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COMPARATIVE EVALUATION OF THE EFFECTIVENESS OF IMMUNOTHERAPY WITH GALAVIT

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SUMMARY
This article presents the results of studying the effect of therapy with the use of Galavit, as well as the results of comparing the effect of similar therapy without Galavit on the condition of patients with MS.

KEYWORDS: Galavit, metabolic syndrome, lipid-lowering therapy, immunoregulatory index.

Topicality
Modern epidemiological data indicate a steady increase in patients with metabolic syndrome (MS). Currently, the prevalence of metabolic syndrome is becoming an epidemic, while accounting for 26 to 42% of the adult population of the planet, depending on the region and ethnicity.[6,7,9] In the next 25 years, its growth rate is expected to increase by 50%. Isolation of patients with metabolic syndrome is of great practical importance, it is the ability to predict disability and from the side of clinical significance, timely adequate treatment, which makes it possible to achieve a significant reduction in the severity of its main components, such as abdominal obesity, dyslipidemia and diabetes mellitus.[2,3,4,5] One of the most discussed processes in recent years, consolidating the components of MS and associated diseases is subclinical chronic inflammation.[6,15] The interpretation of the importance of inflammation in the above diseases has now expanded significantly and covers not only local inflammatory reactions, but also systemic inflammation, which, unlike local, is more demonstrative and available for research in a clinic. Intensive immunological studies in recent years have revealed common features in the pathogenesis of a number of diseases that have different clinical manifestations, but whose pathogenesis involves immunocompetent cells, regulatory molecules and their receptors.[7]

The aim of the research- to study the effectiveness of standard therapy with and without a combination of Galavit in patients with MS

MATERIALS AND RESEARCH METHODS
Of the examined patients with MS, 37 (38.5%) people had impaired immune status indicators (mean age 56.8 ±

1.7 years). The patients were divided into two groups by random sampling: in the control group (n = 17), patients received standard basic therapy, in the main group (n = 20), along with the standard basic therapy, the immunomodulator Galavit was prescribed to patients. Patients with MS received basic standard therapy according to the "Recommendations of experts of the All-Russian Scientific Society of Cardiology for the Diagnosis and Treatment of MS".[14,17] Lipid-lowering therapy was rosuvastatin 10 mg daily; patients were re-examined in dynamics after 3 months.

In patients of the second group, the basic therapy was supplemented with the Galavit immunomodulator, administered intramuscularly, at a dose of 100 mg daily for 5 days, then 100 mg every other day, for a course of 20 injections. Before administration, the drug is diluted in 2 ml of water for injection or 0.9% sodium chloride solution.

The collection of material was carried out in the cardiology department of the City Clinical Hospital No. 7 from 2015 to 2017, as well as at the outpatient appointment of doctors (endocrinologist, cardiologist, immunologist) "Immunogen-Test" **SDC** in 2018. The study is carried out within the framework of the project of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan "Development and implementation of algorithms for immunodiagnostics and immunotherapy in metabolic syndrome" for 2018-2020.

The study did not include patients with acute MI or previous MI in the previous 3 months; arterial hypertension of the III degree (blood pressure (BP)> 159/99 mm Hg); hypotension (BP<100/60 mm Hg);

atrial fibrillation and life-threatening heart rhythm and conduction disturbances; chronic heart failure III-IV FC (NYHA), systolic dysfunction (ejection fraction <45%); Resting heart rate before treatment <60 beats per minute; chronic obstructive pulmonary disease; heart defects; renal and hepatic failure (creatinine level is 1.5 times higher than normal values, total bilirubin level is 1.5 times higher than normal values); dysfunction of the thyroid gland; type 1 and type 2 diabetes mellitus requiring insulin treatment; oncological diseases, as well as patients who have been taking lipid-lowering drugs for a long time before admission; patients with acute or exacerbation of chronic infectious diseases for at least 1 month after the onset of clinical and laboratory remission.

MS criteria were established in accordance with the recommendations of the All-Russian Scientific Society of Cardiology (2009) and the International Diabetic Foundation (IDF, 2005): central obesity: waist circumference ≥94 cm in men and ≥80 cm in women in combination with any two of the following 4 factors:
- Triglycerides (TG)> 1.7 mmol / l (65.73 mg / dl);
- Lowering high-density lipoprotein cholesterol (HDL-C) <1.0 mmol / L (38.67 mg / dL) in men and <1.3 mmol / L (50.26 mg / dL) in women,

- BP≥130/85 mm Hg;
- Fasting plasma glucose> 5.6 mmol / l.

The study of the state of the immune system was carried out by studying the phenotypic characteristics of immunocompetent cells in peripheral blood. At the same time, the relative and absolute content of the main populations and subpopulations of lymphocytes was determined: total T-lymphocytes (CD3 +); natural killer cells NKC (CD16 +), subpopulations of T-helper lymphocytes (CD4 +) and T-suppressors (CD8 +), B-lymphocytes (CD20 +) were assessed by immunophenotyping of CD antigens using the corresponding monoclonal antibodies (Sorbent LLC, Moscow) indirect immunoluminescent method. The immunoregulatory index (IRI) -CD4 + / CD8 + was calculated.

RESULTS AND ITS DISCUSSION

We carried out a comparative analysis of the effectiveness of standard therapy and its combination with Galavit in relation to the subpopulation composition of lymphocytes (Table 1)

Table 1: Immunological characteristics of patients against the background of the use of the immunotropic drug Galavit, (M ± m).

Parameters	The group of practically healthy individuals(n = 36)	The group of individualsbefore therapy (n = 37)	The group of individualsafter standard therapy (n = 17)	The group of individuals after standard therapy + Galavit (n = 20)
Leukocytes, (in 1 μl)	6100±128,0	7265,8±113,5[@@]	5450,2±194,5^^	5900,2±154**
Lymphocytes,%	32,8±0,92	25,4±0,82[@@]	26,2±0,90	29,2±1,2*
CD3+,%	59,5±1,32	38,62±1,33[@]	43,21±1,40^	48,22±1,04**
CD4+,%	34,8±1,25	23,80±1,48[@@]	27,80±1,25^	31,80±1,5**
CD8+,%	18,6±0,65	32,50±2,05[@@]	27,30±1,68	22,30±1,14**
IRI	1,5±0,05	0,89±0,02[@@]	1,13±0,12	1,35±0,07**
CD16+,%	18,6±1,04	24,5±1,09[@@]	22,4±1,25	21,3±1,10*
CD20+,%	19,8±0,7	22,14±1,22[@@]	21,4±1,2	20,1±0,83

Note: * $p<0.05$, ** $p<0.001$ - reliability when comparing the combination therapy group before and in the dynamics of treatment

^ $p<0.05$ ^^ $p<0.001$- reliability when comparing the standard therapy group before and in the dynamics of treatment @ $p<0.01$, @@ $p<0.01$ - reliability when comparing the group before treatment with practically healthy individuals

Comparative analysis of the initial indicators of the immune status of patients with MS (37 patients) noted significantly increased levels of leukocytes by 1.2 times (p <0.001), CD8 + by 1.7 times (p <0.001), CD16 + by 1.3 times (p < 0.001), CD20 + by 1.1 times (p <0.001) in relation to practically healthy individuals. There was also a significant decrease in the% level of lymphocytes by 1.3 times (p <0.001), CD3 + by 1.5 times (p <0.01), CD4 + by 1.5 times (p <0.001), respectively, IRI by 1, 7 times (p <0.001) for them. According to some authors, the development of MS is associated with dysfunction of both humoral and cellular immunity. These disorders are caused by the synthesis and secretion of adipokines into the systemic circulation by adipose tissue, which in turn produce a large number of inflammatory mediators.[10,98,116]

As can be seen from the table, as a result of the therapy received, the average content of leukocytes in the peripheral blood significantly decreased relative to the initial level by 1.3 times (p <0.001) in the first group and 1.2 times (p <0.001) in the second group. It is known that the degree of surface expression of CD3 + receptors on the T-lymphocyte membrane reflects its transmissive function and allows one to identify the total number of T-lymphocytes [27]. Analysis of the immunophenotype of T-lymphocytes revealed a significant increase in the expression of CD3 + on T-lymphocytes by 1.2 times (p

<0.05) in the first group and 1.3 times (p <0.001) in the second group after the treatment in relation to theits initial values before treatment. As noted above, in patients with MS, there was a significant decrease in the expression of CD4 + on T-lymphocytes compared to the values of practically healthy individuals (p <0.001), against the background of the therapy in patients of the first group, their absolute value significantly increased by 1.2 times (p <0.05), and in the second group by 1.3 times (p <0.001).

Analysis of the CD8 + content on T-cytotoxic lymphocytes in MS patients during combination therapy with Galavit revealed a significant 1.5-fold (p <0.001) decrease in the increased (initial) relative content of CD8 + T-cytotoxic lymphocytes. The immunoregulatory index (IRI), which shows the ratio of the number of CD4 + T-helpers / inducers to the number of CD8 + T-lymphocytes, is of essential importance in inflammatory processes. Suppression of CD4 + T-helpers / inducers against the background of an increase in the number of CD8 + T-lymphocytes leads to a decrease in IRI in the group of patients with MS. In the second group, after treatment, there was a significant increase in IRI by 1.5 times (p <0.001), which indicates the clinical efficacy of Galavit.

Further, natural killer cells (NKC) were studied, which are the third population of lymphocytes that provide maintenance of genetic homeostasis and which phenotypically and functionally differ significantly from T- and B-lymphocytes. NKCs belong to the category of the main effectors of natural or innate immunity, which are capable of lyse target cells or carry out antibody-dependent cellular cytotoxicity. [61,107]. Analysis of the NKC subpopulation by membrane immunophenotype - CD16 revealed a significant decrease of 1.2 times (p <0.05) in the increased relative number of CD16 + NKC in the group of combined therapy with Galavit.

In connection with the above, during the treatment of combined therapy with Galovit, there was a significant increase in the absolute number of T-lymphocytes by 1.1 times (p <0.05), an increase in CD3 + expression on T-lymphocytes by 1.3 times (p <0.001), an increase in the expression of CD4 + on T-lymphocytes by 1.3 times (p <0.001), hence an increase in IRI by 1.5 times (p <0.001), a decrease by 1.2 times (p <0.05) in the relative number of CD16 + NKC. Consequently, the inclusion of the immunomodulatory drug Galavit in the standard treatment helps to reduce the systemic inflammatory potential, improves the parameters of cellular and humoral immunity, increases IRI, which is manifested by a clinical improvement in the condition and quality of life of patients with MS.

CONCLUSIONS
1. Against the background of treatment with combination therapy with Galavit, there was an increase in the absolute number of T-lymphocytes by 1.1 times (p <0.05), an increase in CD3 + by 1.3 times (p <0.001), an increase in CD4 + by 1.3 times (p <0.001), increase in IRI by 1.5 times (p <0.001) and decrease in CD16 + by 1.2 times (p <0.05).
2. The inclusion of the immunomodulatory drug Galavit in the standard treatment helps to reduce the systemic inflammatory potential, improves the parameters of cellular and humoral immunity, increases IRI, which is manifested by a clinical improvement in the condition and quality of life of patients with MS.

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