ORIGINAL ARTICLE

Immune responses following COVID-19 infection in multiple sclerosis patients using immunomodulatory therapy

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), has quickly become a global pandemic. Most multiple sclerosis (MS) patients use disease-modifying treatments (DMTs), such as immunomodulators or immunosuppressants. By targeting different types of immune cells, DMTs affect cellular and/or humoral immunity. The potential effects of DMTs on the long-term immune response to COVID-19 is not fully known. Between 16.04.2020 and 15.07.2020, a total of 34 people, 17 of whom were diagnosed with MS according to the 2010 McDonald diagnostic criteria and a control group of 17 individuals who did not have a known systemic disease who were matched according to age, gender, and COVID-19 disease severity, where all received COVID-19 diagnosis with SARS-CoV-2 PCR positivity in nasopharyngeal swab test and immune responses were measured (SARS-CoV-2 IgM and IgG antibody levels COVID 19 ELISA kit), were included in our study. Demographic data of MS patients and the control group, SARS-CoV-2 immune responses, antibody titers and disease year of MS patients, EDSS scores, disease type, and disease duration were determined. All patients were symptomatic for COVID-19. COVID-19 disease severity was divided into three groups as mild, moderate, and severe according to the clinical condition of the patient. Demographic data of MS patients and the control group, SARS-CoV-2 immune responses, antibody titers and disease year of MS patients, EDSS scores, disease type, and disease duration were determined. All patients were symptomatic for COVID-19. COVID-19 disease severity was divided into three groups as mild, moderate, and severe according to the clinical condition of the patient. According to our study results, IgG-type long-term immune responses were lower in MS patients using DMTs than in the healthy population. We hope that our study will provide insight into the COVID-19 vaccine immune responses.

Keywords COVID-19 · Antibody · SARS-CoV-2 · Multiple sclerosis · DMT therapy

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), rapidly became a global pandemic after it was first reported in December 2019 [1]. COVID-19 is mild in most patients, while a serious illness may develop in approximately 15% of them [2]. The mortality rate is high amongst those needing intensive care.

Multiple sclerosis (MS) is a demyelinating autoimmune neurodegenerative disease of the central nervous system (CNS) that requires the use of immunosuppressive or immunomodulating disease-modifying therapy (DMT) [3]. DMTs affect cellular and/or humoral immunity by targeting different types of immune cells. DMTs, which affect the adaptive immune system in particular, may impair the development of long-term immune memory and reduce the effectiveness of vaccines [4]. The risks of developing severe COVID-19 infection due to DMTs in MS have previously been classified, but the potential effects of DMTs on long-term immune responses to COVID-19 infection are not fully known [5]. Knowing the effects of each DMT on the immune system,

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the risks of infection, and the potential impact on future vaccination is essential for the safe management of MS during the COVID-19 pandemic. In this study, we evaluated the immune responses to SARS-CoV-2 of MS patients using DMTs who had COVID-19. We hope that our study will provide guidance for COVID-19 vaccine responses.

Materials and methods

Prior to the study, approval was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (decision no: 21, dated 15.04.2021). Between 16.04.2020 and 15.07.2020, a total of 34 people, 17 of whom were diagnosed with MS according to the 2010 McDonald diagnostic criteria and a control group of 17 individuals who did not have a known systemic disease who were matched according to age, gender, and COVID-19 disease severity, where all received COVID-19 diagnosis with SARS-CoV-2 PCR positivity in nasopharyngeal swab test and immune responses were measured (SARS-CoV-2 IgM and IgG antibody levels Dia.Pro COVID 19 ELISA kit), were included in our study. Demographic data of MS patients and the control group, SARS-CoV-2 immune responses, antibody titers and disease year of MS patients, EDSS scores, disease type, and disease duration were determined. All patients were symptomatic for COVID-19. COVID-19 disease severity was divided into three groups as mild, moderate, and severe according to the clinical condition of the patient. Uncomplicated patients having fever, muscle/joint pain, cough, and sore throat but no respiratory distress (respiratory rate per minute < 24, $SpO_2 > 93\%$ in room air) with normal lung CT scan were considered mild–severity COVID-19 infection. Patients with symptoms such as fever, muscle/joint pain, cough, and sore throat with a respiratory rate < 30/minute, SpO_2 level $> 90\%$ in room air, and mild to moderate pneumonia ($< 50\%$) findings on CT scan were considered moderate–severity COVID-19 infection. Patients with symptoms such as fever, muscle/joint pain, cough, sore throat, tachypnea (≥ 30/minute), SpO_2 level $\leq 90\%$ in room air, and bilateral diffuse pneumonia ($> 50\%$) on CT scan were defined as severe-COVID-19 infection. Demographic and clinical data and IgG and IgM antibody titers of MS patients and the control group were compared.

Data analyses were performed by a blinded investigators.

Statistical analysis

The input and evaluation of the research data was done with the SPSS for Windows version 22. The suitability of numerical variables for normally distributed was examined with the Kolmogorov–Smirnov Test. Categorical variables are expressed as numbers and percentages, while numeric

variables are expressed as mean and standard deviation for those with normal distribution and median (minimum–maximum) for those without normal distribution. To compare the numerical variables, Student's t test was used for data with normal distribution, Mann–Whitney U test and Kruskal–Wallis test were used for data not normally distributed, and Chi-square test was used for the analysis of categorical variables. The significance level in the analysis was accepted as $p < 0.05$.

Results

The data of 34 patients, including 17 MS patients with SARS-CoV-2 serology results who had COVID-19, and 17 controls matched for age, sex, and COVID-19 disease severity, were analyzed. All patients had confirmed COVID-19 in RT-PCR tests on nasal and nasopharyngeal swabs.

The demographic data of the 34 patients included in this study are presented in Table 1. Of the MS patients, 64.7% were women, with median age of 38.2 years, ranging between 23 and 51. Of the patients, 2 were using glatiramer acetate, 1 was using interferon beta, 3 were using teriflunamide, 2 were using dimethyl fumarate, 2 were using fingolimod, 1 was using natalizumab, 4 were using ocrelizumab and 2 were using rituksimab. The severity of COVID-19 was found to be of mild nature in most of the MS patients (70.16%). Three MS patients, of which 1 was using fingolimod and 2 were using ocrelizumab, were of moderate severity (17.6%), while 2 MS patients, of which 1 was using fingolimod and 1 was using ocrelizumab, were of serious severity (11.8%) (Table 2). The median duration between COVID-19 symptom onset and SARS-CoV-2 serology amongst MS patients was 65 days (range: 14–160), whereas in the control group it was 45 days (22–162) and no meaningful variance could be found when the two groups were compared (Table 1). In 8 patients, of which 2 were using glatiramer acetate, 1 was using dimethyl fumarate, and 4 were being treated with anti-CD20 antibodies, the SARS-CoV-2 IgM and IgG antibodies were negative. While 1 patient using teriflunamide (25th day) was IgM positive and IgG negative, 1 patient using dimethyl fumarate (89th day) was IgM negative and IgG positive (Table 2). The mean IgM antibody titer in MS patients was 3.11 ± 3.53, while it was 3.28 ± 2.83 in the control group, and no significant difference was detected between the two groups. Mean IgG antibody titer in MS patients was 2.65 ± 3.11, which was significantly lower than 4.76 ± 3.23 in the control group (Table 1).

There was a negative correlation between the time to look for antibodies and antibody titers after COVID-19; however, this negative correlation was meaningful for IgM antibody titers. IgM and IgG antibody titers according to the drug

Table 1 Clinical and demographic characteristics of COVID-19 MS patients and control group

	MS n = 17	Control n = 17	p
Gender; n (%)			
Female	11 (64.7)	11 (64.7)	–
Male	6 (35.3)	6 (35.3)	
Age, years; Mean ± SD; median (min–max)	38.82 ± 7.68; 40 (23–51)	38.91 ± 7.62; 40 (23–51)	0.782*
MS disease type; n (%)			
RRMS	13 (76.5)		
SPMS	4 (23.5)		
MS disease duration, years Mean ± SD; median (min–max)	9.9 ± 5.8; 10 (2–22)	–	
ARR	0.59 ± 0.45; 0.53 (0.10–2)	–	
EDSS Mean ± SD; median (min–max)	2.35 ± 1.22; 2 (1–4.5)	–	
In treatment, n (%)			
Glatiramer acetate	2 (11.8)	–	
Interferon beta	1 (5.9)	–	
Teriflunamide	3 (17.6)	–	
Dimethyl fumarate	2 (11.8)	–	
Fingolimod	2 (11.8)	–	
Natalizumab	1 (5.9)	–	
Ocrelizumab	4 (23.5)	–	
Rituksimab	2 (11.8)	–	
Treatment duration, months Mean ± SD; median (min–max)	40.35 ± 32.60; 31 (6–119)	–	–
COVID-19 severity			–
Mild	12 (70.16)	12 (70.16)	
Moderate	3 (17.6)	3 (17.6)	
Severe	2 (11.8)	2 (11.8)	
Time between COVID-19 symptom onset and SARS-CoV-2 antibody testing, days Mean ± SD; median (min–max)	79.65 ± 49.94; 65 (14–160)	64.76 ± 47.74; 45 (22–162)	0.397*
Antibody response distribution n (%)			
IgM Antibody positive	9 (52.9)	14 (82.4)	0.06**
IgM Antibody negative	8 (47.1)	3 (17.6)	
IgG Antibody positive	9 (52.9)	15 (88.2)	**0.02****
IgG Antibody negative	8 (47.1)	2 (11.8)	
IgM antibody titer Mean ± SD; median (min–max)	3.11 ± 3.53; 1.56 (0–10.31)	3.28 ± 2.83; 2.36 (0.02–9.06)	0.642*
IgG Antibody titer Mean ± SD; median (min–max)	2.65 ± 3.11; 1.15 (0–11.14)	4.76 ± 3.23; 4.17 (0.19–10.66)	**0.052***

RRMS relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *ARR* annual relapse rate

*Mann–Whitney *U* test

**Chi-square test

treatments used by MS patients are shown in Table 3, and no significant difference was found between drug treatments in terms of antibody titers (Table 3).

Possible relationships amongst MS patients' disease severity, age, disease duration, EDSS, and ARR were examined. Only the EDSS score was significantly higher in moderate–severe COVID-19 patients than in mild–severity patients. Antibody titers of IgG and IgM were compared according to disease severity in MS patients and control groups, and no significant difference was found (Table 4).

Table 2 COVID-19 MS patients clinical features, SARS-CoV-2 serology, IgM and IgG antibody titers

Sex	Age (years)	EDSS	Disease type	Current DMT	DMT duration (months)	Duration between last anti-CD20 administration and symptom onset (days)	SARS-CoV-2 severity	Duration between SARS-CoV-2 clinical onset and SARS-CoV-2 serology (days)	SARS-CoV-2 serology IgG index/positivity	SARS-CoV-2 serology IgM index/positivity
F	41	1.5	RRMS	GA	39	–	Mild	107	0.26/–	0.38/–
F	40	1	RRMS	GA	119	–	Mild	135	0.50/–	0.41/–
F	42	1	RRMS	INF-β	98	–	Mild	40	2.53/+	5.99/+
F	32	1	RRMS	Trf	72	–	Mild	25	0.88/–	1.56/+
M	49	1	RRMS	Trf	6	–	Mild	14	3.97/+	8.28/+
F	50	2	RRMS	Trf	76	–	Mild	158	5.01/+	3.89/+
F	25	1	RRMS	DMF	15	–	Mild	89	1.15/+	0.13/–
F	34	2	RRMS	DMF	48	–	Mild	128	0.46/–	0.31/–
F	41	2	RRMS	Fing	20	–	Severe	32	5.57/+	10.31/+
F	40	3	RRMS	Fing	23	–	Moderate	65	3.43/+	3.47/+
F	23	3	RRMS	Ntz	15	–	Mild	59	7.07/+	4.51/+
M	51	4.5	SPMS	Ocre	10	52	Severe	30	11.14/+	9.38/+
F	39	4	SPMS	Ocre	29	60	Mild	58	0.00/–	0.04/–
M	42	3	SPMS	Ocre	12	45	Moderate	102	2.74/+	3.98/+
M	39	3.5	SPMS	Ocre	31	150	Moderate	130	0.06/–	0/–
M	34	4	SPMS	Rtx	34	88	Mild	160	0.11/–	0/–
M	38	3.5	SPMS	Rtx	39	300	Mild	22	0.20/–	0.35/–

F female, *M* Male, *DMT* disease-modifying therapy, *RRMS* relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *GA* glatiramer acetate, *INF-β* interferon-β, *Trf* teriflunamide, *DMF* dimethyl fumarate, *Fing* fingolimod, *Ntz* natalizumab, *Ocre* ocrelizumab, *Rtx* rituximab

Table 3 COVID-19 MS patients SARS-CoV-2 serology according to treatments

DMT	n (%)	SARS-CoV-2 serology IgM index mean ± SD; median (min–max)	p	SARS-CoV-2 serology IgG index mean ± SD; median (min–max)	p
Glatiramer acetate	2 (11.8)	0.39 ± 0.02; 0.39 (0.38–0.41)	0.313	0.38 ± 0.16; 0.38 (0.26–0.50)	0.326
Interferon-β	1 (5.9)	5.99		2.53	
Teriflunamide	3 (17.6)	4.57 ± 3.41; 3.89 (1.56–8.28)		**3.28** ± 2.14; 3.97 (0.88–5.01)	
Dimethyl Fumarate	2 (11.8)	0.22 ± 0.12; 0.22 (0.13–0.31)		0.80 ± 0–48; 0.80 (0.46–1.15)	
Fingolimod	2 (11.8)	6.89 ± 4.83; 6.89 (3.47–10.31)		**4.50** ± 1.51; 4.5 (3.43–5.57)	
Natalizumab	1 (5.9)	4.51		7.07	
Ocrelizumab	4 (23.5)	3.35 ± 4.43; 2.01 (0–9.38)		3.48 ± 5.26; 1.4 (0–11.14)	
Ritüksimab	2 (11.8)	0.17 ± 0.24; 0.17 (0–0.35)		0.15 ± 0.06; 0.15 (0.11–0.20)	
Total	17 (100)	3.11 ± 3.53; 1.56 (0–10.31)		2.65 ± 3.11; 1.15 (0–11.14)	

Values in bold are statistically significant.

Table 4 MS patients and control groups IgG and IgM antibody titers according to disease severity

	Mild severity COVID-19 n (%)/mean ± SD; median (min–max)	Medium–serious severity COVID-19 n (%)/mean ± SD; median (min–max)	p
MS	12 (70.16)	5 (29.84)	–
Disease type	11	2	–
RRMS SPMS	1	3	
Age	37.25 ± 8.22; 38.5 (23–50)	42.60 ± 4.82; 41 (39–51)	0.139
MS disease duration; years	9.75 ± 4.88; 10.50 (2–17)	10.20 ± 8.43; 6 (2–22)	1
EDSS	1.95 ± 1.05; 1.75 (1–4)	3.30 ± 1.15; 3.5 (1.5–4.5)	**0.036**
ARR	0.60 ± 0.52; 0.51 (0.1–2)	0.58 ± 0.28; 0.6 (0.20–1)	0.791
IgM	2.15 ± 2.81; 0.39 (0–8.28)	5.42 ± 4.32; 3.98 (0–10.31)	0.225
IgG	1.84 ± 2.31; 0.69 (0–7.07)	4.58 ± 4.15; 3.43 (0.06–11.14)	0.206
Control			
IgM	2.87 ± 2.75; 2.38 (0.02–9.06)	4.24 ± 3.10; 2.36 (1.68–8.76)	0.562
IgG	4.05 ± 2.98; 3.77 (0.19–9.90)	6.45 ± 3.51; 6.83 (2.66–10.66)	0.225
Total	24	10	
IgM	2.51 ± 2.74; 1.74 (0–9.06)	4.83 ± 3.60; 3.72 (0–10.31)	0.076
IgG	2.94 ± 2.84; 2.31 (0–9.90)	5.52 ± 3.76; 4.50 (0.06–11.14)	0.067

MS multiple sclerosis, *RRMS* relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *ARR* annual relapse rate

Discussion

In this study of the immune responses of MS patients receiving DMTs who had COVID-19, it was found that IgG-type long-term immune responses were significantly lower than for the healthy population. In our study, antibody titers were higher in severe COVID-19 patients, but this elevation was not significant. In our study, serum antibody levels were reported together with the positivity rate in COVID-19 immune responses.

Immunogenicity and potential duration of this immunity against SARS-CoV-2 in the general population are not fully known [6]. In a study involving 285 patients with COVID-19 infection, seroconversion was shown to develop between 17 and 19 days after symptom onset [7]. In our case series,

there were patients who were positive for SARS-CoV-2 IgM and IgG antibodies after 14 days at the earliest and 162 days at the latest after the onset of symptoms.

Initial reports of the risk of COVID-19 infection in MS patients are largely reassuring [8]. In our study, COVID-19 infection had a mild course in 70.16% of MS patients.

It remains unclear whether the current DMTs used in the treatment of MS during the COVID-19 pandemic will have a negative impact on the future SARS-CoV-2 vaccine. Traditional injectable treatments probably have the safest immune profile. Interferon-β and Glatiramer acetate are immunomodulating agents used in the treatment of MS. Since IFN-β-associated lymphopenia is usually rare and mild, it is unlikely to affect the early or delayed immune response to SARS-CoV-2 or significantly increase infection susceptibility, as GA does not deplete lymphocytes [1]. In influenza vaccine studies, it was reported that IFN-β did not decrease the protective immune response against vaccines [9]. It was shown that antibodies developed in an MS patient using IFN-β who previously had COVID-19 [1]. In our study, one patient who received IFN-β treatment had mild COVID-19 disease severity and had a positive serology. A potential negative effect on the protective immune response to influenza vaccine was found in patients receiving GA, but some studies did not find any negative effects [10–12]. In another study, it was reported that SARS-CoV-2 antibody response was observed on the 51st and 54th days in 2 MS patients who had COVID-19 infection and used GA [13]. In our study, antibody responses were not observed on the 107th and 135th days in our two MS patients who received GA treatment. Negative immune responses may be related to the long duration of post-infection antibody levels. While the effect of GA on the future SARS-CoV-2 vaccine is generally safe, it would be appropriate to monitor immune responses as the exact immune response is unknown.

Teriflunomide reduces the replication of auto-reactive lymphocytes by inhibiting dihydroorotate dehydrogenase [14]. To date, a mild course of COVID-19 infection has been reported in patients receiving teriflunomide. It was described that anti-SARS-CoV-2 antibodies develop after COVID-19 infection in a patient receiving teriflunomide [15, 16]. In our study, there were 3 MS patients using teriflunamide. While COVID-19 infection was asymptomatic in 1 patient, it had a mild course in 2 patients, and IgG-type antibody responses developed in 3 patients.

Although the mechanism of action of dimethyl fumarate is not known exactly, it has an immunomodulatory effect through Nrf-2 protein inhibition [14]. Lymphopenia may develop in 37% of patients [17]. It was reported that the COVID-19 infection progressed mildly in two patients who had previously used DMF [18]. In another study, it was shown that an IgG-type antibody response occurred in one of two patients using DMF who had COVID-19 [13].

In our study, the COVID-19 infection of two MS patients using DMF had a mild course, but the IgG-type antibody responses of both patients were negative (on the 89th and 128th days).

Fingolimod is a sphingosine-1-phosphate (S1P) receptor agonist. Sphingosine-1-phosphate modulators prevent the exit of T cells from the lymph nodes [14] and reduce the migration of lymphocytes to the central nervous system (CNS) [19]. Fingolimod may potentially increase susceptibility to SARS-CoV-2 by depletion of peripheral lymphocytes. However, it was also reported that it may have a beneficial effect in COVID-19 patients with cytokine storm [1]. Fingolimod has been shown to reduce both cellular and humoral immune responses to vaccinations [20]. It was reported that the production of anti-SARS-CoV-2 antibodies was weakened in one of the patients who used fingolimod and had COVID-19 infection [16]. Again, in a multicenter cohort study, it was reported that anti-CD20 treatment and fingolimod treatment resulted in decreased humoral response to mRNA-based SARS-CoV-2 vaccines [21]. In our study, there were 2 patients using fingolimod; they had moderate-to-severe COVID-19 infection. The lymphocyte counts of the patients were $770/mm^3$ and $220/mm^3$, respectively. Anti-SARS-CoV-2 IgM and IgG antibody responses of the patients were positive.

Natalizumab is an alpha-4 integrin antagonist on the surface of leukocytes and thus prevents the migration of leukocytes to the CNS [14]. Although the infectious side-effect profile of natalizumab suggests a slight increase in susceptibility to respiratory viral infections, it is unlikely that natalizumab will significantly increase susceptibility to SARS-CoV-2, since it does not cause lymphopenia [1]. In two MS patients using natalizumab, COVID-19 infection was reported to be mild with complete recovery [22, 23]. In another study, it was shown that IgG-type antibody responses developed on the 68th and 76th days in two patients using natalizumab [13]. In our study, 1 patient using natalizumab had a mild COVID-19 infection and IgM- and IgG-type antibody response developed on the 59th day. Based on the influenza vaccine studies and our study result, natalizumab is not expected to have an adverse effect on future SARS-CoV-2 vaccine response [24].

Ocrelizumab is a humanized MAB that targets CD20 on the surface of B cells, causing prolonged selective B cell lymphopenia [14]. B-cell depletion may impair long-term immunity to the virus and increase the risk of re-infection [25]. In the reported case series, it was reported that the risk and severity of COVID-19 infection in patients treated with anti-CD20 agents (ocrelizumab or rituximab) are not different from the general population, but critical and fatal cases have also occurred [26–30]. B-cell therapies such as ocrelizumab may reduce the humoral protective response against future SARS-CoV-2 [31]. Cases with positive and

negative serology related to antibody development have been reported previously in COVID-19 patients [13, 32]. In a case series, negative SARS-CoV-2 serology was reported in all five patients with confirmed COVID-19 treated with anti-CD20 therapies [13]. In recent studies, post-vaccine humoral responses to mRNA-based SARS-CoV-2 vaccines were found to be lower in MS patients receiving anti-CD20 therapy [21, 33]. In our study, there were 6 patients who received CD19-2O MAB treatment, 2 of which were receiving rituximab. Two patients using rituximab had mild COVID-19 infection, but the IgM- and IgG-type antibody responses on the 22nd and 160th days were negative. Two of the four patients who had COVID-19 while using ocrelizumab had negative serology, while the other two had positive serology. Of the patients who developed antibodies, one had moderate and the other had severe COVID-19 infection.

We also report data on antibody titers in our study. Total IgM and IgG antibody titers of the patients. This result suggests that it was due to the effects of immunomodulatory drugs used by MS patients on antibody levels. Although IgM and IgG antibody responses were negative in patients using GA, rituximab, and DMF, it was observed that there was no significant difference between IgM and IgG antibody levels between DMT drug groups used by MS patients in our study. It was thought that this might be due to the low number of patients in the groups were measured. While there was no significant difference between SARS-CoV-2 IgM levels of MS patients compared to the control group, IgG-type antibody titers were significantly lower.

It has been reported that antibody titres are higher in those who previously had severe COVID-19 disease [34]. In our study, disease severity and antibody titers were compared, and antibody levels were higher in severe COVID-19 patients, but this elevation was not significant. Similar to previous studies, MS patients with severe COVID-19 had a higher EDSS score [35]. Patients' ages, disease duration, and ARR were not significantly different according to disease severity. When the correlation between the time to look at the SARS-CoV-2 antibody results after the disease and the antibody titers was examined, there was a significant negative correlation in the IgM-type antibody response, but the negative correlation in the IgG type antibodies was not significant.

Conclusion

In conclusion, in our study, IgG-type long-term immune responses were lower in MS patients using DMTs than in the normal population. We hope that our study will provide insight into the COVID-19 vaccine immune responses. However, large, controlled cohort studies are needed to better understand the relationship between DMTs in MS and the immune response after SARS-CoV-2 infection.

Declarations

Conflict of interest None.

Data availability statement All data generated or analysed during this study are included in this published article.

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