FIRST LINE THERAPY FOR MULTIPLE SCLEROSIS: CYTOKINE LEVELS AND THE IMPACT OF HERPESVIRUS INFECTION

Baranova NS[1]✉, Gris MS[1], Baranov AA[1], Spirin NN[1], Artyuhov AS[2], Kiselev DV[1]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Pirogov Russian National Research Medical University, Moscow, Russia

The effects of the disease modifying drugs (DMDs) for multiple sclerosis (MS), interferon beta (IFNβ) and glatiramer acetate (GA), on the cytokine levels of individuals with MS are poorly understood. The effects of persistent herpesvirus infection (PHVI) on the cytokine production during treatment with DMDs for MS have not been identified. The role of cytokines and PHVI in the development of the treatment-related adverse events (AEs) has not been determined. The study was aimed to assess serum cytokine levels in patients with MS treated or not treated with DMDs for MS, and to determine the relationships between the cytokine levels, herpesvirus infection, and AEs. A total of 36 patients (12 males and 24 females, median age 38.50 (28.00; 48.50) years) with relapsing-remitting MS (criteria by McDonald, 2010) were examined. PHVI reactivation was observed in 18 individuals; in 10 of them it was associated with the history of the virus-associated exacerbation (VAE) of MS or VAE detected during assessment. A total of 30 patients were treated with DMDs for MS: 16 individuals with IFNβ, 14 individuals with GA. Systemic AEs were reported in 9 individuals. Serum levels of 15 cytokines were determined using the xMAP multiplex technique. Patients with MS showed a significant increase in the levels of IL10 ($p < 0.01$) and IL33 ($p < 0.001$) relative to donors when treated or not treated with DMDs for MS; the increase in IL31 levels was reported only in naïve patients ($p < 0.05$). At the same time, individuals with MS had low levels of IL1β, IL17F, IL22, IL25, IL23, and TNFα ($p < 0.01$). We revealed no differences in cytokine levels in the context of taking IFNβ or GA. Elevated IL10 levels were associated with PHVI reactivation ($p < 0.01$). We revealed significant correlations between high levels of IL31 and VAE ($p < 0.01$), IL33 and PHVI ($p < 0.01$). The IL1β levels were significantly higher in individuals with PHVI reactivation treated with DMDs for MS. There were no differences in cytokine levels associated with the presence or absence of systemic AEs. The latter predominated in individuals with PHVI reactivation and VAE. The cytokine levels of individuals with MS are affected by treatment with DMDs for MS and herpesvirus infections.

Keywords: multiple sclerosis, disease modifying drugs for multiple sclerosis, cytokines, herpes, adverse events

Funding: the study was supported by the Foundation for Assistance to Small Innovative Enterprises in Science and Technology (Innovation Promotion Foundation) within the framework of the program UMNIK: Participant of the Youth Research and Innovation Contest (contracts No. 3560GU1/2014 dated 23.09.2014, No. 8815GU2/2015 dated 17.12.2015).

Author contribution: Baranova NS, Gris MS — study planning and design; Gris MS, Artyuhov AS — data acquisition and research procedure; Baranova NS, Gris MS, Baranov AA — data analysis; all authors — data interpretation; Baranova NS, Gris MS — manuscript drafting; all authors — manuscript editing.

Compliance with ethical standards: the study was approved by the local Ethics Committee of the Yaroslavl State Medical University (protocol No. 1 dated 10 October 2013). The informed consent was submitted by all patients.

✉ **Correspondence should be addressed:** Natalia S. Baranova
Revolutsionnaya, 5, Yaroslavl, 150000, Russia; baranova_ns@mail.ru

Received: 23.04.2024 **Accepted:** 05.05.2024 **Published online:** 19.06.2024

DOI: 10.24075/brsmu.2024.021

ТЕРАПИЯ РАССЕЯННОГО СКЛЕРОЗА ПРЕПАРАТАМИ ПЕРВОЙ ЛИНИИ: УРОВЕНЬ ЦИТОКИНОВ И ВЛИЯНИЕ ГЕРПЕТИЧЕСКОЙ ИНФЕКЦИИ

Н. С. Баранова[1]✉, М. С. Грись[1], А. А. Баранов[1], Н. Н. Спирин[1], А. С. Артюхов[2], Д. В. Киселев[1]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва, Россия

При рассеянном склерозе (РС) недостаточно изучено влияние на уровень цитокинов терапии препаратами, изменяющими течение рассеянного склероза (ПИТРС) — интерферона-бета (ИНФ-β) и глатирамера ацетата (ГА). Не установлено влияние персистирующей герпес-вирусной инфекции (ПГВИ) на продукцию цитокинов на фоне терапии ПИТРС. Не определена роль цитокинов и ПГВИ в развитии нежелательных явлений (НЯ) при лечении. Целью исследования было провести оценку концентрации цитокинов в сыворотке крови у больных РС, находящихся на терапии ПИТРС и без нее, определение связи между уровнем цитокинов, герпес-вирусной инфекцией и НЯ. Обследовано 36 больных (12 мужчин и 24 женщины, медиана возраста 38,50 (28,00; 48,50) года) с ремитирующим течением РС (критерии McDonald, 2010). У 18 человек наблюдали реактивацию ПГВИ, у 10 она сопровождалась развитием вирус-ассоциированного обострения (ВАО) РС в анамнезе или при осмотре. Терапию ПИТРС проводили 30 пациентам: 16 человек — ИНФ-β, 14 человек — ГА. Системные НЯ были у 9 человек. Концентрацию 15 цитокинов в сыворотке крови определяли мультиплексной технологией xMAP. У пациентов с РС по сравнению с донорами были значимо повышены IL10 ($p < 0,01$) и IL33 ($p < 0,001$) при терапии ПИТРС и без нее, уровень IL31 возрос только у наивных больных ($p < 0,05$). Одновременно при РС были низкие значения IL1β, IL17F, IL22, IL25, IL23 и ФНО-α ($p < 0,01$). Не установлено различий в уровне цитокинов на фоне ИНФ-β или ГА. IL10 был повышен при реактивации ПГВИ ($p < 0,01$). Выявлены достоверные связи между высокими значениями IL31 и ВАО ($p < 0,01$), IL33 и ПГВИ ($p < 0,01$). На фоне терапии ИНФ-β при реактивации ПГВИ концентрация IL1β была значимо выше. Уровень цитокинов не различался при наличии или отсутствии системных НЯ. Последние преобладали при реактивации ПГВИ и ВАО. На уровень цитокинов при РС влияют терапия ПИТРС и герпес-вирусные инфекции.

Ключевые слова: рассеянный склероз, изменяющие течение рассеянного склероза препараты, цитокины, герпес, нежелательные явления

Финансирование: работа выполнена при финансовой поддержке Федерального государственного бюджетного учреждения «Фонд содействия развитию малых форм предприятий в научно-технической сфере» (Фонд содействия инновациям) в рамках программы УМНИК: Участник молодежного научно-инновационного конкурса (договоры №3560ГУ1/2014 от 23.09.2014, № 8815ГУ2/2015 от 17.12.2015).

Вклад авторов: Н. С. Баранова, М. С. Грись — планирование и дизайн исследования; М. С. Грись, А. С. Артюхов — сбор данных и проведение исследования; Н. С. Баранова, М. С. Грись, А. А. Баранов — анализ данных; все авторы — интерпретация данных; Н. С. Баранова, М. С. Грись — подготовка черновика рукописи; все авторы — редактирование рукописи.

Соблюдение этических стандартов: исследование одобрено локальным этическим комитетом ФГБОУ ВО ЯГМУ Минздрава РФ (протокол № 1 от «10» октября 2013 г.). Все пациенты подписали добровольное информированное согласие.

✉ **Для корреспонденции:** Наталия Сергеевна Баранова
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; baranova_ns@mail.ru

Статья получена: 23.04.2024 **Статья принята к печати:** 05.05.2024 **Опубликована онлайн:** 19.06.2024

DOI: 10.24075/vrgmu.2024.021

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system with the autoimmune inflammatory and neurodegenerative pathogenetic mechanisms [1]. Interferons beta (IFNβ) and glatiramer acetate (GA) are the main first line disease modifying drugs (DMDs) for MS [1–3]. Today, despite the long-term effective use of high-dose IFNβ and GA in clinical practice, their exact mechanisms of action are poorly understood [4, 5]. The effects of IFNβ and GA on the levels of pro-inflammatory (interleukin (IL) IL1β, IL6, IL17, IL23, tumor necrosis factor — (TNFα), interferon-γ (IFNγ)) and anti-inflammatory (IL4, IL10) cytokines are the most thoroughly studied [6–8].There are sporadic papers focused on comparative assessment of the cytokine profiles of untreated patients and patients using IFNβ or GA [9–13]. In foreign literature, there is a number of studies focused on assessing the effects of these drugs on the levels of IL31 and IL33 [10, 11, 12, 14–17], however, no such studies have been carried out in Russia. Furthermore, the contribution of herpesvirus infection representing one of the etiological factors of the disease and the trigger of exacerbation in some patients with MS to the cytokine profile formation during treatment with IFNβ or GA is poorly understood [18, 19].

We have earlier determined the differences in the cytokine levels associated with the disease exacerbation and remission, as well as their correlations with the clinical manifestations of the persistent herpesvirus infection (PHVI) reactivation [20], however, no assessment of the effects of the ongoing therapy, drugs use, and the treatment-related systemic adverse events (AEs) have been carried out. This study is an extension of scientific research on the issue.

The study was aimed to assess serum cytokine levels in patients treated and not treated with high-dose IFNβ or GA, as well as to determine the relationships between the cytokine levels, herpesvirus infection and the treatment-related AEs.

METHODS

A total of 36 patients (12 males and 24 females) were included in the study. Inclusion criteria: reliable diagnosis of MS based on the criteria by McDonald, et al. (2010). Patients were enrolled November 2013 to June 2017. The patients' median age at the time of examination was 38.50 (28.00; 48.50) years, the age of onset was 27.00 (21.50; 38.00) years, and the disease duration was 9.50 (3.50; 12.50) years. All the patients had relapsing-remitting MS (RRMS), 29 individuals (80.6%) had remission, 7 individuals (19.4%) had exacerbation of the disease. All patients with RRMS were divided into patients with active and inactive MS (17 (47.2%) and 19 (52.8%) individuals, respectively) in accordance with the classification by F. Lublin (2013). Furthermore, patients with highly active MS (6 individuals (35.3%) having two or more exacerbations per year) were further counted among patients with active MS. The neurological status clinical assessment was performed using the double scoring system by J. F. Kurtzke: Functional Systems (FS) and Expanded Disability Status Scale (EDSS).

A total of 30 patients (83.3%) were treated with DMDs for MS (16 with high-dose IFNβ and 14 with GA) and 6 individuals (16.7%) received no therapy. A total of 18 patients (50.0%) had reactivation of PHVI, and in 10 individuals (27.8%) PHVI reactivation was associated with the history of virus-associated exacerbation (VAE) or VAE detected during examination. Tolerability of the ongoing therapy with DMDs for MS was estimated in 28 patients, who filled the questionnaire for identification of the treatment-related AEs. We analyzed systemic AEs reported in 9 individuals (32.1%).

To achieve the objectives, we performed comparative analysis of the clinical characteristics of the groups of patients with MS not treated with DMDs for MS and treated with IFNβ or GA only (Table 1).

The groups compared did not differ in terms of gender, age of onset, fact of detecting serological markers of past EBV infection. The patients' age at the time of examination was significantly higher in the group of patients taking any DMD for MS than in the group not taking such drugs ($p < 0.05$). The same trend was reported for the groups using IFNβ or GA ($p > 0.05$).

The disease duration and the total number of exacerbations were significantly higher in the overall group of patients taking DMDs for MS and the patients taking IFNβ or GA, than in untreated patients. The total amount of neurologic deficit and the time to reach disability (EDSS = 3) were higher in the context of taking DMDs for MS, however, the differences were non-significant. The signs of PHVI reactivation and VAE, serological markers of past cytomegalovirus (CMV) infection were slightly more frequent in these groups.

More active course of MS, higher rates of exacerbations and highly active variant of the disease, the emergence of new foci on MRI compared to patients taking DMDs for MS were reported in patients not treated with such drugs. The average annual exacerbation rate and the rates of disease progression and neurologic deficit increase were significantly higher ($p < 0.05$ and $p < 0.01$). There were no differences in the majority of indicators between the groups of patients taking IFNβ or GA. However, the use of IFNβ was associated with the more severe systemic AE severity, than the use of GA.

We assessed 18 generally healthy donors as controls. The control group was matched by gender — 7 males (38.9%) and 11 females (61.1%); age — 39.10 (29.00; 49.60) years with the group of patients having MS. Exclusion criteria: chronic neurologic disorder; exacerbation of somatic disorder. The standard neurologic examination and history taking aimed to exclude the disorders capable of affecting the assessment results were performed in all patients.

Blood serum testing aimed to determine the levels of type-specific IgM and IgG against type 1 and 2 herpes simplex virus (HSV), IgM and IgG against varicella-zoster virus (VZV), IgM and IgG against the VCA capsid antigen of the Epstein–Barr virus (EBV), IgG against early antigens EA and nuclear antigen NA of EBV, IgM and IgG against CMV were carried out by enzyme-linked immunoassay (ELISA) using the standard reagent kits (Vector-Best; Novosibirsk, Russia) at the clinical and diagnostic laboratory, Set' LLC (Yaroslavl), in accordance with the manufacturer's instructions in all patients with MS and members of the control groups.

Serum levels of 15 cytokines (IL1β, IL4, IL6, IL10, IL17A, IL17F, IL21, IL22, IL23, IL25, IL31, IL33, IFNγ, TNFα, sCD40L) were determined by the xMAP multiplex technique using the Bio-PlexTM 200 System (Bio-Rad; USA) and appropriate reagents (Bio-Rad; USA) at the laboratory of the Research Institute of Translational Medicine, Pirogov Russian National Research Medical University.

Statistical processing of the results was performed using the Statistica 10.0 software package (StatSoft; USA) including the generally accepted parametric and nonparametric analysis methods. As for parameters, the distribution of which was non-normal, the Mann–Whitney U test was used to compare two groups, and the Kruskal–Wallis test was used to compare three or more groups (for independent groups). The results were presented as the median (Me) with interquartile range [25th; 75th percentiles], the mean (M) and standard deviation

Table 1. Clinical characteristics of patients with MS (Me (25th; 75th percentiles), *n* = 36)

Indicator	No therapy with DMDs for MS (*n* = 6)	Therapy with IFNβ or GA (*n* = 30)	Therapy with IFNβ (*n* = 16)	Therapy with GA (*n* = 14)
Gender: males, *n* (%)	2 (33.3)	10 (33.3)	6 (37.5)	4 (28.6)
females, *n* (%)	4 (66.7)	20 (66.7)	10 (62.5)	10 (71.4)
Age (years)	24.50 (23.00; 39.00)	39.00* (34.00; 51.00)	38.50 (33.00; 45.00)	39.00 (35.00; 55.00)
Age of onset (years)	22.50 (22.00; 39.00)	27.00 (21.00; 37.00)	28.50 (22.00; 34.00)	27.00 (21.00; 39.00)
Disease duration (years)	1.00 (1.00; 4.00)	11.00** (6.00; 18.00)	11.00* (5.50; 12.50)	11.00* (6.00; 20.00)
Duration of therapy with DMDs for MS (months)		30.00 (9.00; 67.00)	30.00 (14.00; 73.00)	38.00 (29.00; 74.00)
Highly active, *n* (%)	3 (50.0)	3 (10.0)*	2 (12.5)	1 (7.1)
Exacerbation detected (clinically + MRI), *n* (%)	3 (50.0)	4 (13.3)	3 (18.8)	1 (7.1)
Emergence of new foci on MRI, *n* (%)	4 (66.7)	8 (26.7)	6 (37.5)	2 (14.3)*
EDSS at the time of examination (points)	2.50 (1.50; 3.00)	3.50 (2.00; 4.50)	3.50 (2.50; 4.75)	3.50 (2.00; 4.50)
Total number of exacerbations	2.00 (1.00; 3.00)	4.00** (3.00; 6.00)	4.00* (3.00; 6.50)	4.50** (4.00; 6.00)
Average annual exacerbation rate	1.50 (0.75;2.00)	0.42* (0.32; 0.83)	0.58* (0.31; 0.90)	0.37* (0.32; 0.83)
Progression rate (points/year)	1.75 (0.75; 2.00)	0.28** (0.21; 0.50)	0.46* (0.22; 0.66)	0.23** (0.19; 0.50)
Duration of first remission (months)	6.00 (2.00; 15.00)	12.00 (8.00; 24.00)	12.50 (9.00; 24.00)	12.00 (8.00; 24.00)
Rate of neurologic deficit increase (points)	3.00 (1.50; 5.00)	0.53** (0.33; 1.00)	0.73** (0.35; 1.00)	0.39** (0.27; 1.08)
Total amount of neurologic deficit on the FS scale (points)	5.50 (2.00; 6.00)	7.50 (3.00; 9.00)	7.50 (4.00; 9.00)	7.50 (3.00; 9.00)
Time to reach disability EDSS = 3 (years)	0.50 (0.00; 3.00)	3.50 (0.00; 7.00)	2.75 (0.00; 8.50)	4.00 (0.00; 7.00)
Duration of therapy with DMDs for MS (months)		34.50 (20.00; 74.00)	30.00 (14.00; 73.00)	38.00 (29.00; 74.00)
Systemic adverse events associated with using drugs modifying the course of MS (*n* = 28), *n* (%)		9 (32.1) (*n* = 28)	5 (35.7) (*n* = 14)	4 (28.6)
Severity of systemic AEs associated with DMDs for MS (points)		6.00 (1.50; 11.00)	6.50 (5.00; 12.00)	2.00 (0.00; 11.00)
Reactivation of persistent herpesvirus infection (PHVI) detected, *n* (%)	2 (33.3)	16 (53.3)	10 (62.%)	6 (42.7)
Virus-associated exacerbation (VAE) detected, *n* (%)	1 (16.7)	9 (30.0)	5 (31.3)	4 (28.6%)
Serological markers of past EBV infection detected, *n* (%)	6 (100)	30 (100)	16 (100)	14 (100)
Serological markers of past CMV infection detected, *n* (%)	4 (66.7)	27 (90.0)	15 (93.8)	12 (85.7)

Note: * — $p < 0.05$, ** — $p < 0.01$ compared to the group not treated with DMDs for MS.

(σ). Fisher's exact test was used to compare samples based on the qualitative traits and to assess the occurrence of traits. Spearman's rank correlation was used for correlation analysis. The differences were considered significant at $p < 0.05$.

RESULTS

Cytokine levels in patients with MS and donors

Table 2 provides the results of assessing cytokine levels in the groups of patients, not treated with DMDs for MS, treated with DMDs for MS, using high-dose IFNβ or GA, and donors.

A significant increase in the levels of IL10 ($p < 0.01$) and IL33 ($p < 0.001$) relative to controls was reported for all groups of patients with MS. The IL31 levels significantly higher relative to donors was reported only for the group of patients not treated with DMDs for MS ($p < 0.05$). The upward trend of the IL4 levels associated with MS was reported ($p > 0.05$).

In contrast, the levels of IL1β, IL17F, IL22, IL25, and TNFα were significantly higher in donors, than in patients. There were almost no differences in the levels of IL6, IL17A, IL21, IL23, IFNγ, and sCD40L between groups.

Cytokine levels in patients not treated and treated with DMDs for MS

We revealed a significant increase in the levels of IL10 in the naïve patients compared to patients treated with DMDs for MS. The untreated patients showed a significant increase in the IL31 levels compared to the overall group of patients taking DMDs for MS and GA. These differences were a trend in individuals taking IFNβ ($p = 0.06$). There were no differences in the levels of other cytokines between the groups compared ($p > 0.05$).

We also revealed no differences in the tested cytokine levels in the groups of patients taking IFNβ or GA.

The increase in the levels of IL31 (by more than 15.08 pg/mL; M + 3σ in the group of donors) was found in 5 individuals (13.8%), more often in the group of patients not taking DMDs for MS. High IL33 levels (exceeding 3.40 pg/mL; M + 3σ in the group of donors) were reported in 20 patients (52.8%), the

Table 2. Serum cytokine levels (Me (25th; 75th percentiles)) of patients with MS and donors

Indicator (pg/mL)	Donors (n = 18)	No therapy with DMDs for MS (n = 6)	Therapy with IFNβ or GA (n = 30)	Therapy with IFNβ (n = 16)	Therapy with GA (n = 14)	p
	1	2	3	4	5	
IL1β	1.45 (0.16; 2.18)	0.04 (0.01; 0.05)	0.04 (0.00; 0.08)	0.04 (0.00; 0.09)	0.05 (0.00; 0.06)	$p_{1-2} < 0.05$ $p_{1-3} < 0.001$ $p_{1-4} < 0.01$ $p_{1-5} < 0.01$
IL4	0.01 (0;73; 3.24)	2.39 (2.29; 2.89)	4.71 (2.22; 11.34)	4.88 (2.59; 8.30)	4.40 (1.75; 12.33)	n/s
IL6	1.36 (0.27; 3.68)	0.70 (0.44; 0.96)	0.52 (0.30; 1.11)	0.59 (0.37; 1.30)	0.52 (0.15; 0.74)	n/s
IL10	0.01 (0.00; 0.01)	3.52 (2.73; 5.25)	1.80 (0.90; 2.73)	2.26 (0.90; 2.73)	1.80 (0.60; 2.10)	$p_{1-2} < 0.01$ $p_{1-3} < 0.01$ $p_{1-4} < 0.01$ $p_{1-5} < 0.01$ $p_{2-3} < 0.01$ $p_{2-4} < 0.05$ $p_{2-5} < 0.01$
IL17A	0.58 (0.00; 1.74)	0.64 (0.42; 0.99)	0.57 (0.28; 0.85)	0.54 (0.28; 0.82)	0.57 (0.14; 0.92)	n/s
IL17 F	6.76 (4.02; 10.6)	0.01 (0.00; 0.93)	0.01 (0.01; 0.62)	0.01 (0.01; 0.62)	0.01 (0.00; 1.25)	$p_{1-2} < 0.001$ $p_{1-3} < 0.001$ $p_{1-4} < 0.001$ $p_{1-5} < 0.001$
IL21	0.01 (0.00; 0.49)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.01 (0.00; 0.89)	0.00 (0.00; 0.01)	n/s
IL22	47.43 (38.42; 72.64)	0.00 (0.00; 0.00)	0.24 (0.00; 0.32)	0.08 (0.00; 0.32)	0.32 (0.00; 0.63)	$p_{1-2} < 0.001$ $p_{1-3} < 0.001$ $p_{1-4} < 0.001$ $p_{1-5} < 0.001$
IL23	80.11 (0.00; 114.44)	0.00 (0.00; 2.94)	5.51 (0.00; 8.81)	4.41 (0.00; 10.63)	5.51 (0.00; 8.81)	n/s
IL25	13.73 (6.10; 28.99)	0.27 (0.11; 0.32)	0.11 (0.00; 0.32)	0.11 (0.00; 0.32)	0.11 (0.00; 0.32)	$p_{1-2} < 0.001$ $p_{1-3} < 0.001$ $p_{1-4} < 0.001$ $p_{1-5} < 0.001$
IL31	6.28 (2.87; 8.62)	11.61 (8.81; 15.73)	5.71 (3.00; 8.19)	6.95 (3.85; 10.37)	5.09 (2.63; 7.57)	$p_{1-2} < 0.05$ $p_{2-3} < 0.05$ $p_{2-4} = 0.06$ $p_{2-5} < 0.05$
IL33	0.52 (0.17; 0.78)	3.63 (2.51; 9.55)	4.46 (1.12; 6.67)	5.43 (1.95; 9.14)	4.05 (1.12; 5.84)	$p_{1-2} < 0.001$ $p_{1-3} < 0.001$ $p_{1-4} < 0.001$ $p_{1-5} < 0.001$
IFNγ	0.45 (0.00; 5.33)	0.49 (0.49; 1.48)	0.49 (0.49; 1.23)	0.99 (0.49; 1.11)	0.49 (0.00; 1.48)	n/s
TNFα	17.38 (13.65; 31.61)	0.82 (0.49; 1.17)	0.52 (0.44; 0.74)	0.53 (0.45; 0.88)	0.51 (0.44; 0.68)	$p_{1-2} < 0.001$ $p_{1-3} < 0.001$ $p_{1-4} < 0.001$ $p_{1-5} < 0.001$
sCD40L	110.81 (83.58; 122.55)	83.58 (34.36; 158.24)	76.77 (39.27; 112.69)	81.23 (44.29; 122.56)	65.97 (25.41; 95.32)	n/s

Note: n/s — non-significant differences between groups.

rate was almost the same in all the groups compared. Isolated hyperproduction of IL31 was found in only one patient out of five, while in other cases (80.0%) a simultaneous increase in the IL31 and IL33 levels was observed. The IL17A, IL17F and IL21 levels rarely exceeded the normal reference values (in 2.8%, 5.6% and 5.6% of cases, respectively) and always accompanied the increase in the IL33 levels. The levels of other cytokines exceeded the upper limit of normal range in none of the cases.

Herpesvirus infection, therapy with DMDs for MS, and cytokine levels

Reactivation of PHVI took place in 16 patients taking DMDs for MS, IFNβ or GA put of 30 (53.3%). In 9 cases (30.8%), it was associated with the history of MS exacerbation (VAE+) or the MS exacerbation detected during examination. The IL10 levels were significantly higher in patients with PHVI reactivation, than in patients without it (Table 3). These patients also showed an upward trend of the IL1β, IL23 and IL33 levels ($p > 0.05$). No differences in the levels of other cytokines between the groups compared were revealed. The cytokine levels of patients with or without VAE were the same.

Significant correlations between high IL31 levels and VAE+ ($r = 0.51$; $p < 0.01$), IL33 levels and PHVI ($r = 0.40$; $p < 0.05$) were revealed when using all DMDs for MS.

The levels of IL1β were significantly higher in patients treated with IFNβ with PHVI reactivation, than in patients with no PHVI reactivation (n = 10, 0.07 ± 0.06 pg/mL and n = 6, 0.02 ± 0.04 pg/mL, $p < 0.05$, respectively). In this group, the IL17A and IL33 levels were higher in patients with VAE+, than in individuals without VAE (IL17A — 0.92 ± 0.42 pg/mL, n = 5; 0.49 ± 0.52 pg/mL, n = 11; IL33 — 10.70 ± 5.79 pg/mL, n = 5; and 5.63 ± 7.83 pg/mL, n = 11; $p < 0.05$ in both cases). We also revealed a significant correlation between VAE+ and high levels of IL31 and IL33 ($r = 0.56$ at $p < 0.05$ and $r = 0.52$ at $p < 0.05$, respectively).

Table 3. Serum cytokine levels (Me (25th; 75th percentiles)) of patients with MS treated with DMDs for MS, who had clinical manifestations/no clinical manifestations of PHVI

Indicator (pg/mL)	MS with clinical manifestations of PHVI (*n* = 16)	MS with no clinical manifestations of PHVI (*n* = 14)
IL1β	0.06 (0.02;0.08)	0.01 (0.00; 0.05)
IL4	4.88 (2;63;10.95)	4.61 (1.75; 13.11)
IL6	0.74 (0.23;1.81)	0.44 (0.30; 0.74)
IL10	2.57 (1.65;2.73)**	1.05 (0.30; 1.95)
IL17A	0.64 (0.35;0.96)	0.43 (0.14; 0.57)
IL17 F	0.01 (0.00;0.62)	0.01 (0.00; 1.25)
IL21	0.01 (0.00;2.38)	0.00 (0.00; 0.00)
IL22	0.32 (0.00;0.48)	0.00 (0.00; 0.32)
IL23	8.80 (0.00;11.36)	2.57 (0.00; 5.87)
IL25	0.22 (0.06;0.53)	0.06 (0.00; 0.11)
IL31	6.33 (4.47;8.81)	4.78 (2.63; 7.57)
IL33	5.43 (3.21;9.14)	2.23 (1.12; 5.84)
IFNγ	0.74 (0.49;1.36)	0.49 (0.49; 0.99)
TNFα	0.53 (0.44;1.04)	0.52 (0.45; 0.68)
sCD40L	80.53 (41.85;111.52)	65.97 (25.41; 117.39)

Note: ** — $p < 0.01$ between groups.

In patients treated with GA, there were no differences in the tested cytokine levels between the groups of patients having or not having clinical manifestations of PHVI reactivation or VAE. Furthermore, in contrast to IFNβ, no correlation of high IL31, IL33 levels with the PHVI reactivation or VAE was revealed when using GA.

In patients not treated with DMDs for MS, no analysis of the cytokine levels depending on the fact of PHVI reactivation/no PHVI reactivation or VAE was performed due to small number of patients in each group.

Therapy with DMDs for MS, adverse events, herpesvirus infection, and cytokine levels

Systemic AEs were reported in 9 patients out of 28 (32.1%) treated with DMDs for MS. When treated with IFNβ, 5 individuals (35.7%; *n* = 14) experienced a flu-like syndrome (FLS), and 4 patients taking GA (28.6%; *n* = 14) showed the systemic vasomotor response.

In individuals taking IFNβ and GA having or not having systemic AEs, no differences in the tested cytokine levels and the rate of increased levels of some cytokines were revealed. The systemic AE severity also was not correlated to the cytokine levels.

Predominance of systemic AEs in the groups of patients with PHVI reactivation and VAE+ was reported. Thus, during treatment with IFNβ or GA AEs were observed in 7 patients with PHVI out of 15 (46.7%) and 2 patients without PHVI out of 13 (15.4%) ($p = 0.08$). In individuals with VAE, the AE rates were 44.4% (4 individuals out of 9) and 26.3% (5 individuals out of 19) ($p > 0.05$).

During treatment with IFNβ, the AE rates in the groups of patients showing and not showing PHVI reactivation were 44.4% (4 individuals out of 9) and 20.0% (1 individual out of 5), respectively (in 5 individuals (35.7%; *n* = 14); as for VAE, these were 40.0% (2 individuals out of 5) and 33.0% (3 individuals out of 9) ($p > 0.05$). When using GA, the AE rates in the groups of patients showing and not showing PHVI were 50.0% (3 individuals out of 6) and 12.5% (1 individual out of 8) ($p = 0.17$); as for VAE, these were 50.0% (2 individuals out of 4) and 20.0% (2 individuals out of 10).

During treatment with all the DMDs for MS the systemic AE severity was also higher in cases of PHVI reactivation, than in cases of no PHVI reactivation. Thus, during treatment of the groups compared with IFNβ or GA it was 8.00 (1.00; 12.00) and 5.00 (2.00; 6.00) points, when using IFNβ it was 8.00 (6.00; 15.00) and 6.00 (5.00; 6.00) points, and when using GA it was 6.00 (0.00; 11.00) and 2.00 (0.50; 7.00) points ($p > 0.05$ in all groups). In individuals with VAE, such trend was reported for GA only: 5.50 (0.00; 11.00) and 2.00 (1.00; 85.00) points ($p > 0.05$).

DISCUSSION

Cytokines in the naïve patients with MS treated with DMDs for MS and the donors

The literature contains only a few studies involving comparison of the cytokine levels in patients with MS not receiving DMDs for MS and healthy individuals. High levels of the key pro-inflammatory cytokines (IL1β, IL17A, IL17F, IL23, TNFα, and IFNγ) are usually reported in naïve patients with MS [8, 12, 21–23]. However, according to the data provided by other authors, serum TNFα levels of the patients taking DMDs for MS were the same [9] or lower [10, 13] compared to that of the control group. The results of recent studies are consistent with our data.

In patients with MS not treated with DMDs for MS, the increase in the serum levels of other inflammatory cytokines, IL31 [11, 12, 14] and IL33 [10, 15–17], relative to donors was reported. However, no significant differences in the IL33 levels between naïve patients and the controls were revealed [12].

In contrast, the serum levels of anti-inflammatory IL4 and IL10 in the untreated patients with MS were lower than in donors [9, 13, 22, 23] or were the same as in controls [21, 24]. However, according to the data provided by other researchers, the IL10 levels were higher in naïve patients with MS, than in donors [10, 12], which was also found in our study.

In general, our patients with MS not treated with DMDs for MS showed a significant increase in the levels of IL10, IL31, IL33 relative to controls, along with the upward trend of IL4 levels. At the same time, low levels of IL1β, IL17F, IL22, IL25, IL23, and TNFα were reported. There were no differences in the levels of other cytokines (IL6, IL17A, IL21, IFNγ, and sCD40L) between the comparison groups. Similar patterns were

reported when comparing the serum cytokine profiles of the patients treated with DMDs for MS and healthy controls, except for the IL31 levels. Such results are to some extent consistent with the above data provided by certain authors.

Cytokine levels in patients with MS treated and not treated with DMDs for MS

According to the literature data, the significantly higher levels of IL1β, IL17A, TNFα, IFNγ and lower levels of IL4, IL10 relative to the patients taking IFNβ or GA were revealed in naïve patients [6, 9, 21, 23]. It was noted, that therapy with IFNβ or GA resulted in the significant decreased concentrations of IL17, IL23, TNFα, IFNγ and the increased IL4 and IL10 levels [6, 11,12, 22].

The decrease in the IL31 levels was also found during treatment with DMDs for MS [14] that was considered to be associated with the decrease in the $CD3^{+}CD45RO^{+}$Th2 memory cells being the major IL31 producers [25]. We have also revealed a similar pattern.

The plasma IL33 levels of the patients taking IFNβ1a were significantly lower than that of the untreated patients [15, 17]. However, according to some date, therapy with GA or DMDs for MS did not affect the plasma IL33 concentrations [16]. In our study, there were no differences in the IL33 levels between the groups of patients treated and not treated with DMDs for MS.

In general, our untreated patients showed a significant increase in the IL10 levels compared to all the groups of patients treated with DMDs for MS. The IL31 levels were significantly higher in the naïve patients compared to the patients treated with IFNβ or GA and GA. We had earlier shown the increase in the IL10 concentration associated with the MS exacerbation [20]. In this phase of the disease, high IL31 levels and combined hyperproduction of IL33 and IL17A, IL17F, IL21 and IL31 were reported significantly more often, than during remission.

The identified differences in the cytokine profiles of the naïve patients and patients treated with DMDs for MS associated with remission and exacerbation were confirmed by the genetic test results [26]. The whole transcriptome analysis performed in patients with MS revealed impaired expression of 8800 genes in the patients, who had not previously received therapy, compared to the patients treated with IFNβ. The authors believe that in naïve patients the products of dysregulated genes contribute to inflammatory damage to the CNS and impede restoration of the brain. Furthermore, the groups of patients with the complete (no exacerbation) and partial clinical responses to IFNβ therapy showed differences in expression of 277 genes. During remission or exacerbation, the state of mononuclear cells in the patients not treated with DMDs for MS is characterized by extreme instability and the development of "cytokine storm" [26]. Furthermore, the long-term (longer than 5 years) IFNβ therapy adjusts this phenomenon through the gene expression modulation, which results in the state of cytokine harmony.

It is believed that despite similar clinical efficacy of the high-dose IFNβ and GA, the mechanisms underlying their effects on the immune systems can be different [4, 8, 9, 14]. However, we revealed no differences in the levels of almost all tested cytokines between the groups of patients taking IFNβ or GA, except for IFNγ, the levels of which were significantly higher during treatment with IFNβ, than when receiving GA.

Cytokine and herpesvirus infection in patients treated with DMDs for MS, adverse events

The data on the differences in production of IL10, IL31 and IL33 associated with using DMDs for MS obtained in our study can result from the herpesvirus infection reactivation.

It is well-known, that IL10 having a potent anti-inflammatory effect takes an active part in the immune response associated with the infectious, autoimmune, and autoinflammatory diseases [27]. High levels of IL10B produced by plasmablasts and plasma cells were observed in the MS foci [28]. In individuals with viral infections, the long-term antigen persistence accompanied by the increase in IL10 production results in the antiviral T cell phenotype switched mainly to the IL10-producing T cells [29]. Production of both viral homologue of human IL10 and common IL10 associated with the EBV infection has been revealed [30]. We have earlier more thoroughly discussed the possible mechanisms underlying involvement of these cytokines in the MS pathogenesis [20]. Apparently, these are involved in the IL10 production in our situation as well, especially in naïve patients.

Our findings about the simultaneous decrease in the anti-inflammatory IL10 and pro-inflammatory IL31 concentrations during treatment with DMDs for MS relative to the naïve patients, the correlations between IL31 and VAE+, IL33 and PHVI reactivation confirm an important role of herpesviruses in the MS pathogenesis. It is possible that the larger amount of the common IL10 is synthesized during treatment with IFNβ or GA, rather than its homologue. It has been found that treatment with these DMDs for MS increases systemic activity of the non-viral IL10 [31, 32].

Furthermore, the Th17 phenotype is switched under exposure to DMDs for MS, the number of IL17-secreting cells is reduced, and the number of IL10-producing cells and the double cells secreting IL10 and IL17 is increased [33]. The T cell phenotypic shift to the type 1 regulatory T cells, the decrease in the number of memory B cells and the levels of IL10 they produce have been detected [24]. This is partially confirmed by the decrease in the levels of IL10 during treatment with IFN and GA we have detected, associated with the MS clinical manifestations' relief and almost the same detection rates of EBV markers.

All the above can be associated with certain antiviral effects of DMDs for MS, mostly IFNβ. IFNβ reduces the EBV latent membrane protein 2A expression in the patients receiving treatment, inhibits antigen presentation to T cells, induces memory B cell apoptosis [34, 35]. However, in our study a significant increase in the IL1β concentration was revealed only in patients with PHVI reactivation treated with IFNβ. Furthermore, when using IFNβ, the IL17A and IL33 levels were significantly higher in the group of patients with VAE+, than in the group without VAE+. We also revealed a significant correlation between VAE+ and high levels of IL31 and IL33. These differences are likely to result from the higher prevalence of PHVI among individuals treated with IFNβ, than among those treated with GA.

FLS was the most common systemic AE associated with the IFNβ therapy, while systemic vasomotor response was the most common one associated with the GA therapy [2, 3]. It is believed that FLS results from the temporary increase in plasma levels of IL6 and TNFα following the drug administration, as well as from their direct pyrogenic effect on the hypothalamus [36, 37]. The emergence of systemic AEs during treatment with GA is also considered to be associated with the increase in the IL6 and IL4 levels [30]. Our findings have shown that the presence and severity of the systemic AEs associated with the IFNβ or GA therapy in patients with MS are not related to any of the studied cytokines. However, higher prevalence of systemic AEs in the groups of patients with PHVI reactivation and VAE was reported during treatment with any DMD for MS. The systemic AE severity was also higher in individuals with herpesvirus infection, especially in cases of PHVI reactivation. In general,

our findings are consistent with the data we have acquired earlier [38]. The lack of significant differences is likely to be related to the small number of patients in the studied groups.

It is believed that excess activation of the innate immunity, neuronal death and the neurodegenerative processes based on the impaired type 1 IFN pathway regulation predominate at the late stages of MS [26]. Disrupted expression of RNA and proteins in the pathways controlled by the type 1 IFN precedes the Th1, Th2, Th17 cell pathway disruption; this can impair the adaptive and innate immunity and contribute to neuronal death. It is well known that the DNA damage, necrosis, necroptosis, autophagy, and pronounced innate immunity activation are observed in case of viral invasion and HSV1 replication, while the type 1 IFN signaling pathway occupies a central place in the human body protection and induces a broad spectrum of antiviral proteins and control over the incoming pathogens [39–41]. These processes lead to production of TNFα and IL1β by microglia; TNFα and IL1β, in turn, promote IL33 transcription [42, 43]. The latter initiates the synthesis of IL31 by the Th-2 cells via IL4 [44]. The joint production of these cytokines is likely to enhance the pro-inflammatory potential of each of them [45], which is in line with the correlations between IL33 and PHVI, IL31 and VAE found in our study, as well as with the simultaneous increase in the levels of IL1β, IL31, IL33 in the group of patients with the herpesvirus infection reactivation during treatment with IFNβ.

CONCLUSIONS

Currently, MS is considered not only as an inflammatory disease of the CNS, but also as a consequence of the immune regulation disorders. The IFNβ and GA immunomodulatory properties are targeting multiple pathways of the body's innate and acquired immune response. In our opinion, PHVI reactivation accompanied by the disease exacerbation and the lack of the timely prescribed adequate first line therapy with a DMD for MS represent one of the epigenetic factors causing the enhanced innate immune response and neurodegeneration in individuals with MS. In general, the cytokine profiles of patients with RRMS are affected by not only the fact of receiving or not receiving treatment with DMDs for MS and the disease phase, but also infections, especially herpesvirus ones (EBV, type 1 and 2 HSV, VZV). Their contribution may vary depending on the DMD for MS used (IFN or GA). Our study has a number of limitations related to the small number of participants, however, the study results complement the possible immunological mechanisms involved in the MS pathogenesis, the effects of the ongoing first line therapy with DMDs for MS (high-dose IFNβ and GA), as well as concomitant herpesvirus infection.

References

1. Bojko AN, Gusev EI. Sovremennye algoritmy diagnostiki i lechenija rassejannogo skleroza, osnovannye na individual'noj ocenke sostojanija pacienta. Zhurnal nevrologii i psihiatrii im. S. S. Korsakova. Specvypuski. 2017; 117 (2–2): 92–106. DOI: 10.17116/jnevro20171172292-106. Russian.
2. Wynn DR. Enduring clinical value of copaxone® (glatiramer acetate) in multiple sclerosis after 20 years of use. Mult Scler Int. 2019; 2019: 7151685. DOI: 10.1155/2019/7151685.
3. Cohan SL, Hendin BA, Reder AT, Smoot K, Avila R, Mendoza JP, et al. Interferons and multiple sclerosis: lessons from 25 years of clinical and real-world experience with intramuscular interferon beta-1a (Avonex). CNS Drugs. 2021; 35 (7): 743–767. DOI: 10.1007/s40263-021-00822-z.
4. Melendez-Torres GJ, Armoiry X, Court R, Patterson J, Kan A, Auguste P, et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. BMC Neurol. 2018; 18 (1): 162. DOI: 10.1186/s12883-018-1162-9.
5. Zettl UK, Rommer PS, Aktas O, Wagner T, Richter J, Oschmann P, et al. Interferon beta-1a sc at 25 years: a mainstay in the treatment of multiple sclerosis over the period of one generation. Expert Rev Clin Immunol. 2023; 19 (11): 1343–1359. DOI: 10.1080/1744666X.2023.2248391.
6. D'Angelo C, Reale M, Costantini E, Di Nicola M, Porfilio I, de Andrés C, et al. Profiling of canonical and non-traditional cytokine levels in interferon-β-treated relapsing-remitting multiple sclerosis patients. Front Immunol. 2018; 9: 1240. DOI: 10.3389/fimmu.2018.01240.
7. Rommer PS, Milo R, Han MH, Satyanarayan S, Sellner J, Hauer L, et al. Immunological aspects of approved MS therapeutics. Front Immunol. 2019; 11; 10: 1564. DOI: 10.3389/fimmu.2019.01564.
8. Ganji A, Monfared ME, Shapoori S, Nourbakhsh P, Ghazavi A, Ghasami K, et al. Effects of interferon and glatiramer acetate on cytokine patterns in multiple sclerosis patients. Cytokine. 2020; 126: 154911. DOI: 10.1016/j.cyto.2019.154911.
9. Trenova AG, Slavov GS, Manova MG, Kostadinova II. Cytokines and disability in interferon-β-1b treated and untreated women with multiple sclerosis. Arch Med Res. 2014; 45 (6): 495–500. DOI: 10.1016/j.arcmed.2014.08.001.
10. Sosvorova L, Kanceva R, Vcelak J, Kancheva L, Mohapl M, Starka L, et al. The comparison of selected cerebrospinal fluid and serum cytokine levels in patients with multiple sclerosis and normal pressure hydrocephalus. Neuro Endocrinol Lett. 2015; 36 (6): 564–71.
11. Barcuţean LI, Romaniuc A, Maier S, Bajko Z, Motataianu A, Adina H, et al. Clinical and serological biomarkers of treatment's response in multiple sclerosis patients treated continuously with interferonβ-1b for more than a decade. CNS Neurol. Disord. Drug Targets. 2018; 17: 780–92. DOI: 10.2174/1871527317666180917095256.
12. Maier S, Motataianu A, Barcutean L, Balint A, Hutanu A, Zoltan B, et al. A interferon-β 1a, an immunomodulatory in relapsing remitting multiple sclerosis patients. The effect on pro-inflammatory cytokines. Farmacia. 2020; 68 (1): 65–75. DOI: 10.31925/farmacia.2020.1.10.
13. Melamud MM, Ermakov EA, Boiko AS, Kamaeva DA, Sizikov AE, Ivanova SA, et al. Multiplex analysis of serum cytokine profiles in systemic lupus erythematosus and multiple sclerosis. Int J Mol Sci. 2022; 23: 13829. DOI: 10.3390/ijms232213829
14. de J Guerrero-García J, Rojas-Mayorquín AE, Valle Y, Padilla-Gutiérrez JR, Castañeda-Moreno VA, Mireles-Ramírez MA, et al. Decreased serum levels of sCD40L and IL-31 correlate in treated patients with Relapsing-Remitting Multiple Sclerosis. Immunobiology. 2018; 223: 135–41. DOI: 10.1016/j.imbio.2017.10.001.
15. Christophi GP, Gruber RC, Panos M, Christophi RL, Jubelt B, Massa PT. Interleukin-33 upregulation in peripheral leukocytes and CNS of multiple sclerosis patients. Clin Immunol. 2012; 142 (3): 308–19. DOI: 10.1016/j.clim.2011.11.007.
16. Jafarzadeh A, Mahdavi R, Jamali M, Hajghani H, Nemati M, Ebrahimi HA. Increased concentrations of Interleukin-33 in the serum and cerebrospinal fluid of patients with multiple sclerosis. Oman Med J. 2016; 31(1): 40–45. DOI: 10.5001/omj.2016.08.
17. Alsahebfosoul F, Rahimmanesh I, Shajarian M, Etemadifar M, Sedaghat N, Hejazi Z, et al. Interleukin-33 plasma levels in patients with relapsing-remitting multiple sclerosis. BioMol Concepts. 2017; 8 (1): 55–60. DOI: 10.1515/bmc-2016-0026.
18. Donati D. Viral infections and multiple sclerosis. Drug Discov Today Dis Models. 2020; 32: 27–33. DOI: 10.1016/j.ddmod.2020.02.003.
19. Bjornevik K, Münz C, Cohen JI, Ascherio A. Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. Nat

Rev Neurol. 2023; 19 (3): 160–71. DOI: 10.1038/s41582-023-00775-5.
20. Baranova NS, Gris MS, Baranov AA, Spirin NN, Artyuhov AS, Shakirova KM, et al. Clinical significance of cytokine counting in patients with multiple sclerosis and its relationship with herpes infection. Bulletin of RSMU. 2023; (4): 48–62. DOI: 10.24075/vrgmu.2023.032.
21. Jakushina TI, Lizhdvoj VYu, Vasilenko IA, Andrjuhina OM, Kotov SV. Dopolnitel'nye pokazateli dlja ocenki jeffektivnosti terapii rassejannogo skleroza (predvaritel'nye dannye). Zhurnal nevrologii i psihiatrii im. S. S. Korsakova. Specvypuski. 2013; 113 (2–2): 61–65. Russian.
22. Ospelnikova TP, Morozova OV, Isaeva EI, Lizhdvoj VYu, Kolodjazhnaja LV, Andreeva SA, i dr. Monitoring citokinov u bol'nyh rassejannym sklerozom v processe lechenija preparatom IFNβ-1a. Zhurnal nevrologii i psihiatrii im. S.S. Korsakova. Specvypuski. 2015; 115 (8–2): 71–71. Russian.
23. Sursjakova NV, Kuklina EM, Bajdina TV, Nekrasova IV, Trushnikova TN. Vklad V-limfocitov v produkciju interlejkina 17 pri rassejannom skleroze. Nevrologija, nejropsihiatrija, psihosomatika. 2023; 15 (Pril. 1): 15–21. DOI: 10.14412/2074-2711-2023-1S-15-21. Russian.
24. Masilionyte U, Gedvilaite G, Kaikaryte K, Vilkeviciute A, Kriauciuniene L, Glebauskiene B, et al. IL-10 Gene Polymorphisms and IL-10 Serum Levels in Patients with Multiple Sclerosis in Lithuania. Brain Sci. 2022; 12 (6): 800. DOI: 10.3390/brainsci12060800.
25. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1. J Allergy Clin Immunol. 2014; 133: 448–60. DOI: 10.1016/j.jaci.2013.10.048.
26. Feng X, Bao R, Li L, Deisenhammer F, Arnason BGW, Reder AT. Interferon-β corrects massive gene dysregulation in multiple sclerosis: Short-term and long-term effects on immune regulation and neuroprotection. EBioMedicine. 2019; 49: 269–283. DOI: 10.1016/j.ebiom.2019.09.059.
27. Kwilasz AJ, Grace PM, Serbedzija P, Maier SF, Watkins LR. The therapeutic potential of interleukin-10 in neuroimmune diseases. Neuropharmacology. 2015; 96: 55–69. DOI: 10.1016/j.neuropharm.2014.10.020.
28. Machado-Santos J, Saji E, Troscher AR, Paunovic M, Liblau R, Gabriely G, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. Brain. 2018; 141 (7): 2066–2082. DOI: 10.1093/brain/awy151.
29. Rojas JM, Avia M, Martín V, Sevilla N. IL-10: A Multifunctional Cytokine in Viral Infections. J Immunol Res. 2017; 2017: 6104054. DOI: 10.1155/2017/6104054.
30. Schönrich G, Abdelaziz MO, Raftery MJ. Epstein-Barr virus, interleukin-10 and multiple sclerosis: A me´ nage à trois. Front. Immunol. 2022; 13: 1028972. DOI: 10.3389/fimmu.2022.1028972.
31. Miller A, Shapiro S, Gershtein R, Kinarty A, Rawashdeh H, Honigman S, et al. Treatment of multiple sclerosis with copolymer-1 (Copaxone): implicating mechanisms of Th1 to Th2/Th3 immune deviation. J Neuroimmunol. 1998; 92: 113–21. DOI: 10.1016/s0165-5728(98)00191-x.
32. Rudick RA, Ransohoff RM, Lee JC, Peppler R, Yu M, Mathisen PM, et al. In vivo effects of interferon beta-1a on immunosuppressive cytokines in multiple sclerosis. Neurology. 1998; 50 (5): 1294–300. DOI: 10.1212/wnl.50.5.1294.
33. Zhang L, Yuan S, Cheng G, Guo B. Type I IFN promotes IL-10 production from T cells to suppress Th17 cells and Th17-associated autoimmune inflammation. PLoS One. 2011; 6 (12): 1–11. DOI: 10.1371/journal.pone.0028432.
34. Rizzo F, Giacomini E, Mechelli R, Buscarinu MC, Salvetti M, Severa M, et al. Interferon-β therapy specifically reduces pathogenic memory B cells in multiple sclerosis patients by inducing a FAS-mediated apoptosis. Immunol Cell Biol. 2016; 94 (9): 886–894. DOI: 10.1038/icb.2016.55.
35. Attfield KE, Jensen LT, Kaufmann M, Friese MA, Fugger L. The immunology of multiple sclerosis. Nat Rev Immunol. 2022, 22: 734–50. DOI: 10.1038/s41577-022-00718-z.
36. Dinarello CA, Bernheim HA, Duff GW, Le HV, Nagabhushan TL, Hamilton NC, et al. Mechanisms of fever induced by recombinant human interferon. J Clin Invest. 1984; 74 (3): 906–13. DOI: 10.1172/JCI111508.
37. Langer-Gould A, Moses HH, Murray TJ. Strategies for managing the side effects of treatments for multiple sclerosis. Neurology. 2004; 63 (11): S35–41. DOI: 10.1212/wnl.63.11_suppl_5.s35.
38. Gris MS, Baranova NS, Spirin NN, Kasatkin DS, Kiselev DV, Shipova EG. Rassejannyj skleroz u pacientov s gerpesvirusnoj infekciej: osobennosti klinicheskoj kartiny i techenija. Nevrologija, nejropsihiatrija, psihosomatika. 2021; 13 (Pril. 1): 21–26. DOI: 10.14412/2074-2711-2021-1S-21-26. Russian.
39. Su C, Zhan G, Zheng C. Evasion of host antiviral innate immunity by HSV-1, an update. Virol J. 2016; 13: 38. DOI: 10.1186/s12985-016-0495-5.
40. Danastas K, Miranda-Saksena M, Cunningham AL. Herpes simplex virus type 1 interactions with the interferon system. Int J Mol Sci. 2020; 21 (14): 5150. DOI: 10.3390/ijms21145150.
41. Verzosa AL, McGeever LA, Bhark SJ, Delgado T, Salazar N, Sanchez EL. Herpes simplex virus 1 infection of neuronal and nonneuronal cells elicits specific innate immune responses and immune evasion mechanisms. Front Immunol. 2021; 12: 644664. DOI: 10.3389/fimmu.2021.644664.
42. Nile CJ, Barksby E, Jitprasertwong P, Preshaw PM, Taylor JJ. Expression and regulation of interleukin-33 in human monocytes. Immunology. 2010; 130 (2): 172–80. DOI: 10.1111/j.1365-2567.2009.03221.x.
43. Zhang L, Lu R, Zhao G, Pflugfelder SC, Li DQ. TLR-mediated induction of pro-allergic cytokine IL-33 in ocular mucosal epithelium. Int J Biochem Cell Biol. 2011; 43: 1383–91. DOI: 10.1016/j.biocel.2011.06.003.
44. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. Allergy. 2018; 73 (1): 29–36. DOI: 10.1111/all.13239.
45. Di Salvo E, Ventura-Spagnolo E, Casciaro M, Navarra M, Gangemi S. IL-33/IL-31 axis: a potential inflammatory pathway. Mediator Inflammat. 2018; 2018: 3858032. DOI: 10.1155/2018/3858032.

Литература

1. Бойко А. Н., Гусев Е. И. Современные алгоритмы диагностики и лечения рассеянного склероза, основанные на индивидуальной оценке состояния пациента. Журнал неврологии и психиатрии им. С. С. Корсакова. Спецвыпуски. 2017; 117 (2–2): 92–106. DOI: 10.17116/jnevro20171172292-106.
2. Wynn DR. Enduring clinical value of copaxone® (glatiramer acetate) in multiple sclerosis after 20 years of use. Mult Scler Int. 2019; 2019: 7151685. DOI: 10.1155/2019/7151685.
3. Cohan SL, Hendin BA, Reder AT, Smoot K, Avila R, Mendoza JP, et al. Interferons and multiple sclerosis: lessons from 25 years of clinical and real-world experience with intramuscular interferon beta-1a (Avonex). CNS Drugs. 2021; 35 (7): 743–767. DOI: 10.1007/s40263-021-00822-z.
4. Melendez-Torres GJ, Armoiry X, Court R, Patterson J, Kan A, Auguste P, et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. BMC Neurol. 2018; 18 (1): 162. DOI: 10.1186/s12883-018-1162-9.
5. Zettl UK, Rommer PS, Aktas O, Wagner T, Richter J, Oschmann P, et al. Interferon beta-1a sc at 25 years: a mainstay in the treatment of multiple sclerosis over the period of one generation. Expert Rev Clin Immunol. 2023; 19 (11): 1343–1359. DOI: 10.1080/1744666X.2023.2248391.
6. D'Angelo C, Reale M, Costantini E, Di Nicola M, Porfilio I, de Andrés C, et al. Profiling of canonical and non-traditional cytokine levels in interferon-β-treated relapsing-remitting multiple sclerosis patients. Front Immunol. 2018; 9: 1240. DOI: 10.3389/fimmu.2018.01240.
7. Rommer PS, Milo R, Han MH, Satyanarayan S, Sellner J, Hauer L, et al. Immunological aspects of approved MS therapeutics. Front Immunol. 2019; 11; 10: 1564. DOI: 10.3389/fimmu.2019.01564.
8. Ganji A, Monfared ME, Shapoori S, Nourbakhsh P, Ghazavi A, Ghasami K, et al. Effects of interferon and glatiramer acetate on cytokine patterns in multiple sclerosis patients. Cytokine. 2020; 126: 154911. DOI: 10.1016/j.cyto.2019.154911.
9. Trenova AG, Slavov GS, Manova MG, Kostadinova II. Cytokines

and disability in interferon-β-1b treated and untreated women with multiple sclerosis. Arch Med Res. 2014; 45 (6): 495–500. DOI: 10.1016/j.arcmed.2014.08.001.
10. Sosvorova L, Kanceva R, Vcelak J, Kancheva L, Mohapl M, Starka L, et al. The comparison of selected cerebrospinal fluid and serum cytokine levels in patients with multiple sclerosis and normal pressure hydrocephalus. Neuro Endocrinol Lett. 2015; 36 (6): 564–71.
11. Barcuţean LI, Romaniuc A, Maier S, Bajko Z, Motataianu A, Adina H, et al. Clinical and serological biomarkers of treatment's response in multiple sclerosis patients treated continuously with interferonβ-1b for more than a decade. CNS Neurol. Disord. Drug Targets. 2018; 17: 780–92. DOI: 10.2174/1871527317666180917095256.
12. Maier S, Motataianu A, Barcutean L, Balint A, Hutanu A, Zoltan B, et al. A interferon-β 1a, an immunomodulatory in relapsing remitting multiple sclerosis patients. The effect on pro-inflammatory cytokines. Farmacia. 2020; 68 (1): 65–75. DOI: 10.31925/farmacia.2020.1.10.
13. Melamud MM, Ermakov EA, Boiko AS, Kamaeva DA, Sizikov AE, Ivanova SA, et al. Multiplex analysis of serum cytokine profiles in systemic lupus erythematosus and multiple sclerosis. Int J Mol Sci. 2022; 23: 13829. DOI: 10.3390/ijms232213829
14. de J Guerrero-García J, Rojas-Mayorquín AE, Valle Y, Padilla-Gutiérrez JR, Castañeda-Moreno VA, Mireles-Ramírez MA, et al. Decreased serum levels of sCD40L and IL-31 correlate in treated patients with Relapsing-Remitting Multiple Sclerosis. Immunobiology. 2018; 223: 135–41. DOI: 10.1016/j.imbio.2017.10.001.
15. Christophi GP, Gruber RC, Panos M, Christophi RL, Jubelt B, Massa PT. Interleukin-33 upregulation in peripheral leukocytes and CNS of multiple sclerosis patients. Clin Immunol. 2012; 142 (3): 308–19. DOI: 10.1016/j.clim.2011.11.007.
16. Jafarzadeh A, Mahdavi R, Jamali M, Hajghani H, Nemati M, Ebrahimi HA. Increased concentrations of Interleukin-33 in the serum and cerebrospinal fluid of patients with multiple sclerosis. Oman Med J. 2016; 31(1): 40–45. DOI: 10.5001/omj.2016.08.
17. Alsahebfosoul F, Rahimmanesh I, Shajarian M, Etemadifar M, Sedaghat N, Hejazi Z, et al. Interleukin-33 plasma levels in patients with relapsing-remitting multiple sclerosis. BioMol Concepts. 2017; 8 (1): 55–60. DOI: 10.1515/bmc-2016-0026.
18. Donati D. Viral infections and multiple sclerosis. Drug Discov Today Dis Models. 2020; 32: 27–33. DOI: 10.1016/j.ddmod.2020.02.003.
19. Bjornevik K, Münz C, Cohen JI, Ascherio A. Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. Nat Rev Neurol. 2023; 19 (3): 160–71. DOI: 10.1038/s41582-023-00775-5.
20. Баранова Н. С., Грись М. С., Баранов А. А., Спирин Н. Н., Артюхов А. С., Шакирова К. М. и др. Клиническое значение определения цитокинов у пациентов с рассеянным склерозом и взаимосвязь с герпетической инфекцией. Вестник РГМУ. 2023; (4): 51–65. DOI: 10.24075/vrgmu.2023.032.
21. Якушина Т. И., Лиждвой В. Ю., Василенко И. А., Андрюхина О. М., Котов С. В. Дополнительные показатели для оценки эффективности терапии рассеянного склероза (предварительные данные). Журнал неврологии и психиатрии им. С. С. Корсакова. Спецвыпуски. 2013; 113 (2–2): 61–65.
22. Оспельникова Т. П., Морозова О. В., Исаева Е. И., Лиждвой В. Ю., Колодяжная Л. В., Андреева С. А. и др. Мониторинг цитокинов у больных рассеянным склерозом в процессе лечения препаратом IFNβ-1a. Журнал неврологии и психиатрии им. С.С. Корсакова. Спецвыпуски. 2015; 115 (8–2): 71–71.
23. Сурсякова Н. В., Куклина Е. М., Байдина Т. В., Некрасова И. В., Трушникова Т. Н. Вклад В-лимфоцитов в продукцию интерлейкина 17 при рассеянном склерозе. Неврология, нейропсихиатрия, психосоматика. 2023; 15 (Прил. 1): 15–21. DOI: 10.14412/2074-2711-2023-1S-15-21.
24. Masilionyte U, Gedvilaite G, Kaikaryte K, Vilkeviciute A, Kriauciuniene L, Glebauskiene B, et al. IL-10 Gene Polymorphisms and IL-10 Serum Levels in Patients with Multiple Sclerosis in Lithuania. Brain Sci. 2022; 12 (6): 800. DOI: 10.3390/brainsci12060800.
25. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1. J Allergy Clin Immunol. 2014; 133: 448–60. DOI: 10.1016/j.jaci.2013.10.048.
26. Feng X, Bao R, Li L, Deisenhammer F, Arnason BGW, Reder AT. Interferon-β corrects massive gene dysregulation in multiple sclerosis: Short-term and long-term effects on immune regulation and neuroprotection. EBioMedicine. 2019; 49: 269–283. DOI: 10.1016/j.ebiom.2019.09.059.
27. Kwilasz AJ, Grace PM, Serbedzija P, Maier SF, Watkins LR. The therapeutic potential of interleukin-10 in neuroimmune diseases. Neuropharmacology. 2015; 96: 55–69. DOI: 10.1016/j.neuropharm.2014.10.020.
28. Machado-Santos J, Saji E, Troscher AR, Paunovic M, Liblau R, Gabriely G, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. Brain. 2018; 141 (7): 2066–2082. DOI: 10.1093/brain/awy151.
29. Rojas JM, Avia M, Martín V, Sevilla N. IL-10: A Multifunctional Cytokine in Viral Infections. J Immunol Res. 2017; 2017: 6104054. DOI: 10.1155/2017/6104054.
30. Schönrich G, Abdelaziz MO, Raftery MJ. Epstein-Barr virus, interleukin-10 and multiple sclerosis: A me´ nage à trois. Front. Immunol. 2022; 13: 1028972. DOI: 10.3389/fimmu.2022.1028972.
31. Miller A, Shapiro S, Gershtein R, Kinarty A, Rawashdeh H, Honigman S, et al. Treatment of multiple sclerosis with copolymer-1 (Copaxone): implicating mechanisms of Th1 to Th2/Th3 immune deviation. J Neuroimmunol. 1998; 92: 113–21. DOI: 10.1016/s0165-5728(98)00191-x.
32. Rudick RA, Ransohoff RM, Lee JC, Peppler R, Yu M, Mathisen PM, et al. In vivo effects of interferon beta-1a on immunosuppressive cytokines in multiple sclerosis. Neurology. 1998; 50 (5): 1294–300. DOI: 10.1212/wnl.50.5.1294.
33. Zhang L, Yuan S, Cheng G, Guo B. Type I IFN promotes IL-10 production from T cells to suppress Th17 cells and Th17-associated autoimmune inflammation. PLoS One. 2011; 6 (12): 1–11. DOI: 10.1371/journal.pone.0028432.
34. Rizzo F, Giacomini E, Mechelli R, Buscarinu MC, Salvetti M, Severa M, et al. Interferon-β therapy specifically reduces pathogenic memory B cells in multiple sclerosis patients by inducing a FAS-mediated apoptosis. Immunol Cell Biol. 2016; 94 (9): 886–894. DOI: 10.1038/icb.2016.55.
35. Attfield KE, Jensen LT, Kaufmann M, Friese MA, Fugger L. The immunology of multiple sclerosis. Nat Rev Immunol. 2022, 22: 734–50. DOI: 10.1038/s41577-022-00718-z.
36. Dinarello CA, Bernheim HA, Duff GW, Le HV, Nagabhushan TL, Hamilton NC, et al. Mechanisms of fever induced by recombinant human interferon. J Clin Invest. 1984; 74 (3): 906–13. DOI: 10.1172/JCI111508.
37. Langer-Gould A, Moses HH, Murray TJ. Strategies for managing the side effects of treatments for multiple sclerosis. Neurology. 2004; 63 (11): S35–41. DOI: 10.1212/wnl.63.11_suppl_5.s35.
38. Грись М. С., Баранова Н. С., Спирин Н. Н., Касаткин Д. С., Киселев Д. В., Шипова Е. Г. Рассеянный склероз у пациентов с герпесвирусной инфекцией: особенности клинической картины и течения. Неврология, нейропсихиатрия, психосоматика. 2021; 13 (Прил. 1): 21–26. DOI: 10.14412/2074-2711-2021-1S-21-26.
39. Su C, Zhan G, Zheng C. Evasion of host antiviral innate immunity by HSV-1, an update. Virol J. 2016; 13: 38. DOI: 10.1186/s12985-016-0495-5.
40. Danastas K, Miranda-Saksena M, Cunningham AL. Herpes simplex virus type 1 interactions with the interferon system. Int J Mol Sci. 2020; 21 (14): 5150. DOI: 10.3390/ijms21145150.
41. Verzosa AL, McGeever LA, Bhark SJ, Delgado T, Salazar N, Sanchez EL. Herpes simplex virus 1 infection of neuronal and nonneuronal cells elicits specific innate immune responses and immune evasion mechanisms. Front Immunol. 2021; 12: 644664. DOI: 10.3389/fimmu.2021.644664.
42. Nile CJ, Barksby E, Jitprasertwong P, Preshaw PM, Taylor JJ. Expression and regulation of interleukin-33 in human monocytes. Immunology. 2010; 130 (2): 172–80. DOI: 10.1111/j.1365-2567.2009.03221.x.
43. Zhang L, Lu R, Zhao G, Pflugfelder SC, Li DQ. TLR-mediated induction of pro-allergic cytokine IL-33 in ocular mucosal epithelium. Int J Biochem Cell Biol. 2011; 43: 1383–91. DOI: 10.1016/j.biocel.2011.06.003.
44. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. Allergy. 2018; 73 (1): 29–36. DOI: 10.1111/all.13239.
45. Di Salvo E, Ventura-Spagnolo E, Casciaro M, Navarra M, Gangemi S. IL-33/IL-31 axis: a potential inflammatory pathway. Mediator Inflammat. 2018; 2018: 3858032. DOI: 10.1155/2018/3858032.