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COVID-19

Preliminary evidence of blunted humoral response to SARS-CoV-2 mRNA vaccine in multiple sclerosis patients treated with ocrelizumab

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Abstract

Objectives Several concerns regard the immunogenicity of SARS-CoV-2 vaccines in people with multiple sclerosis (pwMS), since the majority of them is treated with immunomodulating/immunosuppressive disease modifying therapies. Here we report the first data on the humoral response to mRNA SARS-CoV-2 vaccine in a case series of 4 pwMS treated with ocrelizumab (OCR) as compared to a group of healthy subjects (HS).

Methods We collected serum samples at 0, 14, 21 days after the first dose and 7 days after the second dose of BNT162b2-mRNA-Covid-19 vaccine from 55 health-care workers and 4 relapsing pwMS on OCR, with no history of Covid-19 infection. Sera were tested 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. The anti-spike IgGtiters were expressed in Binding Antibody Units (BAU), an international standard unit.

Results At baseline all subjects were negative for anti-spike IgG. Seven days after the second dose of vaccine all HS mounted a significant humoral response (geometric mean 2010.4 BAU/mL C.I. 95% 1512.7-2672) while the 4 pwMS showed a lower response (range <4.81-175 BAU/mL).

Discussion Humoral response to BNT162b2-mRNA-vaccine in pwMS treated with OCR was clearly blunted. Further data are urgently needed to confirm and expand these preliminary results and to develop strategies to optimize the response to SARSCoV-2 vaccines in pwMS on OCR.

Keywords Multiple sclerosis · COVID-19 · SARS-CoV-2 mRNA vaccine · Ocrelizumab · Humoral response

Introduction

The spreading of the SARS-CoV-2 has raised new health concerns for people with multiple sclerosis (pwMS). Previous studies highlighted higher disability and progressive MS course, in addition to risk factors shared with healthy subjects (HS) (i.e. age, sex and comorbidities), as predictors of severe COVID-19 in pwMS [1]. Moreover, preliminary evidences have suggested that recent use of steroids and monoclonal antibodies targeting CD20 B cells (i.e. ocrelizumab [OCR] and rituximab [RTX]) might have an unfavourable impact on COVID-19 course [1, 2].

Since the worldwide launch of the SARS-CoV-2 vaccine campaign, several concerns have raised on the immunogenicity of vaccines in pwMS on treatment with high efficacy disease-modifying therapies (DMTs). In this context, an attenuated humoral response to a range of vaccines has already been reported in pwMS treated with anti-CD20 therapies and fingolimod [3, 4].

Therefore there is an urgent need to know if the response to SARS-CoV-2 vaccines — that has shown to be strong and reliable in HS [5] — is impaired by high efficacy DMTs in pwMS and if so, if there is any strategy to improve protection against COVID-19 through vaccination.

Here we report preliminary data on humoral response to SARS-CoV-2 mRNA vaccine assessed in 4 pwMS treated

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with OCR and compared it with that measured in a sample of HS enrolled in a surveillance programme.

Methods

Since January 5th, 2021, we collected serum samples — at 0, 14, 21 days after the first dose and 7 days after the second dose of BNT162b2 mRNA vaccine (the first available in Italy) — of (i) 55 health-care workers at our Neurology Clinic and (ii) 4 relapsing MS patients on OCR, that were vaccinated at the same time because employed in the National Health System.

All subjects did not have a history of COVID-19 infection as also confirmed by results of an internal surveillance protocol with frequent molecular and/or antigenic nasopharyngeal swabs and/or IgM-IgG antibodies tests.

Sera were stored at – 20 °C and tested using the LIAISON® SARS-CoV-2 TrimericS IgG assay (DiaSorin S.p.A., Saluggia, Italy), an indirect chemiluminescence immunoassay (CLIA) technology for the detection of serum IgG antibodies to SARS-CoV-2 trimeric spike protein (anti-TSP IgG), including neutralizing antibodies [6]. Performance and interpretation of results were done in accordance with the manufacturer's instructions, and the IgG titers were expressed in Binding Antibody Units (BAU), an international standard unit, with 33.8 BAU/mL as cut-off value [7].

Anti-TSP IgG titers above 2080 BAU/mL (maximum allowed limit) were 1:10 diluted to obtain a value in the detectable range.

The local Ethic Committee approved the study and a signed informed consent was obtained from all participants.

Results

All subjects, as expected, were seronegative at baseline. Clinical and demographical data are reported in Table 1. Injection-site-related reactions were commonly reported, while no unexpected and/or serious local and/or systemic side effects were observed.

Seven days after the second dose of BNT162b2 mRNA vaccine, all HS mounted a significant anti-TSP IgG response, while all 4 pwMS showed a very low humoral response, with nearly undetectable antibody titers in two cases (Table 1).

Discussion

As far as we know this is the first report on humoral response to BNT162b2 mRNA vaccine in a case series of pwMS treated with OCR. Our data suggest a clear reduction of anti-TSP IgG titers in pwMS treated with anti-CD20 DMT compared with HS. These results are in agreement with previous data showing a weakened humoral response to (i) vaccines administered in pwMS treated with OCR as well as in patients treated with RTX for immune thrombocytopenia [3, 8] and (ii) COVID-19 infection in pwMS treated with OCR [9, 10].

Notably all 4 vaccinated pwMS had a very low response to SARS-CoV-2 mRNA vaccine, though they were relatively young (median 38.5 years, range 33–51), received few OCR doses (median 1.5, range 1–5), and the last OCR infusion (following international guidelines: https://www.msif.org/) was more than 3 months before the first vaccine dose in all subjects (median 113 days, range 97–184). Interestingly, the patient with the highest humoral response showed countable CD20 circulating B cells and the longest interval since the last OCR dose (Table 1). Furthermore, since IgG levels in pwMS were in the normal range or just below the lower limit of the normal range at the time of the vaccination (Table 1), we do not expect an impact on the humoral response to vaccine.

Beyond the small number of tested patients, another limitation of this report was the inability to assess the cell-mediated and the innate immune response. Indeed, even if anti-CD20 monoclonal antibodies target circulating B-cells, dampening the humoral response, they do not directly interfere with innate immune and antigen-specific cytotoxic T-cells, which play a key role in the response to vaccines and infections.

Larger studies exploring the response to SARS-CoV-2 vaccines in pwMS treated with anti-CD20 drugs and other high efficacy DMTs are warranted in order to confirm and expand these preliminary data. The results of these investigations will be fundamental to address the central question about how to manage such therapies during pandemic and vaccine campaigns. In particular, we urgently need to know if the response to vaccines is modifiable based on manageable factors such as — in the case of anti-CD20 therapies — the count of circulating CD20 cells, IgG levels, time-elapsed since the last infusion and previous DMT use.

Table 1 Socio-demographic, clinical-therapeutic and humoral response to BNT162b2 mRNA vaccine data of HS (N = 55) and pwMS (N = 4)

	HC (55)	Patient 1 — male	Patient 2 — male	Patient 3 — female	Patient 4 — male
Median age (years, P25-P75)	41.2 (31.9–55.9)	33	35	42	51
Female n (%)	32 (58)	–	–	–	–
Disease duration (months)	NA	132	88	221	178
EDSS	NA	2	1.5	6.5	4.5
Relapses during previous year		1*	0	0	0
New MRI lesions during previous year	NA	4	3	1	0
Geometric mean anti-TSP IgG before vaccination in BAU/mL (95% confidence interval)	4.93 (4.78–5.09)	< 4.81**	< 4.81**	< 4.81**	< 4.81**
Geometric mean anti-TSP IgG 14 days after the first BNT162b2 mRNA dose, in BAU/mL (95% confidence interval)	192.3 (145.02–255.1)	< 4.81**	18.3	32.6	< 4.81**
Geometric mean anti-TSP IgG 21 days after the first BNT162b2 mRNA dose, in BAU/mL (95% confidence interval)	259.5 (195.6–344.2)	5.52	60	29	< 4.81**
Geometric mean anti-TSP IgG 7 days after the second BNT162b2 mRNA dose, in BAU/mL (95% confidence interval)	2010.4 (1512.7–2672)	4.9	75.4	175	< 4.81**
Previous DMTs • Pat 1: Cladribine 2010–2011, Interferon beta-1a 44 µg 2013–2015, Teriflunomide 2015–2020 • Pat 2: Fingolimod 2013–2020, Natalizumab 2020 (5 infusions from Apr-2020 to Jul-2020) • Pat 3: Interferon beta-1a 44 µg 2009–2010, Fingolimod 2010–2019 • Pat 4: Interferon beta-1a 44 µg 2007–2012, Natalizumab 2012–2014, Fingolimod 2014–2016, Dimethyl Fumarate 2016–2018					
Ocrelizumab					
Start date	–	20-Aug-2020	01-Oct-2020	23-Jan-2020	10-Jan-2019
Number of 600 mg doses***	–	1	1/2****	2	5
Time elapsed between last infusion and vaccination (days)	–	126	100	184	97
CD20 within 30 days before vaccination (%; cells/mcL)	–	0;0	0;0	2;12	0;0
- IgG mg/dL within 30 days before vaccination; normal range interval 700–1600	–	873	NA	672	620

* Cerebellar relapse occurred 186 days before vaccination, treated with intravenous methylprednisolone 1000 mg for 5 days

** Anti-TSPS IgG titers lower than 4.81 BAU/mL were not detected by the test used (LIAISON®/Diasorin)

*** The first 600 mg dose, as per prescription drug label, were administered in two doses separated by 2 weeks

**** Treatment stopped after first infusion of ocrelizumab 300 mg due to a significant hypertransaminasemia

P25 25thpercentile; *P75* 75thpercentile; *EDSS* Expanded Disability Status Scores; *MRI* magnetic resonance imaging; *anti-TSP IgG* anti-trimeric spike protein specific immunoglobuline G; *BAU/mL* binding arbitrary unit per ml; *DMTs* disease-modifying treatment

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Author contribution Antonio Gallo: study concept and design, analysis and interpretation of data, drafting and revising the manuscript.
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Nicola Coppola: drafting and revising the manuscript.
Gioacchino Tedeschi: study concept and design, analysis and interpretation of data, drafting and revising the manuscript.

Data availability Anonymized data not published within this article will be made available by request from any qualified investigator.

Declarations

Ethics approval The local ethics committee approved the present study.

Informed consent Informed consent was obtained from all participants included in the study.

Conflict of interest AG received speaker's honoraria and/or compensation for consulting service and/or speaking activities from Biogen, Genzyme, Merck, Mylan, Novartis, Roche, Teva. RC, GD, EG, MC, AdA, MG and NC have no disclosures. AB received speaker's honoraria and/or compensation for consulting service and/or speaking activities from Biogen, Genzyme, Merck, Mylan, Novartis, Roche, Teva. GT received speaker's honoraria and/or compensation for consulting service and/or speaking activities from Biogen, Genzyme, Merck, Mylan, Novartis, Roche, Teva.

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