cladribine) were not included in the Under-scrutiny treatments group because their last DMT administrations dated back to September 2019, July 2020, and October 2019, respectively, and they did not have lymphopenia at the time of vaccination (Centonze et al., 2021; Ciotti et al., 2020). Patients in the Under-scrutiny treatments group showed reduced anti-Spike levels (156.4 BAU/ml; IQR 33.4 to 559.1) compared to those included in the Other treatments group (1582.4 BAU/ml; IQR 1296.5 to 2219.0) ($p = 0.001$) (**Fig. 1C**).

3.2. Safety evaluation

37 patients completed the questionnaire at the end of the study (response rate of 94.9%); 33 (89.2%) and 36 (97.3%) of them reported at least one solicited AE after the first or the second dose, respectively. These AEs were all mild to moderate, generally started the same day or the day after the vaccination, and resolved in the following days. After both doses, the two most frequent AEs were pain in the site of injection and fatigue. AEs interfering with working or daily activities were more frequent after the second dose. Medications for AEs were more frequently used after the second dose, with paracetamol being the most used medication, followed by non-steroidal anti-inflammatory drugs (**Table S2**). No COVID-19 cases were reported during the follow-up after the first vaccine dose.

Six patients reported other AEs (15.4%). One patient showed increased transaminases levels after the first vaccine dose. The event was considered unrelated to the vaccine because increased liver enzymes were present before the first BNT162b2 dose since he started dimethyl fumarate in November 2020, and values returned to normal after dimethyl fumarate discontinuation. One patient, affected by essential thrombocythemia, suffered a presyncope the evening after the second vaccine dose while having fever. The AE resolved without intervention. One patient, treated with dimethyl fumarate since 2019, reported the worsening of pre-existing dermatitis about 10 days after the second vaccine dose; dermatitis resolved with topical steroids. Another patient, in treatment with interferon, reported hot flashes in the two days following the second dose; the AE recovered spontaneously without treatment. Two patients (5.1%) had an MS relapse during the study follow-up. One patient experienced a clinical and radiological relapse about one month after the second vaccine dose, with spontaneous recovery. The other presented with new contrast-enhancing lesions at a routine follow-up MRI four days after the first dose and she also experienced a clinical relapse 17 days after the second dose. The patient received methylprednisolone with clinical improvement. A causal relationship between the vaccine administration and the MS relapses could not be established. Further description of relapses is provided in **Supplement S3**.

4. Discussion

We evaluated the serological response to BNT162b2 in MS patients, all HCWs, treated with DMTs or immunosuppressants. A comparison with a control population, not receiving any DMTs or immunosuppressants, showed comparable anti-Spike levels. All controls and the majority of MS patients demonstrated a positive serological response to the vaccination, except for one treated with ocrelizumab. Ocrelizumab is an anti-CD20 monoclonal antibody that can reduce the efficacy of vaccines (Centonze et al., 2021; Ciotti et al., 2020). Recently, a patient receiving ocrelizumab for relapsing-remitting MS, who did not respond to BNT162b2 vaccination and developed COVID-19, has been reported (Chilimuri et al., 2021). Moreover, non-response to BNT162b2 has been reported in a patient vaccinated two months after ocrelizumab infusion (Buttari et al., 2021). In our study, the patient who did not respond to BNT162b2 received ocrelizumab three months before the first vaccine dose. The other two responders treated with ocrelizumab received their last infusion about three and five months before the first vaccine injection, in line with indications for vaccine administration in patients receiving ocrelizumab (Centonze et al., 2021).

Even though almost all MS patients had anti-Spike levels comparable to untreated controls, some DMTs were associated with lower anti-Spike levels. MS patients included in the Under-scrutiny treatments group (DMTs possibly associated with reduced response to BNT162b2; fingolimod, ocrelizumab, natalizumab), demonstrated significantly lower anti-Spike levels compared to those included in the Other treatment group. Interestingly, an observational study comparing untreated MS patients to patients treated with fingolimod, ocrelizumab, or cladribine, reported reduced anti-Spike levels after BNT162b2 in patients receiving ocrelizumab or fingolimod. Conversely, cladribine-treated patients demonstrated anti-Spike levels comparable to untreated MS patients and healthy controls (Achiron et al., 2021b). In comparison, albeit limited by the small sample size, the serological response rate in our patients treated with ocrelizumab was superior, showing a positive serological

Table 1
Study population characteristics

	MS ($n = 39$)	Controls ($n = 273$)
Age, y, median (IQR)	43 (31–53)	46 (38–55)
Female, n (%)	30 (76.9)	195 (71.4)
History of COVID-19, n (%)	4 (10.3)	43 (15.8)
Time of blood sample after the second dose, d, median (IQR)	24 (14–31)	30 (25–47)
Time from disease onset, y, median (IQR)	10.6 (4.7–17.6)	-
Time from disease diagnosis, y, median (IQR)	8.6 (4.3–15.4)	-
EDSS, score, median (IQR)	1 (1–2)	-
Current DMT or immunosuppressant, n (%)		
Dimethyl fumarate	15 (38.5)	-
Fingolimod	5 (12.8)	-
Teriflunomide	5 (12.8)	-
Interferons	4 (10.3)	-
Glatiramer acetate	3 (7.7)	-
Ocrelizumab	3 (7.7)	-
Cladribine	2 (5.1)	-
Alemtuzumab	1 (2.6)	-
Natalizumab	1 (2.6)	-
Current DMT or immunosuppressant duration, y, median (IQR)	3.1 (1.4–4.7)	-
Lymphopenia, n (%)		
No	30 (76.9)	-
Grade 1	4 (10.3)	-
Grade 2	1 (2.6)	-
Grade 3	2 (5.1)	-
Not available	2 (5.1)	-
Follow-up for AEs, w, median (IQR)	9.4 (9.0–11.6)	-

MS = multiple sclerosis; IQR = interquartile range; DMT = disease modifying therapies.
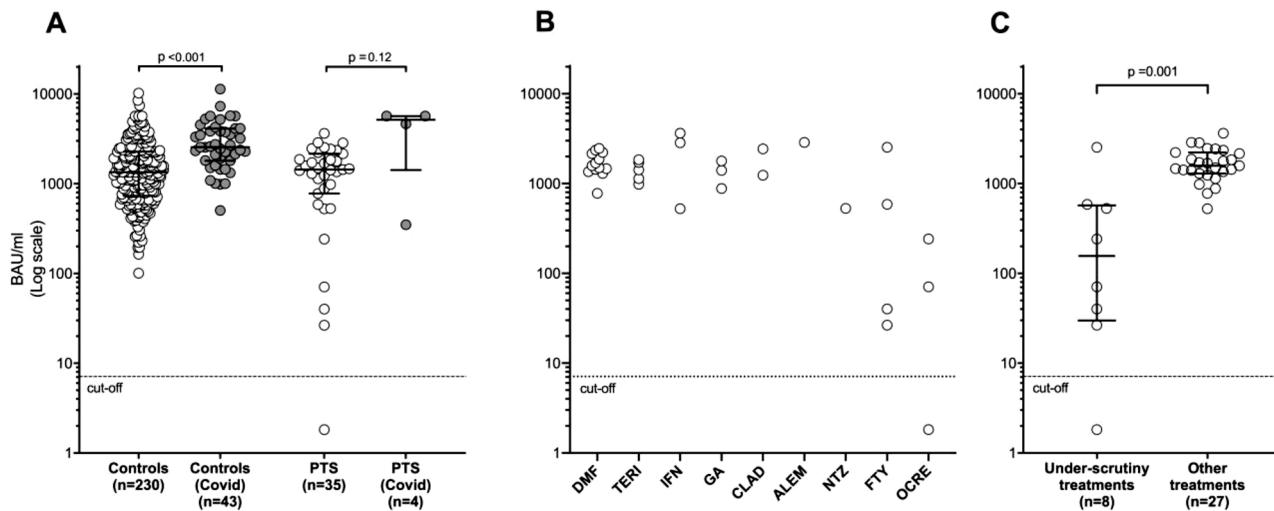
Fig. 1. Anti-Spike IgG levels. (A) Comparison of Anti-Spike IgG levels in MS patients and controls with and without a history of COVID-19. (B) Description of anti-Spike IgG levels by treatment received in patients without a history of COVID-19. (C) Anti-Spike IgG levels in patients without a history of COVID-19 receiving under-scrutiny treatments compared to those receiving other treatments. Under-scrutiny treatments include fingolimod, ocrelizumab, and natalizumab. Other treatments group include dimethyl fumarate, teriflunomide, interferons, glatiramer acetate, cladribine, and alemtuzumab. Statistical analyses were performed with the Wilcoxon-Mann-Whitney test. The cut-off for response is set at 7.1 BAU/ml. Colored circles represent subjects with a history of COVID-19. Abbreviations: MS=multiple sclerosis; PTS=patients; DMF=dimethyl fumarate; TERI=teriflunomide; IFN=interferons; GA=glatiramer acetate; CLAD=cladribine; ALEM=alemtuzumab; NTZ=natalizumab; FTY=fingolimod; OCRE=ocrelizumab.

Table 2
Comparison of serological response between patients and controls

	Controls ($n = 273$)	MS ($n = 39$)	Test for significance
Overall population	1479.0 (813.1–2528.0)	1471.0 (779.7–2357.0)	$p = 0.53$
History of COVID-19, no, n	230/273	35/39	
	1346.0 (731.0–2279.0)	1436.5 (779.7–2163.4)	$p = 0.75$
History of COVID-19, yes, n	43/273	4/39	
	2561.0 (1807.0–4124.0)	5161.0 (1423.0–5680.0)	$p = 0.30$

Comparison of anti-Spike IgG levels between MS patients and controls. Analyses were repeated dividing participants by a history of confirmed COVID-19. Measures are expressed in BAU/ml as median (IQR).
MS = multiple sclerosis; IQR = interquartile range.

response to BNT162b2 in 2 out of 3 patients treated with ocrelizumab. Conversely, despite developing lower anti-Spike levels compared to patients receiving other DMTs, our patients treated with fingolimod had

a superior response rate (Achiron et al., 2021b). In our study, the three patients treated with alemtuzumab or cladribine developed anti-Spike levels comparable to those in the Other treatment group. All patients treated with alemtuzumab or cladribine received their last administration more than six months before the vaccination and had normal blood lymphocyte count.

Hence, our data confirm the observation that ocrelizumab and fingolimod could hamper immune response to BNT162b2 in MS patients (Achiron et al., 2021b). We also confirm that it is advisable to vaccinate MS patients treated with alemtuzumab at least six months after the drug infusion and that patients treated with cladribine should wait for at least four weeks or a complete lymphocyte count recovery before receiving the vaccination (Centonze et al., 2021; Ciotti et al., 2020). Also, our results confirm data from previous studies on the response to other non-COVID-19 vaccines in MS patients receiving DMTs (Ciotti et al., 2020).

It is important to underline that the presence of a serological response does not assure clinical efficacy, since a validated anti-Spike cut-off for efficacy after vaccination against COVID-19 is not yet available. Thus, subjects classified as responders but having lower anti-Spike levels may not be protected against SARS-CoV-2 infection.

In our study, patients and controls with a history of COVID-19 showed increased anti-Spike levels compared to those without a

Table 3
Serological response for each study treatment

Current DMT or immunosuppressant	n	Anti-Spike IgG, BAU/ml, median (IQR)	Lymphopenia, n (%)				
			No	Grade 1	Grade 2	Grade 3	NA
Dimethyl fumarate	13	1582.4 (1436.5–2163.4)	9 (75.0)	3 (25.0)	0	0	1 (6.7)
Fingolimod	4	314.2 (33.4–1561.0)	1 (25.0)	1 (25.0)	0	2 (50.0)	0
Teriflunomide	5	1422.0 (1134.6–1721.4)	5 (100.0)	0	0	0	0
Interferons	3	2852.7 (525.8–3634.4)	3 (100.0)	0	0	0	0
Glatiramer acetate	3	1400.3 (881.0–1785.2)	2 (66.7)	0	0	0	1 (33.3)
Ocrelizumab	3	70.8 (1.8–242.0)	3 (100.0)	0	0	0	0
Cladribine	2	1835.0 (1237.2–2432.8)	2 (100.0)	0	0	0	0
Alemtuzumab	1	2878.1 (NA)	1 (100.0)	0	0	0	0
Natalizumab	1	530.0 (NA)	1 (100.0)	0	0	0	0

Description of anti-Spike levels in patients without a history of COVID-19 grouped by different DMT. Lymphopenia is graded according to CTCAE v5.0.
DMT = disease modifying therapies; IQR = interquartile range; NA = not available/not applicable.

history of COVID-19. The difference was statistically significant only in the control group. The possible explanation for this finding is the small sample size of the patients group and the even lower number of patients with a history of COVID-19.

Consistently with pivotal trials for BNT162b2 and a recent observational study in MS, BNT162b2 was well tolerated in our patients (Achiron et al., 2021a; Polack et al., 2020; Walsh et al., 2020). The majority of patients reported at least one solicited AE after the first and the second dose, similarly to what was observed in pivotal trials (Polack et al., 2020; Walsh et al., 2020). Compared to our results, a recent study reported fewer AEs, possibly due to the different data collection methods (Achiron et al., 2021a).

In our study, two patients experienced a clinical MS relapse after the second dose but establishing causality between the vaccination and these two events was not possible. Vaccination with BNT162b2 was not associated with an increased rate of clinical MS relapses in 555 MS patients in Israel (Achiron et al., 2021a). We reported a slightly superior occurrence of MS relapses. However, our longer follow-up period and our limited sample size could have led to overestimating the occurrence of MS relapses.

Regarding the limitations of our study, pre-vaccination blood samples were not collected and this could have limited our accuracy in identifying patients with previous asymptomatic or unconfirmed SARS-CoV-2 infection. To overcome this problem, we collected information on the history of confirmed COVID-19 and tested all patients for anti-N to exclude a previous SARS-CoV-2 infection, reducing the potential bias magnitude. In addition, since the objective of this exploratory study was to determine the presence of a response to BNT162b2, the effects of this bias would be limited. We did not evaluate the duration of serological response, which might be prematurely reduced in patients receiving DMTs or immunosuppressants, and we could not evaluate unsolicited AEs in a longer period. Another limitation of our early study is that we did not assess cellular immunity. However, this was a preliminary study on serological response, without the power and the design to identify differences in AE reporting, and a power analysis to estimate a minimum sample size was not performed.

5. Conclusion

In conclusion, BNT162b2 induced a serological response in the majority of our MS patients treated with DMTs or immunosuppressants, with anti-Spike levels similar to controls without neuroimmunological conditions and not receiving immunosuppressants. Nevertheless, the possibility of a reduced or absent response to BNT162b2 still exists in patients treated with some DMTs, suggesting the need for well-powered, long-term, studies to assess the safety and efficacy of BNT162b2 in this category of patients as well as the duration of the protection against COVID-19. This is of utmost importance since the COVID-19 pandemic could become an endemic disease, requiring periodic re-vaccination.

CRediT authorship contribution statement

Riccardo Giossi: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Alessandra Consonni:** Investigation, Resources. **Valentina Torri Clerici:** Investigation. **Antonio Zito:** Investigation, Writing – review & editing. **Eleonora Rigoni:** Investigation. **Carlo Antozzi:** Investigation, Writing – review & editing. **Laura Brambilla:** Investigation, Writing – review & editing. **Sebastiano Giuseppe Crisafulli:** Investigation, Writing – review & editing. **Antonella Bellino:** Investigation. **Rita Frangiamore:** Investigation. **Silvia Bonanno:** Investigation. **Fiammetta Vanoli:** Investigation. **Emilio Ciusani:** Investigation, Resources. **Elena Corsini:** Investigation, Resources. **Francesca Andreetta:** Investigation, Resources. **Fulvio Baggi:** Investigation, Formal analysis, Writing – review & editing. **Irene Tramacere:** Methodology, Writing – review & editing. **Renato Mantegazza:** Investigation, Writing – review & editing. **Antonella Conte:**

Investigation, Writing – review & editing, Supervision. **Roberto Bergamaschi:** Investigation, Writing – review & editing, Supervision. **Paolo Confalonieri:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

CRediT authorship contribution statement

Riccardo Giossi: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Alessandra Consonni:** Investigation, Resources. **Valentina Torri Clerici:** Investigation. **Antonio Zito:** Investigation, Writing – review & editing. **Eleonora Rigoni:** Investigation. **Carlo Antozzi:** Investigation, Writing – review & editing. **Laura Brambilla:** Investigation, Writing – review & editing. **Sebastiano Giuseppe Crisafulli:** Investigation, Writing – review & editing. **Antonella Bellino:** Investigation. **Rita Frangiamore:** Investigation. **Silvia Bonanno:** Investigation. **Fiammetta Vanoli:** Investigation. **Emilio Ciusani:** Investigation, Resources. **Elena Corsini:** Investigation, Resources. **Francesca Andreetta:** Investigation, Resources. **Fulvio Baggi:** Investigation, Formal analysis, Writing – review & editing. **Irene Tramacere:** Methodology, Writing – review & editing. **Renato Mantegazza:** Investigation, Writing – review & editing. **Antonella Conte:** Investigation, Writing – review & editing, Supervision. **Roberto Bergamaschi:** Investigation, Writing – review & editing, Supervision. **Paolo Confalonieri:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

R.G. received support for congress participation from Mylan. A.C. has nothing to disclose. V.T.C. acted as an Advisory Board member of Biogen Idec, Novartis, Merck, Roche, Genzyme, and Almirall and received funding for traveling and honoraria for speaking or writing from Teva, Novartis, Genzyme, and Almirall. She received support for research project by Almirall. A.Z. has nothing to disclose. E.R. received support for travel and congress from Merck-Serono, Sanofi-Genzyme. C. A. received funding for congress participation from Biogen. L.B. received honoraria for speaking from Novartis and for traveling from Sanofi-Genzyme and Roche; for Advisory Board from Sanofi-Genzyme, Biogen, and Novartis and is involved as principal investigator in clinical trials for Roche, Merck-Serono, and Novartis. S.G.C. has nothing to disclose. A.B. has nothing to disclose. R.F. received support for congress participation from Argenx, Biogen, Catalyst, Merck, Momenta, Novartis, and Sanofi Genzyme. S.B. has nothing to disclose. F.V. received support for congress participations from Biogen, Kedrion, and Sanofi Genzyme. E.C. has nothing to disclose. E.C. has nothing to disclose. F.A. has nothing to disclose. F.B. received honoraria from Immunovant and Prescript. I.T. has nothing to disclose. R.M. received fees and honoraria for meeting, travel, and advisory board from Alexion, Argenx, Biomarin, Catalyst, Merck Serono, UCB. A.C. has served on scientific advisory boards for Merck-Serono, Sanofi-Genzyme, Biogen, Novartis, Almirall. She has received institutional research support from Roche and Biogen. R.B. has served on scientific advisory boards for Biogen, Merck-Serono, Novartis, Sanofi-Genzyme; he received research support from Almirall, Bayer, Biogen, Merck- Serono, Novartis, Sanofi-Genzyme; he received support for travel and congress from Biogen, Roche, Merck-Serono, Sanofi-Genzyme, Teva; received honoraria for speaking engagement from Biogen, Merck-Serono, Novartis, Sanofi-Genzyme. P.C. received honoraria for speaking or consultation fees from Novartis and Biogen, funding for travel to attend scientific events, or speaker honoraria from Merck Serono, Biogen Idec, Teva, and Roche. He received institutional research support from Merk-Serono, Novartis, and Roche.

Study funding

This study was supported by Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103415.

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