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## THE EVALUATION OF APPROACHES TO THE TREATMENT OF MYASTHENIA GRAVIS

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**Ключові слова:** міастенія, тип лікування, симптоматичне лікування, базове лікування, імуномодулююче лікування, виживаність, ефективність лікування

**Ключевые слова:** миастения, тип лечения, симптоматическое лечение, базовое лечение, иммуномодулирующее лечение, выживаемость, эффективность лечения

**Abstract.** The evaluation of approaches to the treatment of myasthenia gravis. Kalbus O.I., Shastun N.P., Makarov S.O., Bukreyeva Yu.V., Somilo O.V. Myasthenia gravis is a relatively rare autoimmune disease with an undetermined aetiology which affects neuromuscular junctions. Currently, the following approaches to the treatment of myasthenia gravis are mainly distinguished: symptomatic treatment with anticholinesterase inhibitors (AChEIs), immunomodulatory therapy ("basic" therapy) with glucocorticoids, cytostatics, monoclonal antibodies; surgical treatment — thymectomy; short-term treatment with plasmapheresis and intravenous administration of immunoglobulin. The efficiency of treatment approaches to myasthenia gravis in Ukraine remains insufficiently studied. The purpose of this work is to analyse the therapeutic approaches in patients with myasthenia gravis depending on the clinical form and severity of the disease. Between 2014 and 2017, 182 patients with myasthenia gravis have been examined, out of which 147 (80.8%) were the patients with the generalized form of the disease and 35 (19.2%) — with its ocular form. The clinical neurological examination included the collection of complaints, an anamnesis of disease and life as well as a neurological examination. In all the patients, the level of antibodies to acetylcholine receptors (AChR) and to muscle-specific tyrosine kinase (MuSK) has been measured, in terms of quantity as well, using the enzyme-linked immunosorbent assay (ELISA), and the presence of antibodies to titin and SOX1 has also been detected by means of indirect immunofluorescence. Of the total sample, less than a third (28.0%) of the patients examined received basic therapy; among them, there were no patients with the ocular form and only 34.7% — with the generalized form ( $p<0.001$ ). Basic therapy is found more often among the patients with class II myasthenia gravis (51.9%), with a statistically significant ( $p<0.001$ ) higher share of the patients receiving such a therapy than in classes III and IV (26.6% and 22.6% respectively). The structure of therapy in patients with classes III and IV has not shown any statistically significant difference ( $p=0.658$ ), with symptomatic treatment being the predominant type of therapy. Undergoing basic therapy reduces the chances of a severe clinical course of myasthenia gravis (the QMG score of 17 and higher) —  $OR=0.52$  (95.0% CI 0.14-0.90),  $p=0.032$ ; fatal cases of the disease —  $OR=0.36$  (95.0% CI 0.02-0.70),  $p=0.049$ . When basic therapy is used, the survival rate of the patients (Figure 2) is 42.0 years on average (95% CI 42.0-42.7) which is considerably higher ( $p=0.021$ ) compared to that of the patients receiving symptomatic treatment only — 33.0 years (95% CI 30.9-36.7). Immunomodulatory therapy was prescribed for only 28% of the patients in the total sample, for none of the patients with the ocular form of myasthenia gravis, and for 34.7% of the patients with the generalized myasthenia gravis. The prescription of immunomodulatory therapy reduces relative risks of a severe clinical course of myasthenia gravis —  $OR=0.52$  (95.0% CI 0.14-0.90),  $p=0.032$ . The prescription of immunomodulatory therapy decreases the probability of a fatal outcome of the disease —  $OR=0.36$  (95.0% CI 0.02-0.70),  $p=0.049$ . With the use of immunomodulatory therapy, the patient survival rate rises considerably reaching an average of 42.0 years (95% CI 42.0-42.7), which is much higher compared to that in the group of the patients receiving symptomatic treatment only — 33.0 years (95% CI 30.9-36.7),  $p=0.021$ .

**Реферат. Оцінка лікувальних підходів при міастенії. Кальбус О.І., Шастун Н.П., Макаров С.О., Букресєва Ю.В., Соміло О.В.** Міастенія – відносно рідке автоімунне захворювання з невизначеною етіологією, що характеризується ураженням нервово-м'язових синапсів. На цей час виділяють такі основні напрямки лікування міастенії: симптоматичне лікування - антихолінестеразні препарати (АХЕП); імуномодулююче лікування («базове» лікування) – глюкокортикоїди, цитостатики, моноклональні антитіла; хірургічне лікування – тимектомія; короткострокове лікування – плазмаферез, імуноглобулін внутрішньовенно. Оцінка ефективності лікувальних підходів при міастенії в Україні до цього часу залишається недостатньою. Метою цієї роботи був аналіз лікувальних підходів у хворих на міастенію залежно від клінічної форми та тяжкості захворювання. З 2014 по 2017 рік було обстежено 182 хворих на міастенію, з них 147 (80,8%) пацієнтів з генералізованою формою захворювання, 35 (19,2%) – з очною. Клініко-неврологічне обстеження включало збір скарг, анамнезу захворювання та життя, неврологічне обстеження. Усім хворим визначали рівень антитіл до рецепторів ацетилхоліну (AChR) та м'язово-специфічної тирозин-кінази (MuSK) методом імуноферментного аналізу (ELISA), в т.ч. кількісно, а також визначали наявність антитіл до титину та SOX1 методом непрямой імунофлюоресценції. Із загальної вибірки менше третини (28,0%) обстежених пацієнтів приймали базове лікування, серед них жоден пацієнт з очною формою захворювання та лише 34,7% - з генералізованою ( $p < 0,001$ ). Базове лікування більшою мірою було представлено серед хворих з II класом міастенії (51,9%), що статистично значуще перевищувало ( $p < 0,001$ ) частку таких хворих у III та IV класах (26,6% та 22,6% відповідно). Структура лікування у хворих III-го та IV-го класів статистично значуще не відрізнялася ( $p = 0,658$ ) і переважаючим типом лікування була симптоматична терапія. Прийом базової терапії знижує шанси тяжкого перебігу міастенії (QMG від 17 балів та вище) – ВШ=0,52 (95,0% ДІ 0,14-0,90),  $p = 0,032$ ; летальних випадків захворювання – ВШ=0,36 (95,0% ДІ 0,02-0,70),  $p = 0,049$ . При використанні базової терапії виживаність пацієнтів становить у середньому 42,0 роки (95% ДІ 42,0-42,7), що суттєво вище ( $p = 0,021$ ) порівняно з пацієнтами з використанням виключно симптоматичного лікування – 33,0 роки (95% ДІ 30,9-36,7). Імуномодулююче лікування було призначено лише 28% хворих із загальної вибірки, жодному пацієнту з очною формою міастенії та 34,7% хворих з генералізованою міастенією. Призначення імуномодулюючого лікування знижує відносні шанси тяжкого перебігу міастенії (ВШ=0,52 (95,0% ДІ 0,14-0,90),  $p = 0,032$ ). Призначення імуномодулюючого лікування знижує шанси летальних випадків захворювання (ВШ=0,36 (95,0% ДІ 0,02-0,70),  $p = 0,049$ ). При використанні імуномодулюючої терапії виживаність пацієнтів значно підвищується та становить у середньому 42,0 роки (95% ДІ 42,0-42,7), що суттєво вище порівняно з групою пацієнтів, які отримували виключно симптоматичне лікування – 33,0 роки (95% ДІ 30,9-36,7),  $p = 0,021$ .

Myasthenia gravis is a relatively infrequent autoimmune disease, which nevertheless leads to significant economic costs and social losses. It is associated with the production of autoantibodies to acetylcholine receptors (AChR) or to muscle-specific tyrosine kinase (MuSK). Particular role in its development is attributed to titin antibodies. Myasthenia gravis affects post-synaptic terminal of neuromuscular junctions, however the aetiology of this disease is still undetermined [1-4, 10].

Initially, myasthenia gravis presents with fatigue and extraocular muscle weakness at early stages, but at a later stage it advances into the generalized form, while these symptoms progress to pathological fatigue and weakness of limb and/or bulbar muscles [3, 10].

The incidence and prevalence of myasthenia gravis is higher in more economically developed countries. Accordingly, in the United States the incidence of myasthenia gravis reaches 200 cases per 1 million population a year, whereas it varies between other countries and populations, ranging from 17 to 104 cases per 1 million people a year. Despite significant advancements in diagnostics, treatment approaches, and improved overall prognosis of the disease since the beginning of the millennia, the occurrence of the disease has grown largely among the elderly (over 60 years of age) [5-9].

The classification of myasthenia proposed by MGFA (Myasthenia Gravis Foundation of America) is used in most countries around the world. It states that the disease can be divided into 5 classes: class I – ocular form; classes II-IV – generalized form: mild, moderate, and severe respectively; class V – generalized, with patients classified under this category that require intubation and/or mechanical ventilation. Each of the classes II-IV is divided into 2 subclasses: A – with predominant weakness and pathological fatigue of limb muscles; B – with predominant weakness and pathological fatigue of bulbar and/or orofacial muscles. Notwithstanding the ease of use and accessibility of this classification, it does not, however, at all times take into account the individual manifestations of certain symptoms of each particular patient [3, 10, 11].

Currently, the proposed treatment methods of myasthenia gravis are as follows: symptomatic treatment with anticholinesterase inhibitors (AChEIs), immunotherapy (“basic” therapy) with glucocorticoids, cytostatics, monoclonal antibodies; thymectomy (mostly effective in the first 2 years following the onset of primary symptoms); short-term treatment with plasmapheresis and/or intravenous immunoglobulin (in myasthenic crises cases or worsening of symptoms) [4, 10].

The primary goal of therapy is twofold: to achieve complete stable remission (without the use of pharmacological treatment) or to reach pharmacological remission (a patient does not need to take AChEIs). To accomplish sustained pharmacological remission, in most cases, a combination of therapeutic treatments is used. For example, immunotherapy together with symptomatic treatment is generally recommended [3, 10].

Nonetheless, decompensation and development of complications are commonly seen in the treated myasthenia gravis patients in Ukraine. This can be attributed to the fact that the preferred treatment in many instances is symptomatic only, which makes sustained stabilization of the patient's condition impossible.

The efficiency of treatment approaches to myasthenia gravis in Ukraine remains insufficiently studied.

The purpose of this work is to analyse the therapeutic approaches in patients with myasthenia gravis depending on the clinical form and severity of the disease.

#### MATERIALS AND METHODS OF RESEARCH

Between 2014 and 2017, 182 patients with myasthenia gravis were included into the study, out of which 147 (80.8%) were the patients with the generalized form of the disease and 35 (19.2%) – with its ocular form.

The clinical neurological examination included the collection of complaints, an anamnesis of disease and life as well as a neurological examination. Besides, the first symptoms of the disease, the period between the first symptoms and the diagnosis has been evaluated. To determine the clinical form of myasthenia gravis, the MGFA classification has been applied. For the quantitative assessment of myasthenia gravis manifestations, the QMG scale (Qualitative Myasthenia Gravis Scale) has been used. The type of therapy for each individual patient has been evaluated separately by carrying out a statistical analysis of the following types of therapy: symptomatic (with AChEIs), basic (options of a combination of prednisolone and/or cytostatics with/without AChEIs), and the absence of therapy.

In all the patients, the level of antibodies to acetylcholine receptors (AChR) and to muscle-specific tyrosine kinase (MuSK) has been measured, using the enzyme-linked immunosorbent assay (ELISA), and the presence of antibodies to titin and SOX1 has also been detected by means of indirect immunofluorescence. The above-mentioned tests were carried out using the facilities of the clinical diagnostic laboratory of the “Dnipropetrovsk Regio-

nal Clinical Hospital named after I.I. Mechnikov” Municipal Institution.

During mathematical processing, the nonparametric statistical methods have been used due to the deviation of quantitative data values from a normal distribution (the Shapiro-Wilk test). The mean values are represented as a median (Mdn) and an interquartile range (25%; 75%). Computer-aided statistical processing of the research results has been performed by means of the following software products: Microsoft Excel (Microsoft Office 2016 Professional Plus, Open License 67528927) and STATISTICA 6.1 (StatSoft Inc., serial No. AGAR909E415822FA). When testing statistical hypotheses, the threshold value for the significance level has been set at  $p \leq 0.05$ .

The research participants were recruited into the study on the basis of their informed consent in accordance with international standards of medical ethics.

#### RESULTS AND DISCUSSION

Among the examined patients, women prevailed – 128 (70.3%), the number of men was 54 (29.7%); the female to male ratio was 2.37:1. Among the patients with the generalized form of the disease, there was a statistically significant larger proportion of males compared to those with the ocular form ( $p=0.027$ ). However, no statistically significant differences between the disease classes and subclasses ( $p>0.05$ ) in the total sample breakdown by gender have been found (Tab. 1).

At the time of the survey, all the patients ranged in age from 18 to 83 years. The median age of the examined patients was 52.0 years with an interquartile range (34.0; 65.0). The data on the age distribution by the disease forms, classes, and subclasses of myasthenia gravis within the groups and in total could not be modelled using the normal (Gaussian) distribution ( $p<0.05$  according to the Shapiro-Wilks criterion).

The segmentation of the patients by gender, age, and results of the immunological examination is shown in Table 1.

In terms of the structure of therapeutic treatment which included, as mentioned above, symptomatic treatment (AChEIs in isolation), basic therapy (options of a combination of prednisolone and/or cytostatics with/without AChEIs), and the absence of therapy, the difference between the patients with one or another form of myasthenia gravis was statistically significant ( $p<0.001$ ) (Fig. 1).

Of the total sample, less than a third (28.0%) of the patients examined received basic therapy; among them, there were no patients with the ocular form and only 34.7% – with the generalized form ( $p<0.001$ ).

Table 1

**Distribution of the patients by gender, immunologic type, and myasthenia gravis class (according to MGFA)**

Characteristics	Total sample	Ocular form Class I	Generalized form										p*
			Total	II-A	II-B	Class II	III-A	III-B	Class III	IV-A	IV-B	Class IV	
Total number, n (%)	182 (100)	35 (19.2)	147 (80.8)	37 (20.3)	15 (8.2)	52 (28.6)	35 (19.2)	29 (15.9)	64 (35.2)	14 (7.7)	17 (9.3)	31 (17.0)	-

Gender, n (%)

Females	128 (70.3)	30 (85.7)	98 (66.7)	26 (70.3)	10 (66.7)	36 (69.2)	22 (62.9)	19 (65.5)	41 (64.1)	9 (64.3)	12 (70.6)	21 (67.7)	p <sub>1</sub> =0.027 p <sub>2</sub> =0.151 p <sub>3</sub> =0.473
Males	54 (29.7)	5 (14.3)	49 (33.3)	11 (29.7)	5 (33.3)	16 (30.8)	13 (37.1)	10 (34.5)	23 (35.9)	5 (35.7)	5 (29.4)	10 (32.3)	

Detected antibodies, n (%)

AchR-AB	124 (68.1)	16 (45.7)	108 (73.5)	27 (73.0)	8 (53.3)	35 (67.3)	27 (77.1)	20 (69.0)	47 (73.4)	13 (92.9)	13 (76.5)	26 (83.9)	p <sub>1</sub> =0.002 p <sub>2</sub> =0.006 p <sub>3</sub> =0.015
MuSK-AB	16 (8.8)	0 (0)	16 (10.9)	2 (5.4)	4 (26.7)	6 (11.5)	0 (0)	7 (24.1)	7 (10.9)	0 (0)	3 (17.7)	3 (9.7)	p <sub>1</sub> =0.087 p <sub>2</sub> =0.235 p <sub>3</sub> <0.001
TITIN-AB	53 (29.1)	0 (0)	53 (36.1)	17 (46.0)	5 (33.3)	22 (42.3)	10 (28.6)	10 (34.5)	20 (31.3)	7 (50.0)	4 (23.5)	11 (35.5)	p <sub>1</sub> <0.001 p <sub>2</sub> =0.002 p <sub>3</sub> =0.001
SOX1-AB	10 (5.5)	0 (0)	10 (6.8)	2 (5.4)	0 (0)	2 (3.9)	1 (2.9)	5 (17.2)	6 (9.4)	1 (7.1)	1 (5.9)	2 (6.5)	p <sub>1</sub> =0.240 p <sub>2</sub> =0.239 p <sub>3</sub> =0.084

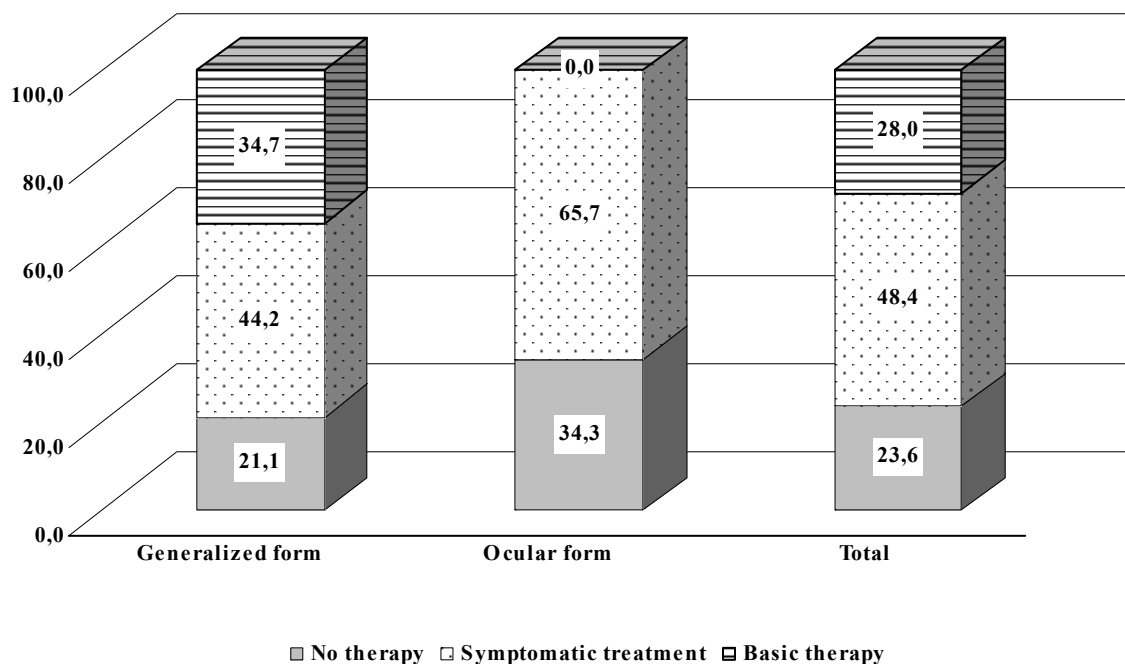
The average level of antibody titer among the patients in whom the relevant antibodies have been detected, Mdn (25%, 75%)

AchR-AB	4.05 (1.55; 6.55)	0.8 (0.6; 1.2)	4.8 (2.4; 7.05)	1.8 (0.9; 2.4)	2.2 (1.05; 3.3)	1.8 (0.9; 2.5)	4.8 (3.5; 8.1)	5.55 (4.45; 6.5)	5.4 (3.9; 6.6)	7.1 (5.4; 9.1)	9.7 (6.9; 10.2)	7.6 (6.1; 9.8)	p <sub>1</sub> <0.001 p <sub>2</sub> <0.001 p <sub>3</sub> <0.001
MuSK-AB	6.0 (1.45; 6.95)	-	6.0 (1.45; 6.95)	1.45 (1.3; 1.6)	1.05 (0.85; 1.65)	1.25 (0.9; 1.6)	-	6.2 (5.9; 6.7)	6.2 (5.9; 6.7)	-	10.8 (9.9; 11.2)	10.8 (9.9; 11.2)	- - p <sub>3</sub> <0.001

Notes: \* – differences between the groups according to the  $\chi^2$  criterion, including the Yates's correction for the index values closest to 0: p<sub>1</sub> – between the forms of myasthenia gravis; p<sub>2</sub> – between the classes of myasthenia gravis; p<sub>3</sub> – between class I of myasthenia gravis and subclasses of classes II-IV of the generalized form of myasthenia gravis.

After analysing the distribution of the type of therapy by the form of myasthenia gravis, the following data have been obtained. Basic therapy is found more often among the patients with class II myasthenia gravis (51.9%), with a statistically significant (p<0.001) higher share of the patients

receiving such a therapy than in classes III and IV (26.6% and 22.6% respectively). The structure of therapy in patients with classes III and IV has not shown any statistically significant difference (p=0.658), with symptomatic treatment being the predominant type of therapy (Tab. 2).



Note. Differences between the groups —  $p < 0.001$  according to the  $\chi^2$  criterion

**Fig. 1. Distribution of the examined patients with different forms of myasthenia gravis by the type of therapy (%)**

From this, a mediated inference that the use of basic therapy leads to reduced manifestations of myasthenia gravis and lowering its class can be drawn. A smaller percentage of the patients with classes III and IV myasthenia gravis undergoing basic therapy indicates the inadequacy of prescribing this therapy for such patients based on clinical manifestations of the disease.

Overall, the findings suggest that the patients with generalized myasthenia gravis among the examined patients are not sufficiently covered by basic therapy, despite its relatively low cost and availability in Ukraine. This may be due to the lack of awareness among some neurologists of the modern principles of myasthenia gravis treatment.

Table 2

**Distribution of the examined patients with myasthenia gravis by the type of therapy according to the disease class (%)**

Therapy	Class I n=35		Class II n=52		Class III n=64		Class IV n=31	
	n	%	n	%	n	%	n	%
No therapy	12	34.3	12	23.1	14	21.9	5	16.1
Symptomatic treatment	23	65.7	13	25.0	33	51.6	19	61.3
Basic therapy	0	0	27	51.9	17	26.6	7	22.6

Note: Differences between the classes —  $p < 0.001$  according to the  $\chi^2$  criterion



When making clinical comparisons, we come to a conclusion that the use of basic therapy is associated with the generalized form of the disease (the phi-coefficient  $\phi=0.30$ ), a higher class ( $\phi=0.40$ ) and subclass ( $\phi=0.44$ ) of myasthenia gravis.

As a result of the rank correlation analysis, reliable ( $p<0.05$ ) correlations between the type of therapy (basic, symptomatic, no therapy) and a thymoma (Spearman's correlation coefficient  $\rho=0.20$ ;  $p=0.006$ ), thymectomy ( $\rho=0.22$ ;  $p=0.002$ ), the intensity of symptoms — the number of the first symptoms ( $\rho=-0.16$ ;  $p=0.026$ ), the presence ( $\rho=0.17$ ;  $p=0.019$ ) and the titer of antibodies to AchR ( $\rho=0.20$ ;  $p=0.006$ ), the presence ( $\rho=-0.15$ ;  $p=0.039$ )

and the titer of antibodies to MuSK ( $\rho=-0.15$ ;  $p=0.039$ ), the presence of antibodies to titin ( $\rho=0.32$ ;  $p<0.001$ ) have been found.

Undergoing basic therapy reduces the chances of a severe clinical course of myasthenia gravis (the QMG score of 17 and higher) – OR=0.52 (95.0% CI 0.14-0.90),  $p=0.032$ ; fatal cases of the disease – OR=0.36 (95.0% CI 0.02-0.70),  $p=0.049$ .

When basic therapy is used, the survival rate of the patients (Fig. 2) is 42.0 years on average (95% CI 42.0-42.7) which is considerably higher ( $p=0.021$ ) compared to that of the patients receiving symptomatic treatment only – 33.0 years (95% CI 30.9-36.7).

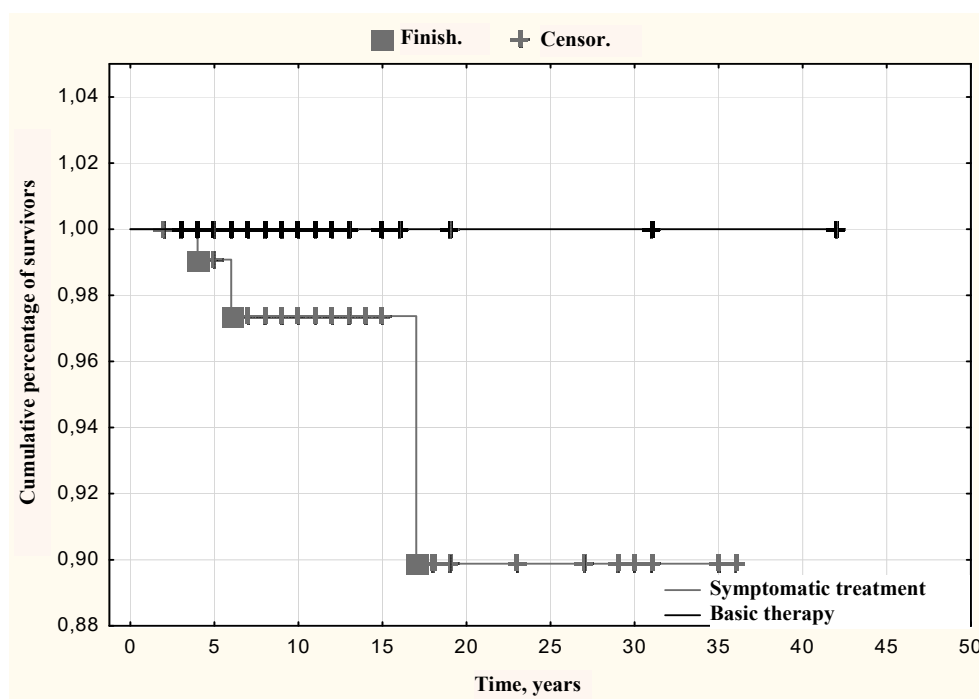


Fig. 2. Cumulative survival rate of the patients with myasthenia gravis by the type of therapy using the Kaplan-Meier method

### CONCLUSIONS

1. Immunomodulatory therapy was prescribed for only 28% of the patients in the total sample, for none of the patients with the ocular form of myasthenia gravis, and for 34.7% of the patients with the generalized myasthenia gravis.

2. The prescription of immunomodulatory therapy reduces relative risks of a severe clinical course of myasthenia gravis – OR=0.52 (95.0% CI 0.14-0.90),  $p=0.032$ .

3. The prescription of immunomodulatory therapy decreases the probability of a fatal outcome of the disease – OR=0.36 (95.0% CI 0.02-0.70),  $p=0.049$ .

4. With the use of immunomodulatory therapy, the patients survival rate rises considerably reaching an average of 42.0 years (95% CI 42.0-42.7), which is much higher compared to that in the group of the patients receiving symptomatic treatment only — 33.0 years (95% CI 30.9-36.7),  $p=0.021$ .

Conflict of interests.

The authors have no conflict of interests.

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