COMPARISON OF EXTRACORPOREAL PHOTOPHERESIS AND GLATIRAMER ACETATE EFFICACY IN THE TREATMENT OF MULTIPLE SCLEROSIS

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Multiple sclerosis is an autoimmune disorder, the development of which involves humoral and cellular immunity. The disease-modifying drugs (DMDs) for multiple sclerosis slow down the disease progression, but the therapy prescribed is not always well tolerated by patients; allergy and other side effects are possible. In this regard, the development of new methods, including non-pharmacological ones, is relevant. These methods include extracorporeal photopheresis involving UV exposure of peripheral blood lymphocytes and its modification — transimmunization (involving incubation of lymphocytes after UV exposure). The study aimed to compare and within a year assess the transimmunization and glatiramer acetate efficacy in patients with relapsing-remitting multiple sclerosis. A total of 19 adult patients with relapsing-remitting multiple sclerosis, who had been prescribed transimmunization, were assessed. Patients over the age of 18, who did not receive treatment by other methods (DMDs for multiple sclerosis, etc.), were included in the study. The comparison group consisted of 48 adult patients with relapsing-remitting multiple sclerosis, who were prescribed subcutaneous glatiramer acetate 20 mg daily. Clinical assessment was performed using EDSS. Brain and spinal cord MRI was performed in the 3.0 and 1.5 T scanners. When performing transimmunization, the decrease in the median overall EDSS score from 2 to 1.5 points was reported. In the comparison group of patients receiving glatiramer acetate, the median EDSS score changed from 1.75 to 2 points. Therefore, transimmunization is comparable with first-line DMDs for multiple sclerosis and can be used to stabilize the disease course.

Keywords: multiple sclerosis, extracorporeal photopheresis, transimmunization, autoimmune disease, glatiramer acetate

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Compliance with ethical standards: the study was approved by the Ethics Committee (protocol No. 16 dated 26 November 2020); the informed consent to participation in the study was submitted by all subjects.

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СРАВНЕНИЕ ЭФФЕКТИВНОСТИ ЭКСТРАКОРПОРАЛЬНОГО ФОТОФЕРЕЗА И ГЛАТИРАМЕРА АЦЕТАТА В ЛЕЧЕНИИ РАССЕЯННОГО СКЛЕРОЗА

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Рассеянный склероз — аутоиммунное заболевание, в развитии которого играет роль гуморальный и клеточный иммунитет. Препараты, изменяющие течение рассеянного склероза (ПИТРС), замедляют прогрессирование болезни, но не все пациенты хорошо переносят назначаемое лечение, возможны аллергические реакции и другие побочные эффекты. В связи с этим актуальна разработка новых методов лечения, включая немедикаментозные. К таким методам относят экстракорпоральный фотоферез, при котором проводится воздействие ультрафиолетовыми лучами на лимфоциты периферической крови, и его модификация — трансиммунизация (с инкубацией лимфоцитов после ультрафиолетового воздействия). Целью работы было сравнить и оценить через год эффективность трансиммунизации и препарата глатирамира ацетата у пациентов с ремиттирующим течением рассеянного склероза. Обследовали 19 взрослых пациентов с ремитирующим рассеянным склерозом, которым назначали трансиммунизацию. В исследование были включены пациенты старше 18 лет, которым не проводили другие методы лечения (ПИТРС и др.). Группу сравнения составили 48 взрослых пациентов с ремитирующим течением рассеянного склероза, которым был назначен глатирамера ацетат в дозе 20 мг подкожно ежедневно. Клиническую оценку проводили по шкале EDSS. МРТ головного и спинного мозга осуществляли на аппаратах с напряженностью магнитного поля 3,0 и 1,5 Тл. При проведении трансиммунизации отмечено снижение медианы общего показателя EDSS с 2 до 1,5 баллов. В группе сравнения пациентов, получающих глатирамера ацетат, медиана EDSS изменялась от 1,75 балла до 2 баллов. Следовательно, трансиммунизация сопоставима с ПИТРС первой линии и может быть применена для стабилизации течения заболевания.

Ключевые слова: рассеянный склероз, экстракорпоральный фотоферез, трансиммунизация, аутоиммунное заболевание, глатирамира ацетат

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Multiple sclerosis is an autoimmune disorder, the development of which involves humoral and cellular immunity. The use of disease-modifying drugs (DMDs) for multiple sclerosis has contributed greatly to slowing down the disease progression, improvement of patients' longevity and quality of life, prevention of exacerbations. However, the therapy prescribed is not always well tolerated by patients; allergy and other side effects are possible. In this regard, the development of new methods, including non-pharmacological ones, is relevant. Such methods include extracorporeal photopheresis (ECP) involving UV exposure of peripheral blood lymphocytes (involving incubation of lymphocytes after UV exposure). Extracorporeal photopheresis was proposed by Richard Edelson (Yale University, USA) in 1987 as a method for cutaneous T-cell lymphoma treatment [1]. The method was originally used for effective treatment of cutaneous T-cell lymphoma. Later indications for its use were expanded: it was used to prevent transplant rejection, for autoimmune disorders [2–13]. Phototherapy with UV radiation has various effects, such as anti-inflammatory, immunosuppressive, and cytotoxic ones. The mechanisms of its action are poorly understood, but include altered antigen presentation, decreased natural killer (NK cell) activity, and apoptosis of T cells and keratinocytes. Photopheresis results in the fact that dendritic cells acquire an antigen from apoptotic lymphocytes, which causes a specific immune response without systemic immunosuppression [14]. Globally, more than 70,000 patients have undergone a total of 3 million procedures.

Positive effect of extracorporeal photopheresis on the course of experimental autoimmune encephalomyelitis (EAE) in animals has been shown [15]. The decrease in severity of clinical disease manifestations has been reported in experimental animals. Histological assessment showed that during treatment by ECP mononuclear cell infiltrates were less prominent, that in the control group. The anti-myelin basic protein antibody (anti-MBP) levels in the Lewis rats with encephalomyelitis, which received ECP, were lower, than in untreated rats (p = 0.03). After receiving ECP animals with experimental autoimmune encephalomyelitis showed a significant decrease in the levels of pro-inflammatory cytokine — tumor necrosis factor alpha (TNFα). Thus, the study results demonstrated ECP efficacy in changing EAE severity and clinical course.

Later the ECP method was used in patients with multiple sclerosis. It was shown that ECP could be effective when used for treatment of the relapsing-remitting disease form, but it did not significantly change the course of the primary progressive form [16–20]. The authors reported safety of the method and some preliminary data on the efficacy obtained when using ECP for treatment of five patients with relapsing-remitting multiple sclerosis: in the majority of cases ECP led to the decrease in relapse rate and EDSS, MRI stabilization. The authors confirmed ECP safety and tolerability; they believe that this therapy can be useful as a therapeutic alternative in the subgroup of patients with relapsing-remitting multiple sclerosis.

The search is being conducted for adequate combinations of extracorporeal photopheresis with other extracorporeal hemocorrection and drug therapy methods that can result in the improved efficacy of autoimmune disorder treatment [21, 22].

The study aimed to compare the efficacy of transimmunization and glatiramer acetate in patients with relapsing-remitting multiple sclerosis within a year.

METHODS

A total of 19 adult patients with relapsing-remitting multiple sclerosis underwent treatment by transimmunization (modified ECP method) at the Vladimirsky Moscow Regional Research and Clinical Institute. Patients over the age of 18, who did not receive treatment by other methods (DMDs for multiple sclerosis, etc.), were included in the study.

Inclusion criteria: the diagnosis of multiple sclerosis verified in accordance with the 2005 revision of the MacDonald international criteria; patients' age at the time of enrollment 18–60 years; no therapy with DMDs for multiple sclerosis before ECP prescription; EDSS disability score below 6.0 at the time of enrollment; the ability to submit the informed consent.

Exclusion criteria: unreliable diagnosis of multiple sclerosis; secondary progressive or primary progressive course; use of DMDs for multiple sclerosis before the beginning of the study; EDSS disability score over 6.0; severe cognitive impairment.

The comparison group consisted of 48 adult patients with relapsing-remitting multiple sclerosis, who were prescribed subcutaneous glatiramer acetate 20 mg daily.

Clinical assessment of the treatment efficacy was based on the data on the patients' neurological status. The Expanded Disability Status Scale (EDSS) was used. EDSS is used to determine the degree of disability depending on the patient's ability to move, as well on the impairment degree based on the FS score. EDSS scores are in the range between 0 points (normal neurological status) and 10 points (fatal outcome of multiple sclerosis). The Kurtzke scales allow one to determine the condition severity, degree of multiple sclerosis progression, and efficacy of treatment measures.

The patients' neurological status was assessed before therapy, then before each ECP course and in case of the disease exacerbation — before prescription of glucocorticoid therapy and after it.

The following 3.0 and 1.5 T MRI scanners were used for brain and spinal cord MRI:

1) Achieva 3.0 T MRI scanner with the superconducting magnet: magnetic field strength 3.0 T, sampling interval 3–5 mm; product license No. 2004/708; certificate of conformity No. ROSS NL CH01B 84154 (Philips Medical Systems Nederland B.V., Netherlands).

2) Optima MR 450 w Gem 1.5 T MRI scanner with the superconducting magnet: magnetic field strength 1.5 T, sampling interval 3–5 mm; product license No. 95/112; hygiene certificate No. 7.99.04.944.D.000967.02.01; certificate of conformity No. ROSS FR IM 02.B08001 (General Electric, USA).

MRI was performed to verify the diagnosis before ECP, every 6 months during follow-up, and in cases of suspected exacerbation of the disease.

ECP method (transimmunization)

Equipment

1. MSC+ blood component collection system (Heamonetics Corporation, USA).

Product license of the Ministry of Health of the Russian Federation 2005/119/28.09.05.

Mononuclear cells are isolated in accordance with the RBCP protocol (stem cell isolation).

Specifications:
– width: 37 cm, length: 57 cm;
– height 44 cm (when closed), 67 cm (when operated);
– weight: 28 kg;
– power supply: 220 V, 60 Hz;
– pump speed: 20–250 mL/min;
– centrifuge speed: 3000–7000 rpm;
– anticoagulant/blood ratio: from 1 : 8 to 1 : 16.

Table 1. Patient distribution by age

Age	18–27 years	28–37 years	38–47 years	48–57 years	58–67 years	≥ 68 years
Number of individuals (*n*)	8	5	3	2	1	–

Table 2. Synoptic table of medical history data

Parameters	Median (LQ, UQ, minimum, maximum)
Males / females	2/17
Age at initiation of therapy (years)	30 [LQ = 26; UQ = 47] 20–60
Age of onset (years)	23 [LQ = 21; UQ = 30] 11–51
Disease duration (years)	6 [LQ = 2,5; UQ = 10] 1–37

Anticoagulant used: sodium citrate 2.2%, citric acid monohydrate 0.8%, glucose monohydrate 2.45%, water for injection to 1000 mL.

2. Julia extracorporeal blood irradiation system OKUFKE-320/400-600/650-01 (Metom, Russia).

Product license of the Ministry of Health of the Russian Federation 29/01040502/4362-02/25.09.2002.

Specifications:

– wavelength range: LUFT-6 quartz lamp — 320–400 nm; LK-6 lamp — 600–650 nm;

– value of incident irradiance of the cell surface within the light spot equal to the dimensions of the cell flow part, at least 3 mW\cm^2 for one lamp;

– AC power supply (220 V);

– power input: no more than 50 VA;

– operation mode cycle: 20 min (operation), 10 min (break);

– weight: no more than 2 kg.

Dimensions 270 × 160 × 80 mm.

3. Disposable container for blood and its components TU 64-2-361-85. Product license number 86/1027-12-1.

4. Photosensitizing drug Ammifurin (8-methoxypsoralen) (VILAR, Russia).

Product license number LS-002598 of 26.10.2011, 20 mg pills

Extracorporeal photochemotherapy (transimmunization) procedure

The patients took oral Ammifurin (8-methoxypsoralen) 2 h before the procedure. The Haemonetics MCS+ cell separator (USA) was used to isolate mononuclear cells in accordance with the PBSC protocol. Then mononuclear cells were exposed to UV radiation for 90 min and incubated for 20 h at a temperature of 37 °C. On the next day the cells were reinfused to the patient. The procedure was conducted twice a week every month throughout 6 months.

In the beginning of treatment ECP was performed once a month throughout 6 months. Then the interval was increased by a month every time. Later treatment was performed once every 6 months. The follow-up gadolinium-enhanced brain MRI was performed once every 6 months. Methylprednisolone pulse therapy was used in cases of clinical exacerbation based on the MRI data.

Statistical analysis

Statistical processing was performed in RStudio 2023.09.0 using R v. 4.3.1. As descriptive statistics for quantitative variables, mean values and standard deviations (M ± SD), median and quartiles (Me [LQ; UQ]), minimum and maximum were calculated. The Mann-Whitney *U* test or Wilcoxon test (for related samples) was used to compare quantitative variables in two groups. Absolute (*n*) and relative (%) rates were calculated for qualitative variables. Comparison of qualitative variables in two groups was performed using Fischer's exact test. The significance level (α) was considered to be 0.05 (null hypotheses were rejected when $p < \alpha$).

RESULTS

A total of 19 patients with relapsing-remitting multiple sclerosis, who had been receiving ECP — transimmunization, had been followed-up within a year. Most of patients were aged 18–27 years (42.1%) (Table 1).

The patients' median age was 30 years (LQ = 26; UQ = 47), between 20 and 60 years (Table 2).

The majority of patients were females (89.5% females and 10.5% males). The male to female ratio was 2/17. The median age of onset was 23 years (LQ = 21; UQ = 30), between 11 and 51 years. The median disease duration was 6 years (LQ = 2.5; UQ = 10), between 1 year and 37 years.

In the majority of cases (42.11%), visual impairment was the first clinical symptom of the disease (Table 3). Sensory disorders ranked second (31.58%). The emergence of pyramidal disorder at the disease onset was reported in 10.52% of cases. Polysymptomatic onset was observed in 15.79% of cases. It included visual impairment, sensory and cerebellar disorders, brain stem and pyramidal disorders, pyramidal disorders and disorders of the pelvis.

Table 4 presents the multiple sclerosis patients' degree of disability based on the EDSS score before treatment. The highest proportion was mild disability (EDSS score ≤ 2.5). It was reported in 15 patients (78.5% of cases). Moderate disability (EDSS score 3.0–5.5) was reported in four patients (21.5%). These patients were able to move without any assistance.

The median EDSS score in the overall group of patients with relapsing-remitting multiple sclerosis, who underwent

Table 3. Clinical manifestations at the disease onset

Clinical manifestations	Abs. (%)
Visual impairment	8 (42.11%)
Sensory disorders	6 (31.58%)
Pyramidal disorders	2 (10.52%)
Polysymptomatic onset	3 (15.79%)

Table 4. Disability severity based on the EDSS score before treatment

EDSS	Group I
0–2.5 (mild disability)	78.95% (15)
3.0–5.5 (moderate disability)	21.05% (4)
Over 6.0 (severe disability)	–
Median EDSS score	1.5 [LQ = 1.5; UQ = 2.5] 1–5.5

extracorporeal photopheresis, was 2 (LQ = 1.5; UQ = 2.5), between 1 and 5.5. This score did not change after a year of treatment: 1.5 (LQ = 1; UQ = 2), between 0 and 3.5. The decrease in EDSS scores was reported in seven patients (36.84%) (see Figure).

Thus, the increase in EDSS scores in the overall group of patients relative to the previous values was reported in 5.26% of cases. In five patients, foci accumulating the contrast agent in the white matter were revealed on MRI within a year after the beginning of treatment.

In the comparison group of patients with relapsing-remitting multiple sclerosis, who underwent treatment with glatiramer acetate, the median EDSS score was 1.75 (LQ = 1.5; UQ = 2.5), between 1 and 5. The difference between this group of patients and the group of patients, who received transimmunization, was non-significant (p = 0.748). In a year the median EDSS score was 2 (LQ = 1.5; UQ = 3), between 1 and 5. The increase in EDSS score within a year after the beginning of treatment was reported in 29.27% of cases. The median EDSS scores reported after a year of treatment with extracorporeal photopheresis — transimmunization showed no negative results relative to the use of first-line DMD for multiple sclerosis, glatiramer acetate (Fig. 1).

Clinical case

The female patient aged 40 years complained of gait disorder, intermittent urinary incontinence. She got ill at the age of 29 years: weakness in the left limbs and a speech disorder emerged. Multiple demyelination foci were found on brain MRI. The ophthalmologist diagnosed partial atrophy of the optic nerve. As for neurological status, the EDSS score of 5.5 was reported. After a single ECP procedure the EDSS score decreased to 5, after four procedures — to 4.5, and after five procedures it was 2.5. Later there was a disease exacerbation, and the EDSS score increased to 3.5, but it did not get worse before the beginning of treatment. Thus, a beneficial outcome was achieved given high EDSS score and long disease duration (11 years).

DISCUSSION

The data on the use of extracorporeal photochemotherapy method and its modification (with blood lymphocyte incubation) in patients with relapsing-remitting multiple sclerosis are reported. The method has proven itself over a long time in various disorders associated of autoimmune manifestations (graft-versus-host disease, autoimmune manifestations in coronavirus infection, Crohn's disease, etc.) [23]. A number of authors used the ECP method without lymphocyte incubation in combination with plasmapheresis in 40 patients with multiple sclerosis [24–26]. When the anti-myelin basic protein antibody levels exceeded 500 μg/L, plasma was removed, and lymphocytes were exposed to UV radiation. When the anti-myelin basic protein antibody concentration was below 500 μg/L, the extracted plasma with the lymphocyte suspension was irradiated and then reinfused. In 36 patients (90%), good and satisfactory therapeutic effect was achieved assessed based on the neurological deficit regression according to the EDSS scores (good effect — 2 points, satisfactory effect — 1 point). In four patients, the effect was considered to be negligible. Patient's condition deterioration or side effect was reported in none of the cases. A one-year follow-up revealed no disease progression. Improvement in the form of EDSS score decrease by 1–2 points was observed. The anti-myelin basic protein antibody titer decreased 2-fold relative to baseline. The decrease in the CD16 natural killer cell and CD4 T helper counts, as well as in mitogen-induced γ-IFN production was

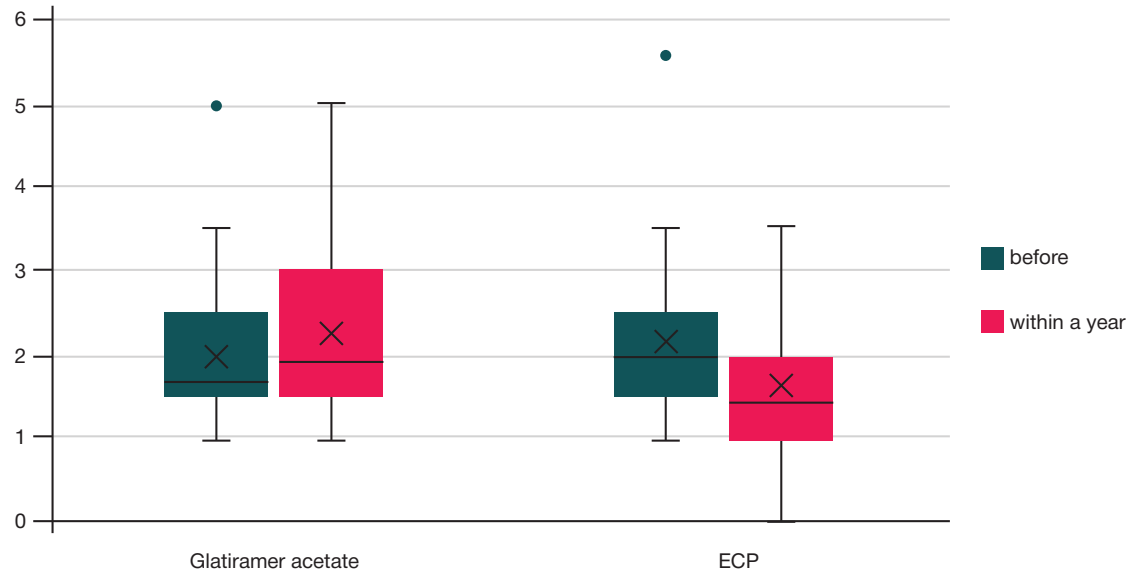

Fig. Changes in EDSS scores of patients with multiple sclerosis treated using extracorporeal photopheresis (ECP) and glatiramer acetate

reported. Examination of patients within 6 months of follow-up revealed no disease exacerbation.

In this study we compared the modified ECP (transimmunization) and glatiramer acetate efficacy in patients with relapsing-remitting multiple sclerosis during the one-year follow-up. The findings show that transimmunization can be comparable with conventional treatment methods, such as glatiramer acetate, which shows that new approaches to therapy of this disease are possible.

Multiple sclerosis is a complex autoimmune disorder, and treatment of the disorder requires a personalized approach. The use of ECP based on the lymphocyte UV exposure has shown its efficacy in terms of decreasing the median EDSS score in patients receiving transimmunization from 2 to 1.5 points. Such a decrease indicates neurological status improvement and stability of the condition in a large number of patients, which represents an important aspect of multiple sclerosis treatment.

Comparison with the group of patients taking glatiramer acetate has shown that the median EDSS score of this group has remained fairly constant: it increased from 1.75 to 2 points. This suggests that transimmunization may not only be effective, but also more preferable for patients, who do not tolerate conventional treatment methods or have side effects.

It is important to note that ECP and its modifications, such as transimmunization, cause no allergy or generation of autoantibodies, which makes these a safe alternative for patients having contraindications for drugs. This is particularly true in the light of the growing need for the development of new treatment methods considering the patients' individual characteristics. However, it should be considered that in our study the increase in EDSS score was observed in some patients, which emphasizes the importance of continuous monitoring of patients' condition and possible use of pulse therapy for rapid exacerbation management. When performing further research, it is necessary to focus on the longer patient follow-up and assessment of the long-term transimmunization effects, as well as on studying its combinations with other treatment methods.

Our findings confirm the possibility of using transimmunization as an effective method for treatment of relapsing-remitting multiple sclerosis.

CONCLUSIONS

The data of the one-year follow-up of patients with relapsing-remitting multiple sclerosis undergoing non-pharmacological treatment by transimmunization, the modified ECP method, are reported. The procedure was prescribed every month throughout up to six months, then the interval was increased by a month every time, and then transimmunization was performed once every six months. The patients had mild-to-moderate disability based on the EDSS scores before the beginning of treatment. During the one-year follow-up we noted a decrease in the median total EDSS score from 2 to 1.5 points. In one case, the increase in EDSS score following the improvement of the patient's clinical condition within six months of transimmunization, but it did not reach the value reported before the beginning of treatment. In the comparison group of patients taking glatiramer acetate, there were also cases of the EDSS score increase relative to baseline requiring methylprednisolone pulse therapy. We have revealed no negative effect of transimmunization on the course of multiple sclerosis within a year of patient follow-up. Thus, the use of blood transimmunization is comparable with the use of first-line DMDs for multiple sclerosis, it causes no allergy or addiction (generation of antibodies against the protein drug), and can be recommended as both initial therapy and therapy after unsuccessful use of first-line DMDs for multiple sclerosis due to side effects. Since it is impossible to completely modify the patients' immune status, the disease exacerbations and the use of pulse therapy for rapid suppression of the active autoimmune process accompanied by inflammation in the central nervous system are possible when performing ECP, as when using other multiple sclerosis treatment methods. To assess the ECP effect on the course of multiple sclerosis, it is possible to follow up these patients undergoing treatment over a longer time. This method can be used in clinical practice for patients with multiple sclerosis as one of the first-line methods to prevent the disease progression. Further studies can be aimed to assess the transimmunization mechanism of action at the cellular level and assess its efficacy when combined with other non-pharmacological treatment methods.

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