Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Correspondence

Humoral response after the booster dose of anti-SARS-CoV-2 vaccine in multiple sclerosis patients treated with high-efficacy therapies

ARTICLE INFO

Keywords
Multiple sclerosis
Anti-SARS-CoV2 vaccine
Booster
Third dose

ABSTRACT

Anti-SARS-CoV2 mRNA vaccines showed a blunted antibody (Ab) response in people with MS (pwMS) on high efficacy therapies, suggesting the need for a booster dose. We evaluated the kinetics of the production of anti-receptor binding domain (RBD) Immunoglobulins G (IgG) after the vaccination cycle and the booster in pwMS receiving ocrelizumab, fingolimod and cladribine. A significant increase of anti-RBD IgG seroconversion was observed after booster respect to the vaccination cycle. Results obtained from this study will be useful for the management of pwMS in relation to their disease modifying therapy (DMT) and for any future vaccination campaign.

1. Introduction

Vaccination is indispensable to protect vulnerable people with MS (pwMS) from Coronavirus disease 2019 (COVID-19). Unfortunately, high-efficacy disease modifying therapies (DMTs) can interfere with immune response to anti-SARS-CoV-2 vaccination in pwMS through different mechanism of action: ocrelizumab depletes B cells by targeting CD20 and thereby may interfere in the process of antibody (Ab) production; fingolimod prevents lymphocyte egression from secondary lymphoid tissues by modulating SPI; the purine analogue cladribine selectively suppress T and B cells inducing severe lymphopenia (Achiron et al., 2021b). A blunted anti-Spike (S) Ab response elicited by anti-SARS-CoV-2 mRNA vaccines has been observed in pwMS treated with ocrelizumab and fingolimod, while cladribine showed an efficient Ab response (Achiron et al., 2021b, 2021a; Bigaut et al., 2021; Drulovic et al., 2021; Sormani et al., 2021). Despite the low Ab response following vaccination, discontinuation of highly effective DMTs has not been recommended due to the high risk of relapse (Giovannoni et al., 2021) and a booster dose was recommended. To date, data on booster have shown an adequate safety profile with a comparable adverse event incidence between the first vaccination cycle and booster (Dreyer-Alster et al., 2022). IgG levels increase after booster in untreated and treated patients (Dreyer-Alster et al., 2022), but data on B-depleting therapies and S1P modulators are not currently available. Here, we evaluated the effects of the booster in pwMS under high-efficacy treatments by measuring anti-receptor-binding domain (RBD) IgG titers, that can be considered as neutralizing Abs (nAb).

2. Methods

2.1. Patients

Subjects were recruited according to the following inclusion/exclusion criteria. Inclusion criteria: subjects diagnosed with MS according to the most recently revised Mc Donald’s criteria and eligible for anti-SARS-CoV2 vaccination. Exclusion criteria: any medical condition that did not allow the signing of informed consent. This study obtained ethics approval from the ethics committee of AOU San Luigi Gonzaga, Orbassano (TO), Italy; Ref. number #117-2021.

2.2. Serum collection

Sera were collected immediately before the first dose of Comirnaty vaccine (Pfizer/BioNTech Inc, BioNTech Manufacturing GmbH) (T0), 4 weeks (±7 days) after the first two doses of anti-COVID-19 vaccination (T1), before booster shot (6 months after vaccination ±15 days) (T6) and 4 weeks (±7 days) after booster (B) shot of Comirnaty or Spikevax vaccine (Moderna, Moderna Biotech Spain S.L.).

2.3. Anti-RBD IgG quantification

Anti-SARS-CoV-2 nAbs were measured with the SARS-CoV-2 RBD IgG ELISA (EIA-6150, RGD Diagnostic; lot number 142K061). Plates were read using iMark™ Microplate reader (Bio-Rad). Results were expressed in IU/ml (log10), and the cut-off threshold corresponded to 1.4 IU/ml (log10), according to manufacturer indications.

2.4. Statistical analysis

Anti-RBD IgG levels were compared between each DMT group using analysis of variance (ANOVA) test. Adjusted P-value cutoffs of p<0.05 indicated statistical significance. Data analyses were performed using Graphpad Prism version 8.2.1 (2019-08-18). A linear regression model, using R version 3.6.0 (2019-04-26), was used to compare IgG titers after booster considering age, sex, type of MS, EDSS, DMT, time between DMT and booster, type of booster (Comirnaty/Spikevax), lymphopenia grade (obtained from last total lymphocytes count within 3 months before booster) and pre-booster Ab levels.
Multiple Sclerosis and Related Disorders 61 (2022) 103776

3. Results

A total of 31 subjects were recruited (12 on ocrelizumab, 12 on fingolimod and 7 on cladribine) and prospectively followed-up for 8 months. The demographic and clinical data of pwMS participating in this study are shown in Table 1. COVID-19 disease was not reported from any of the subjects before vaccination, whereas 5 pwMS (1 on cladribine and 4 on ocrelizumab) had SARS-CoV-2 infection after the booster (median (IQR): 102 (57; 105) days) with mild symptoms and no hospitalization. The evaluation of anti-RBD Abs in the sera indicated that 85.7% of pwMS under cladribine, 41.6% under fingolimod, and 16.6% under ocrelizumab treatment seroconverted after the first vaccination cycle. The booster increased the percentage of pwMS that seroconverted to 100%, 75%, and 58.3%, respectively, showing an Ab response that, although attenuated, was above the cut-off value (Fig. 1).

Furthermore, the levels of anti-RBD IgG after booster were higher respect to T6 where the nAb levels decreased (Cladribine T6 vs B, p = 0.014; Fingolimod T6 vs B, p = 0.025; Ocrelizumab T6 vs B, p = 0.010). By exploring the association of variables to post-booster nAb titers, we observed association with pre-booster nAb titers (coefficient = +0.52; p = 0.013) and the Spikevax booster (coefficient = 0.83; p = 0.09).

4. Discussion

Here we evaluated anti-RBD IgG titers after booster in pwMS under high-efficacy treatments. The additional dose of anti-SARS-CoV-2 mRNA vaccine induced seroconversion of the majority of pwMS on fingolimod and ocrelizumab and of the totality of patients treated with cladribine, indicating that a booster dose could be fundamental in those pwMS that did not develop nAbs after the first vaccination cycle. A drop of nAbs have been shown within six months after the first vaccination cycle (Levin et al., 2021). Although a trend was visible, we did not observe a significant decay in anti-RBD IgG levels at six months, possibly due to a reduced response at one month after vaccination (Levin et al., 2021). Multivariate regression showed higher post-booster nAb titers in pwMS that had more pre-booster nAb titers, and a likely greater efficacy of Spikevax than Comirnaty, as already observed after the first vaccination course in pwMS (Sormani et al., 2021). This could be due to the different dosage (Comirnaty booster contains 30 µg of mRNA while Spikevax booster 50 µg of mRNA) or to heterologous vaccination. The 4 out of 5 SARS-CoV-2 infections observed after the booster occurred in pwMS under high-efficacy DMTs, with a different pattern of antibody response.

Table 1
Clinical characteristics. Results are expressed as Median and Inter-quartile range (IQR).

|                      | Cladribine | Fingolimod | Ocrelizumab |
|----------------------|------------|------------|-------------|
| Patients             | 7          | 12         | 12          |
| Age                  | 49 (43.5; 53.5) | 50.5 (46.3; 56.50 (52.5; 60.3) |
| Female/male          | 5/2        | 10/2       | 10/2        |
| RRMS/SPMS            | 6/1        | 8/4        | 9/3         |
| EDSS                 | 3 (2; 4.8) | 2.25 (2; 6.5) | 5 (1; 6.1) |
| MS disease duration (years) | 9 (5; 14) | 18.5 (9.3; 24) | 10 (8.3; 22) |
| COVID-19 infections before vaccination | no         | no         | no          |
| COVID-19 infections after vaccination | no         | no         | no          |
| COVID-19 infections after booster dose | 1/7        | no         | 4/12        |
| Relapses between vaccination and booster dose | no         | no         | no          |
| Time between vaccination and booster (days) | 161 (161; 180) | 165 (165; 180) | 207 (165; 216) |
| Time between therapy and booster dose (days) | 192 (161; 302.5) | N.A. | 138 (104.8; 220) |
| Booster type (Spikevax/Comirnaty) | 3/4        | 4/8        | 3/9         |
| Lymphopenia grade within 3 months before booster* | 1 (0.5; 2) | 2 (2; 2) | 0 (0; 1) |

*Grade 3 = 200-499 lymphocytes/ul; grade 2 = 500-799 lymphocytes/ul; grade 1 = 800-999 lymphocytes/ul; grade 0 >1000 lymphocytes/ul

Fig. 1. Anti-RBD IgG titers before the first cycle of vaccination (T0), 4 weeks after (T1), 6 months after (T6), and 4 weeks after booster dose (B) in pwMS under high-efficacy DMTs. Dotted line corresponds to cut-off threshold of 1.4 IU/ml (log10). Asterisks correspond to p-values of ANOVA test (P < 0.0001****; P < 0.0002***; P < 0.002**; P < 0.03*).
treated with ocrelizumab that did not develop nAbs after the booster, accounting for the role of Ab response in preventing infections (Sette and Crotty, 2021). However, they efficiently eliminate the infection probably due to a preserved functionality of innate and T cells response (Giovannoni et al., 2021). Overall, the results reported in this study confirmed that cladribine treatment does not compromise the development of a specific humoral response, as previously observed (Achiron et al., 2021b; Dreyer-Alster et al., 2022); for ocrelizumab and fingolimod, a significant Ab response can be achieved with further vaccinations. Studies in larger cohorts, together with B and T cell-mediated responses profiling, will be needed to better clarify the effect of vaccination booster in pwMS in relation to their DMT and for any future vaccination campaign.

Author contribution statement

AM performed immunological experiments and wrote the manuscript; both MoM and RM recruited patients in the study and MoM contributed to sample preparation; MaM retrieved clinical data of recruited patients and performed clinical data analysis; MC conceived the study design and supervised immunological experiments planning and analysis; SR conceived the study design and supervised immunological experiments planning and analysis.

Declaration of Competing Interests

AM, MoM, RM and MaM have nothing to disclose; SR received travel grant from Sanofi-Genzyme; MC received personal compensations for advisory boards, public speaking, editorial commitments or travel grants. Gurevich, M., Achiron, A., 2021b. Humoral immune response to SARS-CoV-2 in patients with multiple sclerosis treated with anti-SARS-CoV-2 antibodies: an observational study. Neurol. Neuroinflamm. 8 https://doi.org/10.1212/WNL.0000000000001055.

Dreyer-Alster, S., Menascu, S., Mandel, M., Shirbint, E., Magalashvili, D., Dolev, M., Flechter, S., Givon, U., Guber, D., Stern, Y., Siron, M., Polliaic, M., Falh, R., Sonis, P., Gurevich, M., Achiron, A., 2022. COVID-19 vaccination in patients with multiple sclerosis: safety and humoral efficacy of the third booster dose. J. Neuro. Sci. 434, 120155 https://doi.org/10.1016/j.jns.2022.120155.

Drolovic, J., Ivanovic, J., Martinovic, V., Taman, O., Veselinovic, N., Cucij, D., Gnjatovic, M., Mesaros, M., Pekmenovic, T., 2021. Humoral response to SARS-CoV-2 COVID-19 vaccines in patients with multiple sclerosis treated with immune reconstitution therapies. Multiple Sclerosis Relat. Disord. 54, 103150 https://doi.org/10.1016/j.msard.2021.103150.

Giovannoni, G., Hawkes, C.H., Lechner-Scott, J., Levy, M., Yeh, E.A., Baker, D., 2021. COVID-19 vaccines and multiple sclerosis disease-modifying therapies. Mult. Scler. Relat. Disord. 53, 103155 https://doi.org/10.1016/j.msard.2021.103155.

Levin, E.G., Lustig, Y., Cohen, C., Fluss, R., Indenbaum, V., Amit, S., Doolman, R., Assraf, K., Mendelson, E., Ziv, A., Rubin, C., Freedman, L., Kreies, Y., Yeger-Yochay, G., 2021. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 Months. N. Engl. J. Med. NEJMoa. 2114583. https://doi.org/10.1056/NEJMoa2114583.

Sette, A., Crotty, S., 2021. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 184, 861–880. https://doi.org/10.1016/j.cell.2021.01.007.

Sormani, M.P., Schiavetti, I., Carmisciano, L., Sormani, M.P., Inglese, M., Laroni, A., Lapucci, C., Ucelli, A., Inglese, M., Lapucci, C., Ucelli, A., Da Rin, G., Serrati, C., Gandoglia, I., Tassinari, T., Perego, G., Bricchetto, G., Gazzola, P., Mannironi, A., Stromillo, M.L., Cordioli, C., Landi, D., Clerico, M., Signoriello, E., Frau, J., Ferro, M. T., Di Sario, A., Pasquali, U., Ulivelli, M., Marinelli, F., Callari, I., Godec, I., Liberatore, G., Caleri, F., Repice, A.M., Cordera, S., Battaglia, M.A., Battaglia, M.A., Salvestri, M., Franciotta, D., Maglione, A., Di Sario, A., Signori, A., Laron, A., Iovino, A., Repice, A.M., Mannironi, A., Ucelli, A., Serrati, C., Nicoletti, C.G., Lapucci, C., Mancini, C.R., Cordioli, C., Bezzini, D., Cagnaglino, D., Brogi, D., Querciotta, D., Landi, D., Orazio, E.N., Cozzo, E., Signoriello, E., Nako, E., Assandri, E., Marinelli, F., Baldi, F., Ansaldi, F., Bovis, F., Caleri, F., Siciliano, G., Cola, G., Perego, G., Lus, G., Bricchetto, G., Icardi, G., Bellucci, G., Rin, G.D., Marfia, G.A., Vazzoler, G., Liberatore, G., Trivelli, G., Callari, G., Gandoglia, I., Maitetta, I., Schiavetti, I., Frau, J., Zucchini, D., Pasquali, L., LoReffice, L., Carmisciano, L., Ruggiero, I., Manzino, M., Bragadin, M.M., Bucarin, M.C., Gagliardi, M., Stromillo, M.L., Sormani, M.P., Ferro, M.T., Rilla, M.T., Clerico, M., Battaglia, M.A., Ponzano, M., Franzoa, M., Sette, D., Inglese, M., Scialabba, M., Bedognetti, M., Ulivelli, M., De Rossi, N., De Stefano, N., Gazzola, P., Bigi, R., Dubbioso, R., Renit, R., Iodice, R., Fabbri, S., Rasia, S., Rolla, S., Platzegger, S., Cordera, S., Tassinari, T., Carlini, V., 2021. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. eBioMedicine 72. https://doi.org/10.1016/j.ebiom.2021.103581.

Alessandro Maglione, Marta Morra, Raffaella Meroni, Manuela Matta, Mariella Clerico1,*, Simona Rolla1

1 Department of Clinical and Biological Sciences, University of Turin, Italy

* Corresponding author.

E-mail address: marinella.clerico@unito.it (M. Clerico).

References

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Dolev, M., Menascu, S., Magalashvili, D., Flechter, S., Givon, U., Guber, D., Sonis, P., Zilka-Falh, R., Gurevich, M., 2021a. Humoral immune response in multiple sclerosis patients following PfizerBNT162b2 COVID19 vaccination: Up to 6 months cross-sectional study. J. Neuroimmunol. 361, 577746 https://doi.org/10.1016/j.jneuroim.2021.577746.

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Flechter, S., Falh, R., Gurevich, M., 2021b. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther. Adv. Neurol. Disord. 14 https://doi.org/10.1177/17562864211012835, 17562864211012836.

Bigart, K., Kremer, I., Fabacher, T., Lanotte, I., Fleurty, M.-C., Collongues, N., Seze, J.de, 2021. Impact of disease-modifying treatments of multiple sclerosis on Anti-SARS-CoV-2 antibodies: an observational study. Neurol. Neuroinflamm. 8 https://doi.org/10.1212/WNL.0000000000001055.

We thank all the subjects enrolled in this study for their kind contribution.

Correspondence

1 share co-senior authorship