IMMUNOGLOBULINS TREATMENT IN THE NEUROLOGICAL PATHOLOGY

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Abstract: *Soon after the description of the immunomodulatory effect of IVIg, neuroimmunological diseases were also treated with IVIg. Guillain-Barre syndrome (GBS), chronic demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), myasthenia gravis, paraneoplastic neurologic syndromes, multiple sclerosis, were successfully treated with IVIg. Immunoglobulins can modulate an immune reaction at the level of T cells, B cells, and macrophages, interfere with antibody production and degradation, modulate the complement cascade, and have cytokine network effect. However, the precise mechanism of action is not clear yet. In general, IVIg therapy side effects are usually minor and self-limiting. This therapy seems to be effective and safe for a variety of neuroimmune-mediated diseases, too.*

Keywords: *intravenous immunoglobulin therapy, applications, side effects, safety*

Rezumat: *Curând după descrierea efectului imunomodulator al imunoglobulinelor administrate intravenos (IgIV) şi afecţiunile neuroimune au început să fie tratate cu succes cu imunoglobiline IV. Între acestea se numără, sindromul Guillain-Barre, polineuropatiile inflamatorii demielinizante cronice (CIDP), neuropatiile multifocale motorii (MMN), miastenia gravis (MG), scleroza multiplă (SM), sindroamele neurologice paraneoplazice etc. IgIV modulează reacţiile imune la nivelul limfocitelor T şi B, al macrofagelor, interferează cu producţia şi degradarea anticorpilor, au efect modulator în cascada complementului, acţionează la nivelul citokinelor. Totuşi, mecanismul precis de acţiune nu este deplin elucidat. Reacţiile adverse, în general la administrarea IgIV sunt minore şi se autolimitează, terapia cu IgIV fiind considerată sigură în afecţiuni neurologice mediate imun.*

Cuvinte cheie: *terapia cu imunoglobuline IV, aplicaţii, reacţii adverse, siguranţă*

INTRODUCTION

The first clinical use of immunoglobulins was recorded more than 100 years ago, being indicated in the prophylaxis and treatment of the infectious diseases.

Starting with 1952, it has been used in the primary therapy of agammaglobulinemia. Initially, Ig was intramuscularly administered, bringing about irritation and local muscle pains. There were also other disadvantages, such as: relatively reduced dose. At the same time with the development of the technology of immunoglobulins purification, they started to be administrated intravenously.

Regarding the neuroimmune diseases, immunoglobulins were for the first time administered intravenously in multiple sclerosis (1982); subsequent successful results were recorded in myasthenia crises and in Guillain –Barre syndrome (1988). There are also other neuroimmune-mediated diseases: chronic demyelinating, polyneuropathies, multifocal motor neuropathies, paraneoplastic neurological syndromes, (Lambert -Eaton, limbic encephalitis, subacute cerebellar degeneration), myositis (dermatomyositis, polymyositis).

Today, neuroimmune-mediated diseases present the most common indication for IVIg of all the neurological diseases (1).

IVIg mechanism of action

Nowadays, literature data sustain that the intravenous administration of immunoglobulins interferes with the immune system at any level (1).

At the level of **B lymphocytes**, the immunomodulatory effects of intravenous immunoglobulins (IVIg) include their inhibition, the neutralization of the self-bodies and the acceleration of their catabolism (table 1).

At the level of the serous complement, IVIg intervenes in certain stages (see table 1); these rings represent the major mechanism in dermatomyositis treatment with IVIg.

Immunoglobulins inhibit antigen presentation at the level of T lymphocytes and LT activation through certain mechanisms (see table 1).

Another effect of IVIg is the intensification of regeneration in the demyelinating diseases of the central nervous system, mainly in multiple sclerosis.

Table no. 1. Immunomodulatory effect of immunoglobulins intravenously administered

Immunomodulatory Effect Of Immunoglobulins Intravenously Administered		
Effect on B cells	**Effect on the complement**	**Effect on T cells**
• Inhibits the activation of B cells; • Induces apoptosis in B cells; • Neutralizes the self-bodies; • Inhibits the production of IL6, necessary for the antibody secretion of the plasmatic cells; • Increases the catabolism of the anti-bodies via FcRn.	• Is related to C1, C3b, C4 complements; • Increase the degradation of C3b component • Is related to C3a and C3b anaphylatoxins.	•Stimulates the production of antibodies, CD4 and CD8 anticells; • Inhibits the maturation of dendrites and consecutively, inhibits the activation of T cells.

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IVIg therapy in neuroimmune-mediated diseases.

The prototype of the immune-mediated peripheral neuropathies is **Guillain-Barre syndrome (SGB)**-defined as an acute demyelinating inflammatory neuropathy with the affection of the peripheral and cranial nerves. The neurological symptomathology is characterized by: weakness of the muscle force, rapidly, asymmetrically and progressively, abolition of osteotendinous reflexes, facial diplegia, orofacial paresis, respiratory disorders, limbs paraesthesia. It starts between 5 days and 3 weeks after a viral infection (respiratory or gastrointestinal). Most frequent incriminated pathogenic agents are the viruses of Haemophilus Influenzae, Citomegalovirus (CMV), and Campylobacter jejuni.

The election treatment is plasmapheresis or IVIg administered as early as possible in the first 2 weeks after the beginning of the disease. IVIg is recommended in a standard dose of 0,4g/Kg C/day, 5 days consecutively (2).

The clinical studies proved the equal efficiency of the two therapeutic methods. In the patients infected with Campylobacter jejuni, IVIg efficiency seems to be superior to plasmapheresis. Recently, a study has been published, mentioning the combined therapy between IVIg and Metylprednisolon 500 mg/day, administered 5 days consecutively, proving the efficiency of this association in the people above 50 years old, with large disability within the disease (3).

Certain multicentric trials made in Germany proved the similar efficiency of IVIg in children. Generally, they have a remission of the neurological symptomathology more rapid than in the adult patients (4).

Chronic demyelating polyneuropathies (CIDP)

Regarding these affections, the election treatment consists in corticosteroids. The clinical studies proved that the motor forms of CIDP may become aggravated after the treatment with corticosteroids. In these cases, IVIg treatment is of first intention. The initial dose is of 0,4g/kgC/day – 5 days with the installation of the benefic effect 2-4 weeks after and with the possibility of repeating the treatment according to the clinical evolution.

Multifocal motor neuropathy (MMN),

The clinical studies proved that IVIg treatment is efficient, being indicated as a first line treatment in similar doses with CIDP. Severe forms of MMN respond well to the combined therapy between IVIg and cyclophosphamid (2).

IVIg in paraneoplastic neurological syndromes

Regarding the paraneoplastic neurological syndromes, Lambert – Eaton syndrome, dermatomyosis, limbic encephalitis associated with anti-bodies anti-VGKC registered good responses to IVIg treatment.

IVIg administration in these syndromes is indicated only after the certain diagnosis of these diseases emphasized by paraneoplastic specific markers (antoneurolnal antibodies, for example: antiHu (ANNA1), anti-VGCC etc.).

IVIg in multiple sclerosis

Recent literature data, published as a result of different clinical studies, indicate the use of IVIg in recurrent-remissive multiple sclerosis (SMRR), as a second line treatment, when the other treatments (interferon beta, glatiramer acetate) are not tolerated or present adverse reactions. The recommended dose is of 0,2 g/Kg C, administered monthly in order to avoid dose-related side effects.

Within the isolated clinical syndrome of multiple sclerosis, IVIg use is indicated as a therapeutic option in the situation in which other immunomodulatory treatments (example: interferon beta) cannot be administered. IVIg is not indicated in secondary progressive multiple sclerosis treatment.

Today, clinical studies are developing in order to test IVIg postpartum efficiency in the female patients with multiple sclerosis. It is not recommended in breastfeeding patients. The indicated dose is 0,4 g/Kg C iv, 5 days consecutively, in the first postpartum week, with booster dose at 6 and 12 weeks (6).

IVIg in miastenia gravis

The use of IVIg is indicated in miastenia gravis, only in myastenic crisis. As a result of the clinical studies, it was concluded that the patients with myastenic crisis responded well to the IVIg treatment, in comparison with plasmapheresis. IVIg dose is of 0,4g/KgC, 5 consecutive days;

IVIg in epilepsy

Intravenous gammaglobulins were successfully used in epilepsy treatment, in the severe cases with refractory crises in children. Generally, the cryptogenic forms of epilepsy respond better to this treatment than in those symptomatic. In the children with frequent crises within the West and Lennox-Gastaut syndromes, doses of 0,4g/Kg C are administered 5 days and afterwards, once

every two weeks for the first three months. The frequency of crises will be reduced with 70% on average and the improvement of EEG modifications, 4-6 weeks after the beginning of the treatment.(7)

Side effects in IVIg treatment regarding the neurological diseases.

IVIg therapy is considered the only one in the immune-mediated neurological diseases, The data published in the specialized literature indicate a prevalence of side effects between 11 and 81%.

The majority of the patients present minimal side effects; asymptomatic reversible alterations of laboratory tests occur most frequently. Out of these, we mention: increase of Erythrocyte Sedimentation Rate, leucopoenia with mild lymphopenia, increase of sanguine viscosity.

Among the mild side effects of IVIg administration, mention must be made of: headaches, chest pains, fever, myalgia. Headaches are the most common side effects, encountered especially in the older patients whose administration rate of IVIg is higher than 10g/hour.

Aseptic meningitis, headaches, meningism, photophobia, fever accompanied by pleocytosis and the increase of IVIg in the cerebrospinal fluid is a rare secondary reaction, encountered in less than 5% of the patients who receive high doses of IVIg and in those with headaches history.

In the patients with headaches history, beta-blockers prophylaxis is recommended before IVIg.

Rare but serious side effects are: thromboembolic complications, cerebral and myocardial infarction (8). Deep venous thromboses were also registered, especially in the immobilized patients. In these cases, IVIg administration increases the blood viscosity and there is the risk for venous thromboses due to prolonged immobilization. In such cases, the prophylaxis of deep venous thromboses with heparin is recommended (9). Severe renal complications, such as: acute tubular necrosis may occur in the patients suffering from renal insufficiency. A very rare complication is the anaphylactic shock, occurring in the patients with selective deficiency of IgA. If it is possible, the serous level of IgA should be established before starting the IVIg treatment. The administration will be made under strict medical supervision.

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