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Analysis of seroconversion following COVID-19 vaccination among multiple sclerosis patients treated with disease--modifying therapies in Poland

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ABSTRACT

Clinical rationale for the study. The rapid spread of SARS-CoV-2 throughout the world has highlighted the importance of vaccinations to control the pandemic and to protect people at risk for severe disease courses. Disease-modifying therapies (DMT) in multiple sclerosis (MS), whether immunomodulatory or immunosuppressive, may affect the immune response. Therefore, the question arose as to whether these vaccinations would be effective.

Aim of the study. We planned a study to assess the immune response to SARS-CoV-2 vaccines by type of therapy.

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Material and methods. Participants were recruited from 14 Polish MS centres. The data was obtained by neurologists using a questionnaire. We collected data on 353 MS patients (269 females, 84 males) who received complete primary SARS-CoV-2 vaccination. All persons with MS (PwMS) were treated with disease-modifying therapies.

Results. 305 out of 353 PwMS (86.4%) were positive for IgG Abs against SARS-CoV-2 S domain S1 Ag after vaccination. A strong immune response was noted in 129 PwMS (36.5%). The rate of seroconversion after SARS-CoV-2 vaccination in PwMS who received immunomodulatory DMTs (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab) was 91.5%, in PwMS receiving immune reconstruction therapy (alemtuzumab, cladribine) was 92%, and in immunosuppressive DMTs (fingolimod, ocrelizumab), the seroconversion rate was 59%.

Conclusions and clinical implications. Our study shows that, in PwMS receiving immunomodulatory therapy, the immune response to vaccination is generally excellent. Even in immunosuppressive patients, seroconversion is satisfactory.

Keywords: multiple sclerosis, disease-modifying therapies, vaccines, COVID-19, immune response, antibodies, immunosuppressive therapy

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Introduction

The COVID-19 pandemic has caused significant morbidity and mortality worldwide. Vaccination is the primary method for preventing and controlling the pandemic, but vaccination in autoimmune diseases, including multiple sclerosis, has posed a significant challenge. Although recommended by international MS societies and expert panels [1, 2], vaccinating against SARS-CoV-2 is associated with significant patient concerns about the safety of vaccines. In recent years, research has been carried out on, inter alia, vaccination against influenza or hepatitis. However, the COVID-19 pandemic made it imperative that patients with multiple sclerosis be immunised rapidly. At that time, there were many questions regarding the safety and effectiveness of vaccines, especially since a new type of vaccination — the mRNA vaccine — was being widely used. There is international consensus that mRNA vaccinations are safe in PwMS [1, 3, 4]. While COVID-19 infections themselves may be associated with an increased relapse risk, this has not been observed for vaccinations [5]. Unfortunately, some patients, especially those who had been ill for longer, were afraid of vaccinations. These concerns also arose from the level of acceptance of COVID-19 vaccination in society [6, 7]. Disease-modifying therapies in multiple sclerosis are often immunosuppressive and may therefore influence the immune response. The main question was whether all vaccines were equally effective and recommended for PwMS. Another question was the influence of other factors such as age, the severity of the autoimmune disease, and comorbidities. Therefore, we analysed immune response to SARS-CoV-2 vaccination in a cohort of Polish PwMS.

The Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society reacted very quickly to the new situation in which doctors and PwMS found themselves at the outbreak of the pandemic. As soon as April 2020, there was a statement on the treatment of MS in the case of the risk of infection with the coronavirus causing COVID-19, and in February 2021, a statement on the vaccination of patients with MS was released [5]. It was also decided to collect data from PwMS on the safety of vaccination [2, 3, 9], as well as its effectiveness.

Material and methods

The Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society published an announcement about the study at www.ptneuro.pl, and every MS centre in Poland was invited to participate. Eventually, participants were recruited from 14 Polish MS centres, and data was obtained by neurologists using a questionnaire. The same questionnaire was used at each MS centre. Patients were recruited to the study during standard visits to a particular MS centre. During these visits, blood samples were taken, including for antibody testing. PwMS diagnosed according to the 2010 and 2017 McDonald criteria who had received the anti-SARS-CoV-2 vaccines and who underwent serological testing for SARS-CoV-22 neutralising antibodies, i.e. anti-Spike protein (anti-S), at least one month following the completion of the vaccination cycle (two doses) were included.

All PwMS were treated with one of the DMTs available in Poland (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, cladribine, natalizumab, or ocrelizumab). Disability was assessed using the Expanded Disability Status Scale (EDSS).

We collected patient demographics, data regarding specific features of multiple sclerosis, comorbidities, information about vaccination against SARS-CoV-2, the presence of leukopenia or lymphopenia, SARS-CoV-2 infection before vaccination, relapse and treatment with corticosteroids within the three months prior to vaccination, and anti-SARS-CoV-2 antibodies concentration.

We collected data until 15 January, 2022. By that time in Poland, most patients had received two doses of the SARS-CoV-2 vaccination; hence, data on the booster dose was not taken into account. The study was conducted retrospectively. The study was approved by the Bioethics Committee at the Medical University of Warsaw, Poland.

The presence and titre of SARS-Cov2-neutralising (anti-S) antibody response were measured. Anti-S antibody testing was performed in accredited medical laboratories with electrochemiluminescence immunoassay (ECLIA)-based methods (commercial kits Elecsys, Roche Diagnostics Ltd, Switzerland) or anti-SARS-CoV-2 QuantiVac ELISA IgG (Euroimmun); antibody titres were expressed in binding antibody units per mL (BAU/mL). Antibody titres below the lower detection cut-off, according to the manufacturer's instructions, were recorded as negative.

Categorical variables were characterised by frequency and percentage. The collected research material was developed with the use of basic descriptive statistics, presenting the values of mean and standard deviations and other parameters. A sample t-test was used to compare the differences between the groups that were independent with normal distribution. In the absence of such a distribution (Gaussian), the non-parametric Mann–Whitney U test was used. Pearson's chi-squared test of independence was used to compare the incidence. A significance level alpha = 0.05 was assumed. All calculations were performed using Statistica 13.0 software. First of all, we assessed whether the PwMS at least developed positive antibodies. Among these PwMS, we selected a group in whom the immune response was very strong (the maximum concentration of anti-SARS-CoV-2 antibodies specified by the manufacturer of the test). The presence or absence of an immune response and its strength was correlated with various variables such as age, sex, course of multiple sclerosis, neurological status (EDSS), type of vaccine used, comorbidities, any relapse treated with corticosteroids in the three months prior to vaccination, type of therapy, presence of leukopenia or lymphopenia, and previous history of COVID-19.

Results

We collected data on 353 PwMS (269 females, 84 males) who received the complete primary SARS-CoV-2 vaccination. The mean age of patients was 41.5 ± 10.4 years (range, 19–67; median, 41.0), the mean duration of the disease was 9.8 ± 6.8 years (range, 1–48; median, 9.0), and the mean EDSS, 3.2 ± 1.2 (range, 0–7.0; median, 3.0). The PwMS had different courses of the disease: relapsing–remitting — 291 people; secondary progressive — 46; and primary progressive — 16. Demographic and clinical data is set out in Table 1. The anti-SARS-CoV-2 antibody concentration was assessed a mean 3.2 ± 1.9 months (median, 3 months; range, 1–10) after the second dose of vaccination. In 80% of cases, antibodies were measured 1-5 months after the second dose of vaccination

According to the local regulations, patients received two doses of the Comirnaty (BioNTech/Pfizer), the Moderna, or the Vaxzevria (AstraZeneca) COVID-19 vaccine or one dose of the Johnson & Johnson's Janssen COVID-19 vaccine. Most PwMS (n = 243) were vaccinated with the Comirnaty vaccine (BioNTech/Pfizer), 64 received the COVID-19 AstraZeneca (Vaxzevria) vaccine, 36 PwMS received the Moderna COVID-19 vaccine, and eight received the Johnson & Johnson's Janssen COVID-19 vaccine. The system of administering COVID-19 vaccines in Poland was nationwide and the intervals between doses were strictly controlled. The interval between two doses of the Comirnaty and the Moderna vaccine was five weeks. For the COVID-19 AstraZeneca vaccine, it was 12 weeks. All PwMS received vaccination in this regime.

For ocrelizumab, which is given every six months, the interval between the last dose of the drug and the first dose of vaccination was on average 4.5 months (median, 4; range, 3–6).

Most PwMS (n = 216) had no comorbidities. Arterial hypertension, hyperlipidemia, and thyroid disease were reported in 137 persons. A history of COVID-19 infection confirmed by PCR was demonstrated in 116 PwMS.

Twenty-six PwMS had a relapse of MS in the three months prior to vaccination, of whom 22 were treated with intravenous methylprednisolone (1,000 mg/day for five days).

All the PwMS were treated with DMT (see Tab. 1). Seventy-four patients had lymphopenia: grade 1 (800–999/mm^3) or 2 (500–799/mm^3) — 70 persons; grade 3 (200–499mm^3) — four persons; and grade 4 (< 200 mm^3) — 0. PwMS with lymphopenia had been treated with the following drugs: interferon beta — 6; glatiramer acetate — 0; teriflunomide — 9; natalizumab — 0; fingolimod — 23; alemtuzumab — 0; ocrelizumab — 8; and cladribine — 3. Fifty-one patients had leukopenia: grade 1 (3.0–3.9 × 10^3/mm^3) — 43; and grade 2 (2.0–2.9 × 10^3/mm^3) — 8. PwMS with leukopenia had been treated with the following drugs: interferon beta — 5; glatiramer acetate — 0; teriflunomide — 8; natalizumab — 0; fingolimod — 11; alemtuzumab — 0; ocrelizumab — 3; and cladribine — 9.

In total, 305 out of 353 PwMS (86.4%) were positive for IgG Abs against SARS-CoV-2 S domain S1 Ag after vaccination. A strong immune response was noted in 129 PwMS (36.5%).

Seroconversion was not influenced by gender, age, duration of MS, course of multiple sclerosis, neurological status (EDSS), comorbidities, MS relapse treated with intravenous corticosteroids in the three months prior to vaccination, or type of vaccination. The correlation between a previous COVID-19 infection and the presence of antibodies after vaccination was not statistically significant (p = 0.089). The type of therapy and the presence of lymphopenia had a significant influence on the occurrence of anti-SARS-CoV-2 antibodies.

Forty-eight PwMS did not develop antibodies despite undergoing a complete vaccination course. Patients were treated with the following drugs: interferon beta — 4 (10.8% of patients); glatiramer acetate — 1 (6.2%); teriflunomide

Table 1. Demographics and clinical characteristics of patients with MS

	N	%	Mean	Median	SD
Study population	353	100%			
Female	269	76.2			
Male	84	23.8			
Age (years)			41.57	41.0	10.42
EDSS			3.19	3.0	1.27
Disease duration			9.87	9.0	6.8
MS relapses	26	7.4			
Treatment with intravenous corticosteroids	22	6.2			
Comorbidities	137	38.8			
Disease course					
RRMS	291	82.43			
SPMS	46	13.03			
PPMS	16	4.53			
DMTs					
Interferon beta	37	10.48			
Glatiramer acetate	16	4.53			
Dimethyl fumarate	115	32.57			
Teriflunomide	72	20.39			
Natalizumab	44	12.46			
Fingolimod	33	9.34			
Ocrelizumab	23	6.51			
Alemtuzumab	3	0.84			
Cladribine	9	2.54			
Confirmed COVID-19	116	32.86			
Lymphopenia before vaccination	74	20.96			
Grade 1 or 2	70	19.83			
Grade 3	4	1.13			
Grade 4	0	0			
Type of vaccination					
mRNA vaccine	279	79.03			
Vector-based vaccine	74	20.97			

DMTs — disease-modifying therapies; EDSS — expanded disability status scale; MS — multiple sclerosis; PPMS — primary progressive multiple sclerosis; RRMS — relapsing-remitting multiple sclerosis; SD — standard deviation; SPMS — secondary progressive multiple sclerosis

— 7 (9.7%); dimethyl fumarate — 12 (10.5%); fingolimod — 14 (42.4%); ocrelizumab — 9 (39.1%); and cladribine — 1 (11.1%). According to these figures, treatment with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, or cladribine did not significantly affect the immune response against the SARS-CoV-2 virus. An interesting result was obtained in PwMS treated with natalizumab — 100% of persons had positive antibodies against SARS-CoV-2 ($p = 0.004$). A similar situation occurred in PwMS treated with alemtuzumab, but the number of persons was small ($n = 3$), and all patients had received the last course of the drug more than 18 months earlier. Treatment with fingolimod or ocrelizumab was associated with a decreased immune response (fingolimod $p < 0.0001$; ocrelizumab $p = 0.0002$).

The rate of seroconversion after SARS-CoV-2 vaccination in PwMS who received immunomodulatory DMTs (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab) was 91.5%, in PwMS receiving immune reconstruction therapy (alemtuzumab, cladribine) was 92%, and in immunosuppressive DMTs (fingolimod, ocrelizumab), the seroconversion rate was 59%.

The factors that influenced the development of a strong immune response after vaccination against COVID-19 (the maximum antibody concentration provided by the manufacturer of a given test) were also assessed. In this case, this was also not affected by gender, age, duration of MS, EDSS, comorbidities, form of multiple sclerosis, disease relapse treated with intravenous corticosteroids within the three months

Table 2. Characteristics of PwMS depending on immune response to COVID-19 vaccination

	IgG Abs against SARS-CoV-2		
	Negative n (%)	**Positive n (%)**	**Maximum concentration specified by manufacturer of test n (%)**
Study population	48 (13.6)	305 (86.4)	129 (36.5)
Female	39	230	102
Male	9	75	27
Age (years)	41.66	41.55	40.97
EDSS	3.15	3.46	3.15
Disease duration (years)	8.72	10.05	9.63
Disease course			
RRMS	36	255	108
SPMS	6	40	19
PPMS	6	10	2
DMTs			
Interferon beta	4 (10.8)	33 (89.2) p = 0.60	15 (40.5%) p = 0.59
Glatiramer acetate	1 (6.2)	15 (93.8) p = 0.38	8 (40.0%) p = 0.25
Dimethyl fumarate	12 (10.5)	102 (89.5) p = 0.24	37 (32.4) p = 0.28
Teriflunomide	7 (9.7)	65 (90.3) p = 0.28	37 (51.4) p = 0.003
Natalizumab	0	44 (100%) p = 0.004	18 (40.9) p = 0.52
Fingolimod	14 (42.4) p < 0.0001	19 (57.6)	4 (12.2)
Ocrelizumab	9 (39.1) p = 0.0002	14 (60.9)	3 (13.0)
Alemtuzumab	0	3 (100) p = 0.49	1 (33.3) p = 0.9
Cladribine	1 (11.1)	8 (88.9) p = 0.82	5 (55.5) p = 0.23
Lymphopenia before vaccination	18 (24.3) p = 0.002	56 (75.7)	22 (29.7)
Grade 1 or 2	16	54	22
Grade 3	2	2	0
Grade 4	0	0	0

DMTs — disease-modifying therapies; EDSS — expanded disability status scale; PPMS — primary progressive multiple sclerosis; PwMS — persons with MS; RRMS — relapsing-remitting multiple sclerosis; SPMS — secondary progressive multiple sclerosis

prior to vaccination, or the type of vaccination. Previous COVID-19 infection significantly influenced the generation of a strong immune response (p = 0.002). Leukopenia and lymphopenia did not have a significant effect on a strong immune response. Treatment with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, or cladribine resulted in a strong immune response. In the case of a strong response, treatment with natalizumab did not influence its occurrence. Treatment with fingolimod and ocrelizumab significantly reduced the occurrence of a strong response to vaccination against SARS-CoV-2 (fingolimod p = 0.002; ocrelizumab p = 0.01). High levels of antibodies were obtained in patients treated with the following drugs: interferon beta—15 (40.5% of patients); glatiramer acetate — 8 (50.0%); teriflunomide — 37 (51.4%); dimethyl fumarate — 37 (32.4%); natalizumab — 18 (40.9%); fingolimod — 4 (12.2%); alemtuzumab — 1 (33.3%); ocrelizumab — 3 (13.0%); and cladribine — 5 (55.5%). The characteristics of PwMS depending on the immune response to COVID-19 vaccination are set out in Table 2.

Discussion

The rapid spread of SARS-CoV-2 throughout the world has highlighted the importance of vaccinations to control the pandemic and to protect people at risk for severe disease courses. Studies have provided data on factors influencing the effectiveness of COVID-19 vaccinations. Parameters such as age, disease duration, course of MS, and neurological status (EDSS) do not affect the effectiveness of SARS-CoV-2 vaccination. This is important information, because earlier studies [10] showed that the immune response to vaccination decreases with age. The explanation for this phenomenon is that most of our patients are young (median age — 41 years). Decreased responsiveness to vaccination has been demonstrated in older people (> 65 years) [10]. The young age of patients can also explain the lack of influence of the presence of comorbidities on seroconversion.

Recommendations on the use of high doses of corticosteroids and vaccinations are not uniform. Some experts recommend an interval between corticosteroid treatment and vaccination only in live vaccines [11, 12]. Others recommend delaying vaccination for 2–4 weeks when administering high doses of corticosteroids. [13]. In our study, disease relapse treated with intravenous methylprednisolone had no effect on the emergence of a vaccine response. Most likely, doctors followed the recommendations of the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society [8] to postpone the vaccination for 4–6 weeks after treatment with high doses of corticosteroids.

The rate of seroconversion after SARS-CoV-2 vaccination in PwMS who received DMTs was very high (86.4%). Among the PwMS being treated with immunomodulatory DMTs, the rate of seroconversion was excellent (91.5%). Other researchers have obtained similar results [14–16].

DMTs, such as interferon beta, glatiramer acetate, dimethyl fumarate, and teriflunomide, do not affect the efficacy of vaccination against SARS-CoV-2. Consequently, there is no need to reschedule treatment for MS, and PwMS receive the same protection against infection from vaccination as the rest of the population. For high-efficacy disease-modifying therapies, the formation of a humoral immune response to COVID-19 vaccination depends on the type of drug and, in many cases, on the time elapsed since the last dose of the drug. Natalizumab is an example of a high-efficacy disease-modifying therapy which makes possible a very good immune response to vaccination. In our study, 100% of pwMS treated with natalizumab had positive anti-SARS-CoV-2 antibodies. Other researchers have obtained similar results [17].

In PwMS treated with immunosuppressive DMTs, the rate of seroconversion after SARS-CoV-2 vaccination was 64.7%, but this was clearly drug dependent. In the case of alemtuzumab, 100% of PwMS achieved seroconversion, and 88.8% achieved seroconversion in the case of cladribine. However, conclusions must be limited due to the small size of these groups (three and nine patients, respectively). The most important fact in both cases was that the time between the last treatment course and vaccination was long (alemtuzumab — over 18 months; cladribine — over four months; most others over 12 months). Slightly worse results were obtained for fingolimod (57.6%) and ocrelizumab (60.9%), but still more than half of the patients seroconverted after two doses of the SARS-CoV-2 vaccine. These figures are much better than those presented in other works. Achiron et al. [18] reported seroconversion in only 22.7% of patients treated with ocrelizumab and 3.8% with fingolimod. Sormani et al. [19] achieved better results. The percentage of patients on fingolimod and ocrelizumab with antibody levels above the cut-off of positivity was 90.6% and 40.5% respectively among PwMS vaccinated with Comirnaty COVID-19 vaccine. Such differences can arise due to several reasons. The antibody testing in our study was performed, on average, three months after the second dose of vaccination, but in the case of an Israeli study, it was one month. PwMS treated with ocrelizumab were vaccinated at least three months after the last dose, usually after 4–5 months. Sormani et al. showed that the Moderna COVID-19 vaccine elicits 3.25-times higher antibody levels than the Comirnaty vaccine. We did not find such a relationship, which might be due to the small group of patients vaccinated with Moderna COVID-19 vaccine. Another important factor may be when the antibodies were tested. In our group, the tests were performed three months after vaccination, whereas in an Italian work this interval was one month. Many papers, as shown in the meta-analysis by Wu at al. [20], have described a reduced response to vaccination in the case of anti-CD20 or sphingosine-1-phosphate receptor modulators therapy, but the scale of this problem is also important. Our work shows that with good planning of therapy and treatment, most patients achieve post-vaccination immunity. The need to plan vaccination treatment cycles and administer booster doses of SARS-CoV-2 vaccinations has also been emphasised by other authors [21].

We still do not know what antibody level is sufficient to obtain protection against COVID-19, especially since the cellular response must also be taken into consideration. Therefore, it is important to know which PwMS treated with which preparations obtain a very high concentration of antibodies, and therefore have a better chance of avoiding infection. The best results were achieved in PwMS treated with cladribine (55.5%), teriflunomide (51.4%), glatiramer acetate (50.0%), natalizumab (40.9%), and interferon beta (40.5%). Up to 13% of PwMS treated with ocrelizumab and 12% treated with fingolimod developed a strong immune response. It is worth noting that none of these people had COVID-19 before vaccination.

A great advantage of our study is that it is a result of multicentre cooperation. We have collected data from large MS centers from all over Poland.

However, it also has its limitations. We could only determine the humoral response to vaccination, and we do not have

data on the cellular response, so the conclusions of our work can only be partial. Another limitation of our work concerns the COVID-19 vaccination system in Poland in the initial phase of the pandemic. In Poland, mainly the Comirnaty vaccine was available and the vast majority of PwMS were vaccinated with it. For this reason, differences between the effectiveness of different vaccines may have been obscured due to too few patients being vaccinated with other types of vaccine.

However, these limitations do not detract from the fact that this study shows the influence of various DMTs on the formation of the humoral response to vaccination.

Clinical implications

The COVID-19 pandemic is over, but the SARS-CoV-2 infection has stayed with us and can still be dangerous for some people. The annual influenza epidemics are a challenge. In the current demographic situation with a return to ease of travel, further pandemics can be expected. Data on the effect of multiple sclerosis treatment on seroconversion after vaccination is still very important.

Conclusions

The currently obtained data on the efficacy of vaccinations in patients with multiple sclerosis treated with DMT is very valuable. We now know that, in PwMS receiving interferon beta, glatiramer acetate, dimethyl fumarate, and teriflunomide and natalizumab, the immune response to vaccination is very good. In the case of reconstitution therapies, the immune response was also very good, but the groups of these patients in our study were very small. In PwMS treated with immunosuppressants (sphingosin-1 receptor modulators and anti-CD20 B-cell-depleting therapies), seroconversion was significantly reduced, although it still occurred in more than half of the patients. In the case of long-acting immunosuppressants, it is still important that the vaccination and therapy are well planned. Insufficient humoral immune response in some patients under immunosupressive therapies underlines the importance of fulfilling vaccinations, e.g. against hepatitis B, before such a therapy is started.

Article information

Data availability statement: *Data may be made available.*
Ethics statement: *The study was approved by the Bioethics Committee at the Medical University of Warsaw, Poland.*
Authors' contributions: *conceptualisation: A.P-P.; methodology: A.P-P., M.N., and J.S. (Janusz Sierdziński); software : J.S. (Janusz Sierdziński); validation: A.P-P. and J.S. (Janusz Sierdziński); formal analysis: A.P-P. and J.S.; investigation: A.P-P., A.K., H.B-P., K.R., M.A-S., A.G. and W.B.; resources: J.S. (Jakub Stawicki), B.L., M.P., A.P., A.J-W., J.C., K.K-B., N.N., K.W., E.J., P.P., E.K., A.L-B., A.W-H., A.S., M.P-O., B.K., A.K. (Aleksandra Karuga), and B.S.; data curation: A.P-P.; writing — original draft preparation: A.P-P.; writing — review and editing: A.P-P., M.M., W.B., J.C., A.K., M.A-S., K.R., and H.B-P.; supervision: B.Z.-P. All authors read and agreed to published version of manuscript.*
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