EFFICACY OF TREATMENT WITH INTRAVENOUS IMMUNOGLOBULINS AND PULSE THERAPIES WITH METHYLPREDNISOLONE AND CYCLOPHOSPHAMIDE IN PATIENTS WITH ACTIVE SLE

V. Reshkova, R. Rashkov

Rheumatology Clinic, "Sv. Ivan Rilski" Multiprofile University Hospital for Active Treatment, Medical University – Sofia

Abstract. *Immunoglobulin preparations for intravenous administration (IVIG) contain highly purified native molecules of human IgG, freed from high-molecular aggregates and vasoactive substances stabilized with glucose, maltose, glycine, sorbitol, etc. Intravenous immunoglobulins can be used as adjunctive therapy in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APLS) with recurrent miscarriages. The aim of the clinical observation is to establish the efficacy of the treatment of immunovenin in a scheme, in parallel with pulse therapies with methylprednisolone (MP) and cyclophosphamide (CYC) in patients with active SLE, compared with the application of pulse therapies with methylprednisolone and cyclophosphamide alone. When comparing the effect of treatment with immunovenin 400 mg/kg body weight every 3 months for a period of 12 to 18 months, in parallel with pulse therapies with methylprednisolone and cyclophosphamide 1 g monthly intravenously in disease activity, a significant difference in positive influence on organic brain syndrome, cranial nerve function, arthritis/arthralgias and proteinuria was observed. In both groups, the concentration of anti dsDNA and ACLA decreased to the same extent. Treatment with immunovenin has a positive effect on influencing disease activity in SLE, added to treatment with pulse therapies with methylprednisolone and cyclophosphamide.*

Key words: *intravenous immunoglobulins, pulse therapies, SLE*

Introduction

Immunoglobulin preparations for intravenous administration (IVIG) contain highly purified native molecules of human IgG, freed from high-molecular aggregates and vasoactive substances stabilized with glucose, maltose, glycine, sorbitol, etc.

Intravenous immunoglobulins contain minimal amounts of IgM, IgA molecules (purified in some preparations), soluble CD4, CD8 and HLA-molecules, and cytokines. The half-life of immunoglobulins ranges from 21 to 33 days. Donors are screened for viral infections – HIV-1/HIV-2 Abs, HIV p24 Ag, HBVs Ag, HCV Abs, and parvovirus B19. Deep freezing of the plasma is applied for a period of 60 days. A repeated anamnesis and screening of the selected pools are carried out. Additional viral inactivation is performed by pasteurization, dry heat, at low pH. Solvent/detergent techniques and anion chromatography (virus absorption) are used. Additional identification of prions by Western blot1 is applied.

Intravenous immunoglobulins can be used as adjunctive therapy in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APLS) with recurrent miscarriages.

A. Mechanisms of action of IVIG in systemic connective tissue diseases [2]:

1. Anti-idiotype hypothesis.

Interaction between anti-idiotypic antibodies in IVIG and antibodies directed against dsDNA, factor VII, forming anti-idiotypic networks.

2. Blockage of Fc receptors

The anti-idiotypic antibodies in IVIG activate the inhibitory FcγRIIb, leading to an "off signal" on B-cells and suppression of autoantibody production. Thus, the immunoregulatory mechanisms of Fc-receptors are manifested in the suppression of inflammation. IVIG controls the migration of B cells from the bone marrow to secondary lymphoid organs, and suppresses specific autoreactive B lymphocytes.

3. Cytokine network hypothesis

IVIG inhibits differentiation and maturation of dendritic cells, reduces interleukin 12 secretion after activation, lowers IL-1β, TNF-α increases the secretion of interleukin 10, reduces the expression of co-stimulatory molecules, neutralizes bacterial toxins. The result is inhibition of autoreactive T-cell activation and proliferation. IVIG reduces the production of interleukin 2 and IFN-γ by Th1 and restores the balance between Th1 and Th2 in autoimmune diseases.

IVIG has anti-inflammatory effects – reduces complement-mediated damage, reduces inflammation from immune complexes, induces anti-inflam-

matory cytokines, inhibits endothelial cell activation, neutralizes microbial toxins, and reduces the need for high-dose corticosteroids. IVIG binds activated C3b and C4b and lowers plasma levels of these components.

4. Hypothesis of increased catabolism.

IVIG contain antibodies against CD4, CD5, the non-polymorphic chain of HLA-I, the B-cell antigen receptor, the T-cell antigen receptor, adhesion molecules – ligands for integrins [3].

For treatment of SLE Immunovenin intact is administered in a dose of 400-800 mg/kg to 1-2 g/kg (in severe cases) in three applications every other day. In case of antiphospholipid syndrome, IVIG is administered in a dose of 400 mg/kg monthly from the establishment of pregnancy until 28-32 weeks [4].

Several medicinal preparations containing immunovenin for intravenous administration are present on the Bulgarian market: Immunovenin intact 5% IgG1, Privigen 100 mg/ml, Octagam 10%. One of the main differences between the various preparations is the IgA content. The most widely used immunoglobulin preparation in daily rheumatology practice is Immunovenin intact [4].

In daily rheumatology practice, intravenous immunoglobulins are used in the treatment of:

● Systemic lupus erythematosus with high immunological activity;

● Systemic lupus erythematosus, occurring with cerebrovasculitis, lupus nephritis, vasculitis and/or autoimmune hemolytic anemia, thrombocytopenia;

● Systemic lupus erythematosus with underlying antiphospholipid syndrome;

● Systemic lupus erythematosus with recurrent infections [4].

B. Adverse drug reactions occurring with the administration of IVIG

Most often, side reactions occur during the infusion of intravenous immunoglobulins and several hours after. During the infusion, the rate may be reduced or stopped. In the presence of adverse reactions, the patient should be prepared with analgesics/antipyretics, antihistamines and corticosteroids.

Mild side effects of immunovenin infusion are: headache, back pain, dizziness, tachycardia, abdominal pain and nausea.

Serious side effects are chest pain, eczema, anaphylaxis, heart attack, hemolysis and hemolytic anemia, neutropenia, pulmonary edema, thromboembolic events – deep vein thrombosis, retinal vasculitis and panuveitis, azotemia, and renal failure.

Purpose and Tasks

The aim of the clinical observation is to establish the efficacy of the treatment of immunovenin in a scheme, in parallel with pulse therapies with methylprednisolone (MP) and cyclophosphamide (CYC) in patients with active SLE, compared with the application of pulse therapies with methylprednisolone and cyclophosphamide alone.

Tasks include tracking the reduction in the number and intensity of clinical symptoms before and after completion of treatment in active SLE: epileptiform seizures, organic brain syndrome, cranial nerve dysfunction, headache, cerebrovascular accidents, proteinuria, skin symptoms, arthritis and arthralgias, elevated anti dsDNA, ACLA, vasculitis.

Clinical Material/Patients and Methods

A clinical observation of the efficacy of intravenous administration of intravenous immunoglobulins in patients with systemic lupus erythematosus was conducted in a rheumatology clinic. Two groups of patients were monitored:

First group – 29 women aged 20 to 60 years, mean age 46.6 year, treated with immunovenin 400 mg/kg body weight every 3 months for a period of 12 to 18 months, in parallel with pulse therapies with methylprednisolone and cyclophosphamide 1 gram per month intravenously during disease activity.

Second group – 23 women aged 20 to 70 years, mean age 49.8 year, treated for a period of 12 to 18 months with pulse therapies with methylprednisolone and cyclophosphamide 1 gram per month intravenously for disease activity.

Results

All patients were treated with methylprednisolone 8 to 16 mg daily. Patients who have epileptiform seizures take trileptal or kerpa for at least 3 months before follow-up. The clinical condition of the patients was evaluated at the beginning and end of the treatment according to the decrease in intensity and absence of the clinical symptom/manifestation, change in the values of anti dsDNA, ACLA (Table 1).

First group – patients with SLE, treated with immunovenin + pulse therapies with methylprednisolone and cyclophosphamide 1 g monthly intravenously during disease activity.

1. Before the treatment, there was 1 patient with epileptiform seizures, after the end of the treatment there were no patients with epileptic seizures;

Table 1. Clinical manifestations in both groups of patients with SLE, before and after treatment

Patient group		Patients with SLE, treated with immunovenin + pulse therapies with MP and CYC		Patients with SLE, treated with pulse therapies with MP and CYC	
		First group		Second group	
		Before the treatment	After treatment	Before the treatment	After treatment
1	Epileptiform seizures	1	0	12	2
2	Organic brain syndrome	5	1	3	1
3	Disorder of cranial nerves	3	1	6	4
4	Headache	12	10	22	15
5	Cerebrovascular accidents	3	1	11	1
6	Proteinuria	19	1	11	2
7	Skin symptoms	12	1	22	1
8	Arthritis/arthralgia	29	2	23	3
9	Elevated anti dsDNA	20	12	23	11
10	ACLA	2	2	1	1
11	Vasculitis	4	2		

2. Before the treatment, 5 patients had an organic brain syndrome, after the end of the treatment, 1 patient remained with symptoms (Fig. 1) ($p < 0.05$ for the first versus the second group), the improvement in the group was 80%;

3. Before the treatment, 3 patients had a disorder of cranial nerves, after the end of the treatment, 1 patient remained with symptoms, the improvement in the group was 66.6% (Fig. 2);

4. Before the treatment, 12 patients had a headache with SLE, after the end of the treatment 10 patients remained with symptoms; the improvement in the group was 16.6% (Fig. 3);

5. Before the treatment, cerebrovascular accidents were registered in 3 patients, after the end of the treatment 1 patient remained with symptoms, the improvement in the group was 66.6%;

6. Before the treatment, 19 patients had proteinuria, after the end of the treatment, 1 patient remained with symptoms, the improvement in the group was 91% (Fig. 4);

7. Before the treatment, 12 patients had skin symptoms, after the end of the treatment, 1 patient remained with symptoms, the improvement in the group was 91.7% (fig. 5);

8. Before the treatment, 29 patients had arthritis/arthralgia, after the end of the treatment, 2 patients remained with symptoms, the improvement in the group was 94% (Fig. 6);

9. Before the treatment, 22 patients had elevated anti dsDNA, after the end of the treatment normal values were established in 10 patients, the improvement in the group was 60% (Fig. 7);

10. ACLA was found elevated in 2 patients at the beginning and after the end of the treatment (Fig. 8).

11. Before the treatment, 4 patients had vasculitis, after the end of the treatment, 2 patients remained with symptoms, the improvement in the group was 50%

Second group – patients with SLE, treated with pulse therapies with methylprednisolone and cyclophosphamide 1 g monthly intravenously during disease activity.

1. Before the treatment, 12 patients had epileptiform seizures, after the end of the treatment, a reduction in the number of seizures was observed in 10 of the patients, the improvement in the group was 83%;

2. Before the treatment, 3 patients had an organic brain syndrome, after the end of the treatment, 1 patient remained with symptoms, the improvement in the group was 66.6% (Fig. 1) ($p < 0.05$ for the first versus the second group);

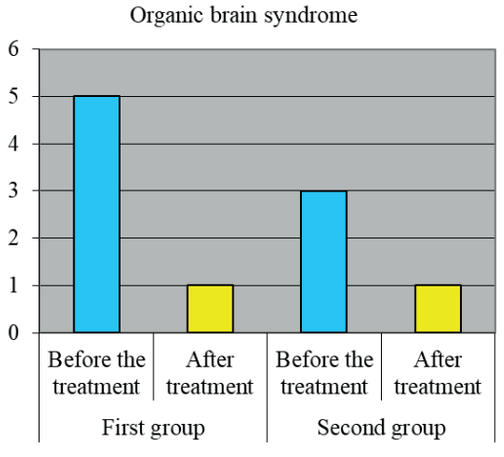


Fig. 1. Influence of the organic brain syndrome in both groups of patients (p < 0.05 for the first versus the second group)

3. Before the treatment, 6 patients had a disorder of cranial nerves, after the end of the treatment, 4 patients remained with symptoms, the improvement in the group was 66.6% (Fig. 2);

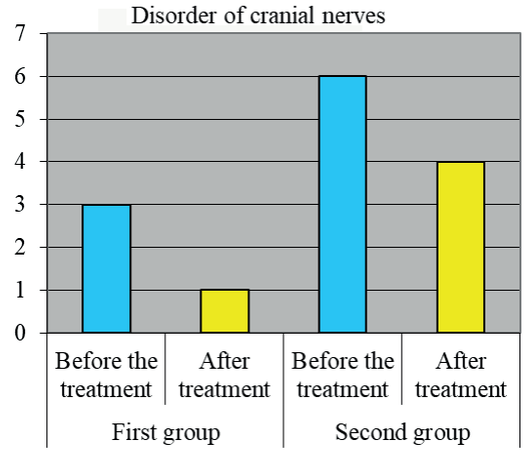


Fig. 2. Influence of the function of the cranial nerves in both groups of patients (p < 0.05 for the first versus the second group)

4. Before the treatment, 22 patients had SLE headaches, after the end of the treatment 15 patients remained with symptoms; the improvement in the group was 31% (Fig. 3);

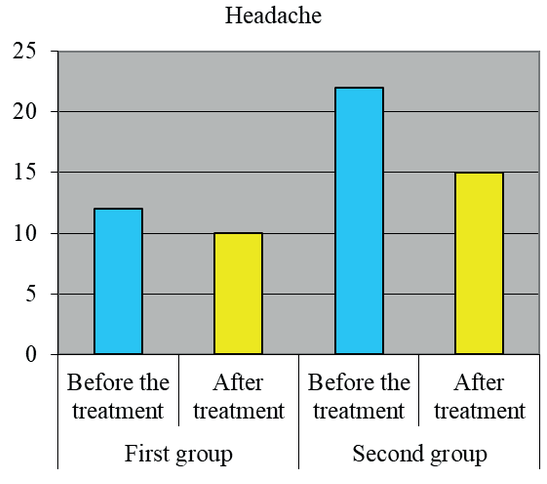


Fig. 3. Effect on headache in both groups of patients

5. Before the treatment, cerebrovascular accidents were registered in 11 patients, after the end of the treatment, 1 patient remained with symptoms;

6. Before the treatment, 11 patients had proteinuria, after the end of the treatment, 2 patients remained with symptoms, the improvement in the group was 82% (Fig. 4);

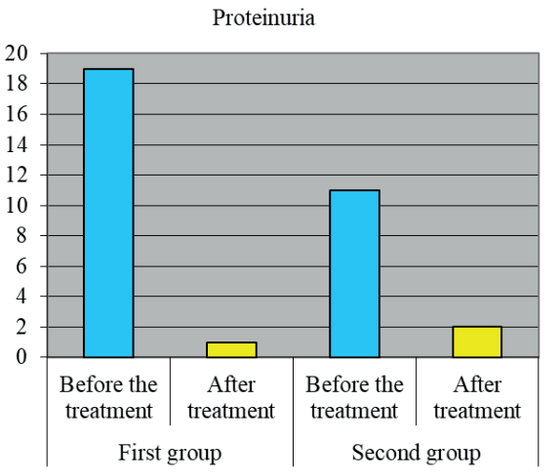


Fig. 4. Effect on proteinuria in both groups of patients (p < 0.05 for the first versus the second group)

7. Before the treatment, 22 patients had skin symptoms, after the end of the treatment, 1 patient remained with symptoms, the improvement in the group was 91.7% (Fig. 5);

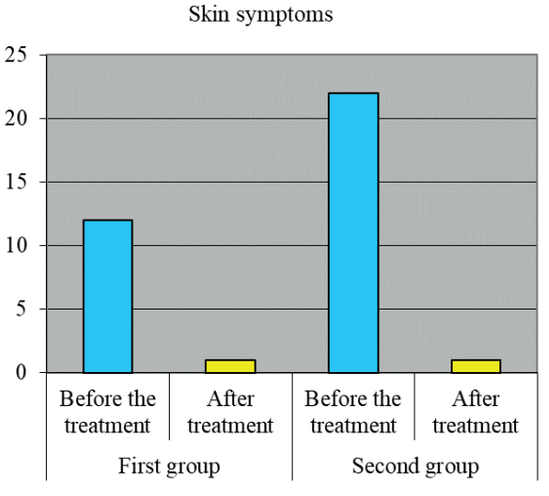


Fig. 5. Effect on skin symptoms in both groups of patients

8. Before the treatment, 23 patients had arthritis/arthralgias, after the end of the treatment 3 patients remained with symptoms; the improvement in the group was 94% (Fig. 6);

9. Before the treatment, 23 patients had elevated anti dsDNA, after the end of the treatment; a decrease in antibody values was found in 11 of them (Fig. 7);

10. ACLA was found elevated in 1 patient at the beginning and after the end of the treatment (Fig. 8).

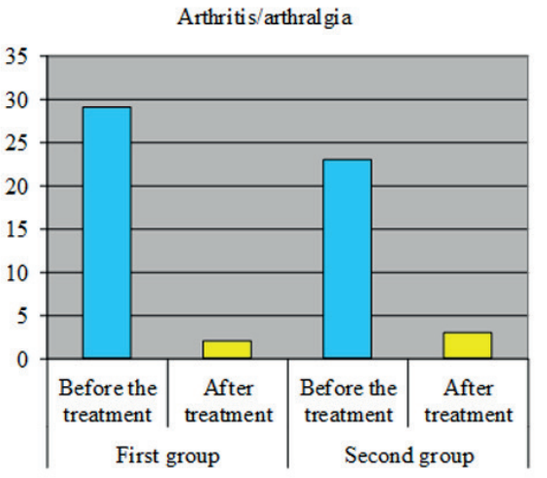


Fig. 6. Effect on arthritis/arthralgias in both groups of patients ($p < 0.05$ for the first versus the second group)

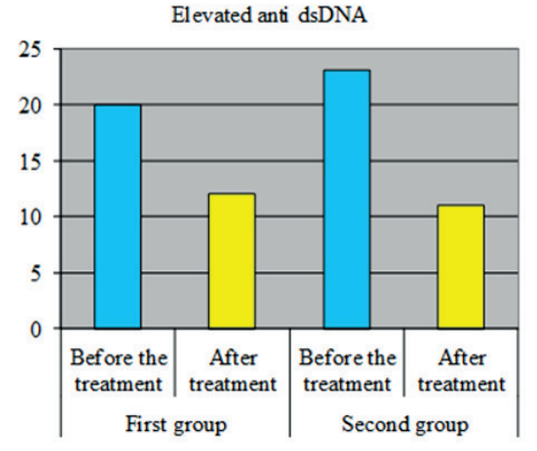


Fig. 7. Influence of the values of anti dsDNA in both groups of patients

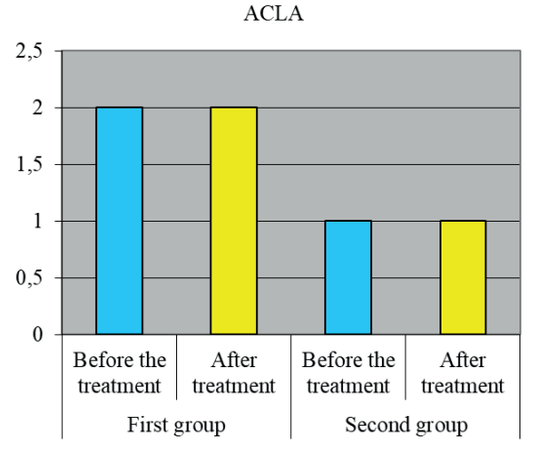


Fig. 8. Influence of ACLA values in both groups of patients

Discussion

The clinical efficacy and indications for IVIG need further investigation due to the current lack of large-scale double-blind randomized clinical trials. However, a number of case series have been reported with encouraging results, although evidence is limited by the heterogeneity of protocols applied and the variability of clinical manifestations successfully treated [2].

Our clinical observation shows that a significant difference is found in positive impact on organic brain syndrome, cranial nerve function, arthritis/arthralgias and proteinuria.

Therefore, on the basis of the currently available evidence, human polyclonal IVIG were administered. The protocol most often used in clinical practice entails high-dose IVIG infusion, consisting of a total amount of 2 g/kg body weight, usually divided into five daily doses of 400 mg/kg each to minimize the risk of adverse events. Remarkably, an unprecedented clinical response was noted 72 hours after the first dose, and included every affected organ and system, along with concurrent progressive normalization of the major immunological parameters. Regardless of their long-term efficacy, these positive results should encourage thoughtful use of IVIG in all cases refractory to conventional therapies or uncontrolled with high doses of corticosteroids [5].

Two small studies tested the efficacy of IVIG in SLE as well as four open trials and one retrospective study. These studies include 150 patients in total [6].

Fourteen lupus nephritis patients who had already been induced into remission with i.v. CYC were randomized to receive monthly IVIG (400 mg/kg) or i.v. CYC7. After a follow-up period of 18 months, there was no significant difference between IVIG and CYC in maintaining remission, leading the authors to conclude that IVIG could be an alternative treatment to CYC. However, it is recognized that significant differences between lupus nephritis treatment outcomes may take 5 years to become apparent [8, 9].

In our clinical observation, a better effect of the additional application of immunovenin to the pulse therapy with methylprednisolone and cyclophosphamide was established.

Uncontrolled open trials all report positive results for IVIG.

Francioni C looked at the treatment of chronically active lupus rather than acute flares and administered IVIG (400 mg/kg) for 5 days every month for 6-24 months. Of 12 patients, 11 showed clinical and serological improvement after treatment, although no comment was made on concurrent medication changes [3].

Schroeder JO also demonstrated a significant improvement in mild flares of lupus as measured by a reduction in their SLAM scores from 7.33 to 5.25 ($P < 0.001$) with a total of 10 infusions 20 days apart, although this improvement was only very modest considering the intensity of the infusion protocol [10].

Levy Y describe 20 patients with various manifestations of SLE treated with monthly IVIG (400 mg/ kg/day for 5 days). Out of all the 20 patients, 17 responded fully after one to eight courses of monthly IVIG, with a mean reduction in SLAM score from 19.3 to 4.0 ($P < 0.0001$). Encouragingly, 8 of 15 patients taking glucocorticoids were able to reduce their dose by the end of the trial [11].

Hundt M studied the treatment of lupus exacerbations in 13 patients with 5 consecutive days of IVIG (400 mg/kg/day) as measured by mECLAM scores. Although concurrent glucocorticoid dose was increased in six of these patients, it was noted that the remaining seven patients, in whom the glucocorticoid dose was kept constant, were full responders with a median reduction in their mECLAM score of 8 points. When these results are taken together, they suggest that IVIG may be useful in acute flares of SLE, with most benefit seen during severe flares. They also suggest that the most common symptoms to improve are those of fatigue, fever and pain [12].

A larger retrospective study by Sherer Y looked at 62 patients given IVIG as part of their treatment for lupus. Patients were treated for a variety of symptoms, including mucosal ulcers, fever, rash, pleurisy and pericarditis, with a single dose of IVIG (500 mg/ kg). Good responses were noted with a reduction in SLEDAI score from 15 to 5. Overall, the results from this study were promising, although there was no information about the dosing regimen of IVIG for each patient or other treatments they were receiving [13].

Conclusions

1. When comparing the effect of treatment with immunovenin 400 mg/kg of body weight in 3 months for a period of 12 to 18 months, in parallel with pulse therapies with methylprednisolone and cyclophosphamide 1 g monthly intravenously in disease activity, a significant difference in positive impact on organic brain syndrome, cranial nerve function, arthritis/arthralgias and proteinuria was observed. In both groups, the concentration of anti dsDNA and ACLA decreased to the same extent.

2. Treatment with immunovenin has a positive effect in influencing disease activity in SLE, added to treatment with pulse therapies with methylprednisolone and cyclophosphamide.

Conflict of Interests Statement: *The authors declare that there is no conflict of interests related to the publication.*

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✉ *Адрес за кореспонденция:*
Д-р Валентина Решкова, дм, доктор на науките
e-mail: v_reshkova@abv.bg

✉ *Correspondence address:*
Valentina Reshkova, MD, PhD, DSc
e-mail: v_reshkova@abv.bg