УДК 616.8-039.42-085.373.032.14
https://doi.org/10.20538/1682-0363-2023-1-174-182

Best practices in the use of human immunoglobulin preparations for intravenous administration in the treatment of rare neurological diseases

Tereshchenko N.M., Kushnir Ya.B., Abramova M.P., Gotovchikov A.A., Krasnov V.S., Sokolov A.Yu., Totolyan N.A., Amelin A.V.

Pavlov First Saint Petersburg State Medical University
6–8, Lva Tolstogo Str., Saint Petersburg, 197022, Russian Federation

ABSTRACT

Aim. To describe best practices in using human normal immunoglobulin in patients with immune-mediated neurological disorders according to the data of one clinical center.

Materials and methods. From 2016 to 2021, 20 patients with various autoimmune disorders of the peripheral and central nervous system were treated with human normal immunoglobulin at the Neurology Unit No.1 of Pavlov First Saint Petersburg State Medical University. Treatment efficacy was assessed by changes in the neurological examination data according to specialized scales for specific diseases or clinical manifestations (INCAT, QMGS, MoCA, EDSS). Safety of the therapy was assessed considering the instructions to the drug.

Results. In the vast majority of patients, treatment allowed to stabilize the course of the disease or was accompanied by pronounced regression.

Conclusion. The considered clinical cases of the use of human normal immunoglobulin preparations demonstrate the possibility of their use in the treatment of a number of autoimmune neurological diseases for unregistered indications.

Keywords: human normal immunoglobulin, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, autoimmune encephalitis, Guillain – Barré syndrome, immunotherapy, intravenous administration

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Tereshchenko N.M., Kushnir Ya.B., Abramova M.P., Gotovchikov A.A., Krasnov V.S., Sokolov A.Yu., Totolyan N.A., Amelin A.V. Best practices in the use of human immunoglobulin preparations for intravenous administration in the treatment of rare neurological diseases. *Bulletin of Siberian Medicine.* 2023;22(1):174–182. https://doi.org/10.20538/1682-0363-2023-1-174-182.

Опыт применения препаратов иммуноглобулина человека для внутривенного введения в лечении редких неврологических заболеваний

Терещенко Н.М., Кушнир Я.Б., Абрамова М.П., Готовчиков А.А, Краснов В.С., Соколов А.Ю., Тотолян Н.А., Амелин А.В.

Первый Санкт-Петербургский государственный медицинский университет (ПСПбГМУ) им. акад. И.П. Павлова
Россия, 197022, г. Санкт-Петербург, ул. Л. Толстого, 6-8

✉ *Tereshchenko Nikolai M.,* nickolaitereshenko@yandex.ru

РЕЗЮМЕ

Целью работы является обобщение опыта применения иммуноглобулина человека нормального у пациентов с имуноопосредованными неврологическими заболеваниями по данным одного клинического центра.

Материалы и методы. С 2016 по 2021 г. на базе неврологического отделения № 1 ПСПбГМУ им. И.П. Павлова проведено лечение иммуноглобулином человека нормальным 20 пациентов с различными аутоиммунными неврологическими заболеваниями периферической и центральной нервной системы. Оценку эффективности лечения проводили, анализируя динамику данных неврологического осмотра в соответствии со специализированными для конкретных заболеваний или клинических проявлений шкалами (INCAT, QMGS, MoCA, EDSS). Безопасность терапии оценивали с учетом инструкции по применению лекарственного препарата.

Результаты. У подавляющего числа пациентов лечение позволило стабилизировать течение болезни или сопровождалось выраженным регрессом симптомов.

Заключение. Рассмотренные клинические случаи применения препаратов иммуноглобулина человека нормального демонстрируют возможность их использования в лечении ряда аутоиммунных неврологических заболеваний по незарегистрированным показаниям.

Ключевые слова: иммуноглобулин человека нормальный, миастения, острая и хроническая воспалительная демиелинизирующая полинейропатия, мультифокальная моторная нейропатия, аутоиммунный энцефалит, синдром Гийена – Барре, иммунотерапия, внутривенное введение

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Терещенко Н.М., Кушнир Я.Б., Абрамова М.П., Готовчиков А.А, Краснов В.С., Соколов А.Ю., Тотолян Н.А., Амелин А.В. Опыт применения препаратов иммуноглобулина человека для внутривенного введения в лечении редких неврологических заболеваний. *Бюллетень сибирской медицины.* 2023;22(1):174–182. https://doi.org/10.20538/1682-0363-2023-1-174-182.

INTRODUCTION

Currently, for the treatment of a wide range of immune-mediated diseases of the central and peripheral nervous system (Guillain – Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), autoimmune encephalitis, etc.), drugs with various patented names and a single international non-proprietary name “human normal immunoglobulin” are used. The dosage forms of these drugs are intended primarily for intravenous administration and are often referred to as “intravenous immunoglobulins” (IVIG).

IVIG preparations contain human multispecific immunoglobulins (Ig), predominantly of class G, obtained from the blood plasma of healthy donors, which contain antibodies (AB) to a variety of antigens, given a high level of viral safety is ensured [1, 2]. They may differ in the ratio of Ig A and Ig G and in the mechanisms of antigen inactivation. For the maximum therapeutic effect, the drug must contain at least 95% Ig G with distribution in subclasses 1–4 comparable to normal serum and with a minimum amount of Ig A [2, 3].

IVIGs are used not only in replacement therapy for various immunodeficiencies, but also as immunomodulatory agents; however, the mechanism of their pharmacological and biological effects is not fully understood. Depending on the predominant participation of Fab- (fragment antigen binding) or Fc- (fragment crystallizable) fragments of immunoglobulin in the reactions, two possible mechanisms are considered [1, 3].

The first group includes Fab-mediated neutralization of autoantibodies, proinflammatory cytokines, and activated complement components, induction of apoptosis, inhibition of leukocyte adhesion molecules, and restoration of the idiotypic – anti-idiotypic network. It is believed that anti-idiotypic AB can bind auto-AB, for example, to Nm acetylcholine receptors in myasthenia gravis or to gangliosides in Guillain – Barré syndrome [3]. The second probable mechanism, involving the Fc fragment, includes activation or inhibition of macrophages, monocytes, and dendritic cells, as well as suppression of autoreactive B cells and interaction with natural killers [3]. The listed effects partly develop already in the process of

infusion, however, a clinically significant effect after IVIG administration is usually recorded after the second day and lasts about 3–5 weeks, depending on the half-life of a particular drug, which is determined both by the properties of the molecule and, in some cases, by factors of the body. It is the pharmacokinetic parameters that determine the average duration of the IVIG course, which ranges from 3 to 5 days [3]. According to studies, IVIG drugs have an anti-inflammatory effect at high doses, while at low doses they can have an undesirable proinflammatory effect [1]. When choosing an IVIG preparation for treatment of autoimmune neurological diseases, the absence of restrictions on single and daily doses, the maximum allowable rate of administration, and the stabilizer used in the manufacturing are very important [2]. According to the current guidelines in the Russian Federation (https://grls.rosminzdrav.ru), indications for the use of IVIGs in neurology are limited to Guillain – Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN) (Table 1).

Table 1

Human normal immunoglobulin preparations for intravenous administration registered in the Russian Federation for the treatment of neurological diseases (State Register of Medicines, 09.02.2021)

Disease	Trade name of IVIG *
Guillain – Barré syndrome	Kiovig, Immunoglobulin Sigardis, Immunoglobulin Sigardis MT, Privigen, Octagam, Intratect, Octagam 10%, Gabreglobine-IgG, Flebogamma 5% DIF, I.G.Vena, Gamunex-C
Chronic inflammatory demyelinating polyneuropathy	Privigen, Intratect, Gamunex-C
Multifocal motor neuropathy	Kiovig, Intratect

Note: according to the instructions to the drug, Pentaglobin, Imbioglobulin, Immunovenin, Gabreglobine, and Immunoglobulin human normal (manufactured by Microgen and Nizhny Novgorod Regional Blood Center named after N.Ya. Klimova) intended for intravenous administration can only be used for replacement therapy for immunodeficiencies.

Despite the fact that in some cases the use of IVIGs is optimal in terms of safety and efficacy, there is a fundamental problem in the form of the absence of indications for some rare neurological disorders in the instruction to the drug. Human normal immunoglobulin preparations are widely used in international practice for treatment for myasthenia gravis (MG), idiopathic inflammatory myopathies, stiff person syndrome, CIDP associated with monoclonal gammopathy of undetermined significance (MGUS), some forms of epilepsy, and active multiple sclerosis in women during pregnancy. In these diseases, off-label use of IVIGs takes place. At the same time, they are included in the standards of medical care for CIDP, MG, and acute disseminated encephalomyelitis (ADEM) [3, 4]. The aim of this work was to describe best practices in using human normal immunoglobulin in patients with immune-mediated neurological disorders according to the data of the Neurology Department No.1 at Pavlov First Saint Petersburg State Medical University.

MATERIALS AND METHODS

A monocenter, observational, retrospective and prospective cohort study on the efficacy and safety of IVIG in the treatment of immune-mediated neurological diseases was conducted on the basis of the neurological department No.1 of Pavlov First Saint Petersburg State Medical University in 2016–2021. The study included 20 people (14 women and 6 men), median onset of the disease was at the age of 49.5 [35.3; 58.5] years. Of these, 3 patients were diagnosed with MMN, 9 – with CIDP, 3 – with MG, 2 with autoimmune encephalitis, 2 – with neuromyelitis optica spectrum disorders (NMOSD), 1 – with stiff person syndrome (Table 2). IVIG preparations were used following medical indications according to the instructions or by the decision of an expert board of physicians in cases of off-label use when assessing the risk – benefit ratio (according to the order of the Ministry of Health and Social Development of the Russian Federation No. 494 of 09.08.2005 "On the procedure for using drugs in patients for health reasons" and the Federal Law No. 323-FZ of 21.11.2011). The therapy used human normal immunoglobulin preparations of various trade names.

All patients signed an informed consent to IVIG treatment. Medicines were administered intravenously by trained medical staff directly in the patient's ward. The procedure was carried out in accordance with the instructions and clinical recommendations or according to the data of expert working groups in the case of off-label application. Prior to infusion, adequate hydration was performed, hematocrit, IgA, and creatinine levels were determined [2], and thromboembolism risks were assessed. In order to prevent the development of systemic post-infusion reactions, premedication with paracetamol (1,000 mg, orally) and chloropyramine (20 mg, intramuscularly) was performed in all cases [5]. During the infusion and within an hour after its completion, the patient was under the supervision of a physician assessing the somatic status.

The dynamics of the neurological status was assessed daily using scales developed for the respective diseases (INCAT, QMGS, MoCA, EDSS). Safety of IVIG therapy was assessed by the presence and severity of adverse events [5]. Follow-up from the initiation of the therapy ranged from 2 to 30 months.

Statistical processing of the obtained results was not carried out due to the small sample size and the heterogeneity of the data.

RESULTS

The main characteristics of the patients, as well as regimens and results of IVIG therapy are presented in Table 2.

Among patients with CIDP, the phenotype of sensorymotor neuropathy was present in 7 patients, predominantly motor phenotype – in 2 individuals. In 4 cases, a progressive course of polyneuropathy was observed, in 5 – recurrent. Two patients (22%) with CIDP after two courses of IVIG therapy according to the INCAT scale showed partial regression of symptoms. Five patients (56%) had stabilization and no progression of symptoms after two courses of therapy with IVIG at a dose of 2 g / kg. In four (80%) out of five patients with a recurrent course, new exacerbations were prevented during the entire follow-up period.

In a patient with CIDP associated with MGUS, within 7 months of continuous monthly IVIG therapy with a starting dose of 2 g / kg (134 g within 5 days) in the first month and subsequent monthly course doses of 1 g / kg (67 g within 3 days), complete clinical remission was observed. A patient with an atypical variant of CIDP and concomitant podocytopathy after a course of therapy at a total dose of 2 g / kg developed an exacerbation 5 days after the end of the therapy.

In the case of a patient with stiff person syndrome, after 7 courses of regular IVIG therapy (at a dose of 1–2 g / kg), a clinical improvement was observed in the form of a decrease in axial and limb hypertonicity, as well as a decrease in the severity of dysarthria.

In 2 patients with autoimmune encephalitis associated with antibodies to GAD, after 6 and 12 months of treatment, respectively, stabilization of the condition, no progression of cognitive deficit, and regression of epileptic seizures were observed.

In a patient with an exacerbation of NMOSD in the second trimester of pregnancy and a clinical presentation of complete transverse myelitis at the cervical level, after a course of IVIG, significant regression of symptoms was noted with changes in the EDSS score from 4.0 to 2.5. Against the background of subsequent administration of the drug at maintenance doses for 2 months, no exacerbations were observed during the six-month follow-up.

A patient with NMOSD associated with SLE and severe lymphopenia underwent IVIG anti-relapse therapy for 3 months monthly, at a starting dose of 2 g / kg and a maintenance dose of 0.4 g / kg until the level of lymphocytes was restored. No exacerbations and negative trend in the EDSS score were registered during the follow-up. Subsequently, the therapy was shifted to rituximab.

All patients with stage IVb and V MG according to MGFA showed partial regression of symptoms and an improvement by 13 points according to the QMGS scale. Tolerability of IVIG therapy was assessed as good. No infusion reactions were reported in any of the cases. No delayed adverse events were observed during the follow-up period.

DISCUSSION

The results of our observational study indicate that long-term course use of IVIG preparations in a heterogeneous group of neurological patients in most cases leads to stabilization of the disease course and regression of symptoms. Immunoglobulin was effective and safe not only in cases of its use according to indications, but also in off-label application, due to a lack of other optimal or approved treatment options for severe diseases of the peripheral and central nervous system. The starting and maintenance doses were determined by the instructions to the drug or clinical guidelines and expert working groups in the case of off-label use. The duration of therapy and follow-up varied, from 5 days to 2.5 years, depending on the disease and clinical situation.

Our positive experience with the use of IVIG in the treatment of a number of autoimmune neurological diseases confirms the data obtained by other authors [2–4]. It is known that IVIGs are approved for the treatment of a number of diseases and are a first-line therapy in emergency neurological practice. For example, in patients with GBS, IVIGs are effectively used at a dose of 0.4 g / kg / day for a course of 3 to 5 days (up to 2 g /kg per course) [3, 4]. There were no patients with GBS among the participants in our observational study, and, therefore, a comparative assessment of the effectiveness of IVIG in this pathology was not carried out.

Table 2

Clinical and demographic characteristics of patients receiving IVIGs and features of the therapy

No.	Sex/age of disease onset/initiation of IVIG therapy (years)	Diagnosis	Therapy before IVIG administration	Course dose, number of courses (1 course – 5 days, monthly)	Duration of follow-up since the initiation of therapy	Dynamics of the patient's condition during follow-up	Assessment using standard scales	
							Before treatment	After treatment
1	F/47/55 years	CIDP	GCS	2 g/ kg, 1 course	2 months	E -, P -, PR	INCAT for arms 3, for legs 3	INCAT for arms 3, for legs 3
2	M/50/51 years	CIDP	GCS	2 g/ kg, 2 courses	4 months	E -, P -, PR	INCAT for arms 4, for legs 2	INCAT for arms 2, for legs 2
3	F/60/60 years	CIDP	GCS, plasmapheresis	2 g/ kg, 2 courses	4 months	E -, P -, PR	INCAT for arms 4, for legs 3	INCAT for arms 1, for legs 0
4	M/58/59 years	CIDP	GCS	2 g/ kg, 1 course	2 months	E -, P -, PR	INCAT for arms 1, for legs 2	INCAT for arms 1, for legs 2
5	F/58/58 years	CIDP	Did not have	2 g/ kg, 2 courses	2 months	E -, P -, PR	INCAT for arms 3, for legs 2	INCAT for arms 3, for legs 2
6	M/27/27 years	CIDP	GCS	2 g/ kg, 1 course	2 months	E -, P -, PR	INCAT for arms 4, for legs 3	INCAT for arms 4, for legs 3
7	M/64/65 years	CIDP	GCS, plasmapheresis	2 g/ kg, 1 course	2 months	E -, P -, PR	INCAT for arms 3, for legs 1	INCAT for arms 3, for legs 1
8	F/33/34 years	CIDP +MGUS	Plasmapheresis	2 g/ kg, 1 course 1 g/ kg, 6 courses	7 months	E -, P -, CR	INCAT for arms 1, for legs 1	INCAT for arms 0, for legs 0
9	M/56/56 years	CIDP + podocytopathy	GCS, plasmapheresis	2 g/ kg, 1 course	4 months	E +, P +, PR	INCAT for arms 4, for legs 5	INCAT for arms 4, for legs 5
10	F/67/69 years	MMN	Did not have	2 g/ kg 1 g/ kg 2 courses	4 months	E -, P -, PR	INCAT for arms 3, for legs 0	INCAT for arms 3, for legs 0
11	F/38/41 years	MMN	Did not have	2 g/ kg 24 courses	30 months	E -, P -, CR	INCAT for arms 4, for legs 0	INCAT for arms 1, for legs 0
12	M/52/56 years	MMN	Did not have	2 g/ kg 1 course	2 months	E -, P -, PR	INCAT for arms 3, for legs 0	INCAT for arms 2, for legs 0
13	F/49/50 years	Stiff person syndrome	GCS	2 g/ kg, 3 courses 1 g/ kg, 4 courses	11 months	E -, P -, PR	*	*

14	F/30/30 years	AE, GAD +	GCS, Rituximab	2 g/ kg, 1 course 0,4 g/ kg, 6 courses	12 months	E -, P -, PR	**MoCA 11	**MoCA 11
15	F/37/40 years	AE, GAD +	Did not have	2 g/ kg, 5 courses	6 months	E -, P -, PR	***	***
16	F/26/30 years	NMOSD, AQP4-IgG+, Exacerbation, 23 weeks pregnant	Did not have	2 g/ kg 0.4 g/ kg 0.4 g/ kg 3 courses	6 months	E -, P -, PR	EDSS 4.0	EDSS 2.5
17	F/36/37 years	NMOSD AQP 4-IgG+, SLE, immunodeficiency	GCS, Rituximab	2 g/ kg 0.4 g/ kg 0.4 g/ kg 3 courses	4 months	E -, P -, PR	EDSS 1.5	EDSS 1.5
18	F/21/25 years	MG, exacerbation	GCS, Azathioprine, plasmapheresis	2 g/ kg 1 g/ kg 1 g/ kg 1 g/ kg 4 courses	4 months	E -, P -, PR	QMGS 26	QMGS 13
19	F/67/68 years	MG, exacerbation	GCS	2 g/ kg 1 course	2 months	E -, P -, PR	QMGS 23	QMGS 10
20	F/63/64 years	MG, exacerbation	GCS, Azathioprine, plasmapheresis	2 g/ kg 1 course	2 months	E -, P -, PR	QMGS 26	QMGS 13

Note: AE – autoimmune encephalitis; GCS – glucocorticosteroids; F – female; NMOSD – neuromyelitis optica spectrum disorders; M – male; MG – myasthenia gravis; MGUS – monoclonal gammopathy of undetermined significance; MMN – multifocal motor neuropathy; E – exacerbation, yes (+) / no (-); P – progression, yes (+) / no (-); CR / PR – complete / partial regression of symptoms; SLE – systemic lupus erythematosus; CIDP – chronic inflammatory demyelinating polyneuropathy; AQP4-IgG – antibodies to aquaporin 4; EDSS – Expanded Disability Status Scale; GAD – anti-glutamic acid decarboxylase antibodies; INCAT – Inflammatory Neuropathy Cause and Treatment Disability Score; MoCA – Montreal Cognitive Assessment; QMGS – Quantitative Myasthenia Gravis Score.

* There are no validated symptom scores for stiff person syndrome; against the background of the therapy, there was a decrease in the severity of stiffness.

** There are no validated symptom scores for autoimmune encephalitis. The patient's clinical presentation was dominated by cognitive impairment, thus, the MoCA scale was used.

*** The clinical presentation was dominated by generalized tonic – clonic seizures; there are no validated symptom scores for autoimmune encephalitis; against the background of the therapy, there was a decrease in the frequency of seizures.

IVIG is used as a drug of choice in the treatment of CIDP, including CIDP associated with diabetes mellitus and uncontrolled arterial hypertension, as well as in an atypical course of the disease, including motor phenotypes [6–8]. The generally accepted starting dose is 0.4 g / kg / day, from 3 to 5 days (up to 2 g / kg per course). In the maintenance regimen for CIDP, IVIG can be administered according to different schemes: a) a total dose of 0.4 g / kg within 1 day, 1–2 times a week; b) 1 g / kg within 2–3 days every 3–4 weeks; c) 2 g / kg within 3–5 days every 4–6 weeks.

When the patient's condition stabilizes during IVIG therapy for 6–12 months, gradual dose reduction or an increase in the interval between injections is recommended. A combination of glucocorticosteroids (GCS) and IVIG is allowed, as well as administration of IVIG after completion of the course of plasmapheresis [6–8]. In our cohort of patients, the majority of individuals were diagnosed with CIDP, and in all but one case, positive dynamics was noted after 1–2 courses of immunotherapy. An exception was the case of atypical CIDP with an acute onset, etiologically associated with podocytopathy, characterized by an aggressive course and resistance to GCS, plasmapheresis, and IVIG. The features of the disease in the patient were the presence of a pronounced nephrotic syndrome caused by minimal change disease (non-proliferative glomerulonephritis with podocytopathy). Presumably, such clinical presentation of CIDP is typical when the target of an autoimmune attack is neurofascin, which is localized both in the peripheral nervous system and in the podocyte cytoskeleton [9].

Within 5 days after the infusion, there was no increase in neurological deficit, but then bulbar disorders and tetraplegia began to rapidly increase, leading to intubation and follow-up in the intensive care unit. In the future, a combination of cytostatic therapy (cyclosporine and rituximab) and corticosteroids (oral prednisolone) had a dramatic positive effect. The lack of an adequate response to immunoglobulin can probably be explained by the gradually progressive nephrotic syndrome.

The off-label use of IVIG may be effective in the treatment of paraproteinemic demyelinating polyneuropathy associated with MGUS with Ig A and Ig G [10, 11] and as second-line therapy in patients with inflammatory myopathies (dermatomyositis, polymyositis). The dose may vary from 0.4 g / kg to 2 g / kg, depending on the severity of clinical symptoms. Currently, there are no unambiguous data on the effectiveness of IVIG in inclusion body myositis and necrotizing autoimmune myositis [4, 12, 13].

With MMN, the effectiveness of IVIG has been proven as the only method of pathogen-specific therapy. The starting course dose should be at least 2 g / kg for 3–5 days. The total maintenance dose can be 1 g / kg for 2–3 days every 2–4 weeks or 2 g / kg for 3–5 days every 1–2 months, although in our work in one case it was possible to reduce it to 0.5 g / kg. As a rule, patients with MMN require long-term, continuous maintenance therapy with IVIG [14, 15].

Stiff person syndrome is a rare autoimmune neurological disease associated with the presence of antibodies to glutamate decarboxylase (GAD) and amphiphysin. Currently, there are no generally accepted schemes for its therapy, however, along with GCS, IVIG and plasmapheresis have proven efficient. IVIG is administered at a course dose of 2 g / kg, followed by repeated courses at a dose of 1 g / kg. The duration of treatment and the interval between injections are determined by the level of autoantibodies and the severity of clinical symptoms [16]. In our cohort, a patient diagnosed with stiff person syndrome received 7 courses of IVIG infusions, during which a steady decrease in the severity of clinical manifestations was observed.

AE is a group of rare immune-mediated inflammatory diseases of the central nervous system. Its clinical presentation is dominated by encephalopathy of non-infectious origin, associated with the presence of autoantibodies of different specificities (to proteins of presynaptic terminals – GAD or amphiphysin; to synaptic proteins in neurons – GABAa,b receptors, AMPA receptors, VGC channels, NMDA receptors, etc.). Along with GCS and plasmapheresis, IVIG is referred to as first-line therapy, with a recommended dose of 2 g / kg per course. Second-line drugs include rituximab and cyclophosphamide [17]. In our study, for the patient with ineffective previous treatment with rituximab, IVIG therapy was accompanied by stabilization of the disease course throughout the year.

IVIGs are not included in the standard treatment regimen for multiple sclerosis (MS) and NMOSD. However, in MS and NMOSD, they are used in certain clinical situations, namely in children, in pregnant women, sometimes in severe exacerbations or verified immunodeficiency [3, 18–20]. In NMOSD, therapy with IVIG preparations to prevent the development of relapses can be carried out in the presence of contraindications to immunosuppressants [20]. In our cohort, in one patient with NMOSD, an exacerbation

developed during pregnancy, and in the second patient, it developed due to lymphopenia, the genesis of which was initially unclear, and later SLE was diagnosed as a comorbid condition. IVIG treatment in both cases was accompanied by rapid suppression of disease intensity, in the second case – after ineffective anti-relapse therapy with GCS and rituximab.

Of course, our observational study has a number of significant limitations, such as a small sample and demographic heterogeneity of patients, analysis of a wide range of diseases, use of various IVIG drugs, and a lack of randomization and a comparison group. Nevertheless, the results of the study seem to be important evidence of the efficacy and safety of IVIG preparations in the treatment of a number of immune-mediated diseases of the nervous system. They are often used in situations when other approved treatments are not effective or contraindicated, or when there is no approved therapy for certain nosological entities.

CONCLUSION

The use of IVIGs for the treatment of rare severe neurological diseases is possible not only within the approved indications, but also in the off-label fashion, taking into account known data on the pathogenesis and after assessing the risk – benefit ratio for patients in accordance with the order of the Ministry of Health and Social Development of the Russian Federation No. 494 of 09.08.2005 "On the procedure for the use of medicines in patients for health reasons" and Federal Law No. 323-FZ of 21.11.2011. These drugs have a good efficacy / safety ratio and in some cases may be the only means of treating life-threatening conditions and preventing profound disability. Potential systemic infusion reactions (fever, myalgia, asthenia, nausea, anaphylaxis) can be prevented by premedication. Further studies of IVIG preparations are required to determine their optimal doses, frequency of administration, as well as the duration of therapy for various neurological diseases in order to scientifically substantiate the expansion of the list of diseases for their use in the standards of medical care for neurological patients.

REFERENCES

1. Seredavkina N.V., Reshetnyak T.M., Nasonov E.L. The role of intravenous immunoglobulin in rheumatic diseases. *Modern Rheumatology Journal*. 2015;9(4):59–67 (in Russ.). DOI: 10.14412/1996-7012-2015-4-59-67.
2. Suponeva N.A., Piradov M.A. Features of the intravenous therapy in the neurology clinic. *Efficient Pharmacotherapy*. 2014;(58):12–23 (in Russ.).
3. Lünemann J.D., Quast I., Dalakas M.C. Efficacy of intravenous immunoglobulin in neurological diseases. *Neurotherapeutics.* 2016;13(1):34–46. DOI: 10.1007/s13311-015-0391-5.
4. Nikitin S.S., Boriskina L.M. Immunoglobulins in neurological practice: a review of the literature. *Neuromuscular Diseases*. 2019;9(1):32–51 (in Russ.). DOI: 10.17 650 / 2222-8721-2019-9-1-32-51.
5. Souayah N., Hasan A., Khan H.M. et al. The safety profile of home infusion of intravenous immunoglobulin in patients with neuroimmunologic disorders. *J. Clin. Neuromuscul. Dis.* 2011;12(4):1–10. DOI: 10.1097/CND.0b013e3182212589.
6. Lehmann H.C., Burke D., Kuwabara S. Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment. *J. Neurol. Neurosurg. Psychiatry*. 2019;90(9):981–987. DOI: 10.1136/jnnp-2019-320314.
7. Oaklander A.L., Lunn M.P.T., Hughes R.A.C. et al. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. *Cochrane Database Syst. Rev.* 2017;1(1):CD010369. DOI: 10.1002/14651858.CD010369.pub2.
8. Van den Bergh P.Y., Hadden R.D., Bouche P. et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. *Eur. J. Neurol.* 2010;17(3):356–363. DOI: 10.1111/j.1468-1331.2009.02930.x.
9. Bukhari S., Bettin M., Cathro H.P. et al. Anti-neurofascin-associated nephrotic-range proteinuria in chronic inflammatory demyelinating polyneuropathy. *Kidney Med.* 2020;2(6):797–800. DOI: 10.1016/j.xkme.2020.06.016.
10. Chaudhry H.M., Mauermann M.L., Rajkumar S.V. Monoclonal gammopathy-associated peripheral neuropathy: Diagnosis and management. *Mayo Clin. Proc.* 2017;92(5):838–850. DOI: 10.1016/j.mayocp.2017.02.003.
11. Nobile-Orazio E., Bianco M., Nozza A. Advances in the treatment of paraproteinemic neuropathy. *Curr. Treat. Options Neurol*. 2017;19(12):43. DOI: 10.1007/s11940-017-0479-9.
12. Schmidt J. Current classification and management of inflammatory myopathies. *J. Neuromuscul. Dis.* 2018;5(2):109–129. DOI: 10.3233/JND-180308.
13. Barsotti S., Lundberg I.E. Current treatment for myositis. *Curr. Treatm. Opt. Rheumatol*. 2018;4(4):299–315. DOI: 10.1007/s40674-018-0106-2.
14. Joint Task Force of the EFNS and the PNS European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. *J. Peripher. Nerv. Syst*. 2010;15(4):295–301. DOI: 10.1111/j.1529-8027.2010.00290.x.
15. Beadon K., Guimarães-Costa R., Léger J.M. Multifocal motor neuropathy. *Curr. Opin. Neurol.* 2018;31(5):559–564. DOI: 10.1097/WCO.0000000000000605.
16. Sarva H., Deik A., Ullah A. et al. Clinical Spectrum of Stiff Person Syndrome: A Review of Recent Reports. *Tremor. Other Hy-*

perkinet. Mov. (NY). 2016;6:340. DOI: 10.7916/D85M65GD.
17. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. *J. Clin. Neurol.* 2016;12(1):1–13. DOI: 10.3988/jcn.2016.12.1.1.
18. Achiron A., Kishner I., Dolev M. et al. Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis. *J. Neurol*. 2004;251(9):1133–1137. DOI: 10.1007/s00415-004-0495-z.
19. Bisaga G.N., Skulyabin D.I., Popov A.E. Intravenous immunoglobulins: prospects in multiple sclerosis. *S.S. Korsakov Journal of Neurology and Psychiatry.* 2015;115(8-2):36–43 (in Russ.). DOI: 10.17116/jnevro20151158236-43.
20. Trebst C., Jarius S., Berthele A. et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J. Neurol.* 2014;261(1):1–16. DOI: 10.1007/s00415-013-7169-7.

Authors information

Tereshchenko Nikolai M. – Neurologist, Senior Laboratory Assistant, Department of Neurology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, nickolaitereshenko@yandex.ru, https://orcid.org/0000-0001-9594-8926

Kushnir Yana B. – Neurologist, Neurology Department No. 1, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, kushnir.yana2014@yandex.ru, https://orcid.org/0000-0001-7891-9883

Abramova Maria P. – Clinical Resident, Department of Neurology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, maria.p.abramova@gmail.com, https://orcid.org/0000-0001-7081-8455

Gotovchikov Andrey A. – Neurologist, Head of the Neurology Department No. 1, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, gotovchikov_73@mail.ru, https://orcid.org/0000-0002-8567-6442

Krasnov Vladimir S. – Can. Sci. (Med.), Associate Professor, Department of Neurology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, krasnov_volod@mail.ru, https://orcid.org/0000-0002-9769-447X

Sokolov Alexey Yu. – Dr. Sci. (Med.), Professor, Department of Pharmacology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, alexey.y.sokolov@gmail.com, https://orcid.org/0000-0002-6141-486X

Totolyan Natalya A. – Dr. Sci. (Med.), Professor, Department of Neurology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg , ntotolyan@mail.ru, https://orcid.org/0000-0002-6715-8203

Amelin Aleksander V. – Dr. Sci. (Med.), Professor, Department of Neurology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, avamelin@mail.ru, https://orcid.org/0000-0001-6437-232X

(✉) **Tereshchenko Nikolai M.,** nickolaitereshenko@yandex.ru

Received 29.04.2022;
approved after peer review 19.05.2022;
accepted 08.09.2022