Neuroscience and Behavioral Physiology, Vol. 41, No. 4, May, 2011

Potential of Preventive Treatment of Alzheimer's Disease: Results of a Three-Year Prospective Open Comparative Trial of the Efficacy and Safety of Courses of Treatment with Cerebrolysin and Cavinton in Elderly Patients with Mild Cognitive Impairment Syndrome

S. I. Gavrilova,[1] I. V. Kolykhalov,[1] Ya. B. Fedorova,[1] N. D. Selezneva,[1] Ya. B. Kalyn,[1] I. F. Roshchina,[1] M. M. Odinak,[2] A. Yu. Emelin,[2] A. V. Kashin,[2] A. V. Gustov,[3] E. A. Antipenko,[3] Yu. A. Korshunova,[3] T. A. Davydova,[3] and G. Messler[4]

Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 110, No. 1, pp. 62–69, January, 2010.

Studies were performed in three Russian centers (Moscow, St. Petersburg, Nizhnii Novgorod). The cohort consisted of 110 patients whose mental state corresponded to the concept of "mild cognitive impairment" (MCI). Patient status was assessed using widely accepted scales (MMSE, GDS, CDR, etc.) and a battery of neuropsychological tests. ApoE genotypes were also identified. Patients were divided into two comparable groups depending on treatment: 55 patients received cerebrolysin and 55 received Cavinton. The data provided evidence that treatment with cerebrolysin was more effective than treatment with Cavinton in terms of slowing the progression of cognitive deficit and delaying the time at which the patients qualified for the diagnosis of Alzheimer's disease. Cerebrolysin was more effective in patients with MCI and the ApoE4+ genotype, i.e., patients in the high risk group for Alzheimer's disease. Adverse events were rare in both groups.

KEY WORDS: mild cognitive impairment, Alzheimer's disease, preventive treatment, cerebrolysin, Cavinton.

Dementia due to Alzheimer's disease (AD) is among the major causes of invalidity in the elderly. Although this disease has been known for more than 100 years, major steps in studies of its neurobiological basis and attempts to find treatment methods have been actively pursued only during the last quarter of the last century. Studies of AD in the economically developed countries have now become a priority in the development of medical science and healthcare.

In 2007, according to data from the Alzheimer's Association, there were some 5.1 million patients with AD in the US, the number being expected to increase to 13 million by 2050 [13]. AD and other dementias in the elderly account for some 3.2 million hospitalizations per year. The overall (direct plus indirect) costs of AD in the US exceed 100 billion dollars annually [19].

The total costs of care for patients with dementia have increased rapidly over the last decade, because of the

[1] Department for the Study of Alzheimer's Disease and Associated Disorders, Scientific Center for Mental Health, Russian Academy of Medical Sciences, Moscow; e-mail: sigavrilova@yandex.ru.
[2] Department of Nervous Diseases, Military Medical Academy, St. Petersburg.
[3] Department of Neurology, Neurosurgery, and Psychiatry, Center for Higher Qualification and Professional Specialist Training, Nizhnii Novgorod State Medical Academy.
[4] Ebewe Neuro Pharma GmbH, Austria.

0097-0549/11/4104-0391

increased number of patients [17]. Data from the Delphi Consensus Study (2005) indicate that 24.3 million people throughout the world suffer from dementia, due in most cases to AD. Some 4.6 million new cases of dementia are recorded throughout the world every year, i.e., one new case of acquired mental deficit every seven seconds. The international expert group taking part in this study predicted that the number of cases of dementia would double every 20 years. The expectation is that by 2020 there will be 42.3 million people in the world with dementia, the number reaching 81.1 million by 2040 [17].

Official Russian statistics on the occurrence of AD are significantly lower (compared with world data). However, population epidemiological studies performed in the Center for the Study of Alzheimer's Disease, Russian Academy of Medical Sciences, have shown that 4.5% of elderly people in Moscow (aged 60 years and older, i.e., one in every 22 elderly people) have AD [8]. Extrapolation of population epidemiological data to Russian demographic measures in 2004[1] allowed the total number of patients with dementia in the Russian Federation to be modeled. Mathematical modeling showed that 1,851,432 people in the territories of the Russian Federation are afflicted with dementia [1].

The continuing aging of populations of both developed and developing countries and the lack of methods of treating AD result in a continually increasing burden on national healthcare systems in many states [26].

Current strategies for the treatment of AD, based on the use of acetylcholinesterase (AChE) inhibitors and NMDA receptor antagonists, yield only temporary and moderate therapeutic effects. There are no data supporting any prolonged and clear actions stabilizing or delaying the course of illness. However, developments in neuroscience are leading to ever increasing knowledge of the pathogenetic mechanisms of Alzheimer's-type neurodegeneration, which provides grounds for identifying possible targets for preventive therapeutic interventions at the earliest (preclinical) stages of disease.

Along with the development of antiamyloid strategies in the treatment of AD, increasing attention is being paid to methods based on the blockade of excessive phosphorylation of tau protein as a potential target for prophylactic and therapeutic treatments using neuroprotective and neurotrophic approaches, including the use of neurotrophins, neurotrophic factors, and stem cells. However, most of these methods are in the preclinical or early clinical trial stages.

No less important than the development of new strategies and new agents for the treatment of AD is identification of the targets for these treatments. It is well known that the first clinical signs of this disease take at least 10–15 years to become clear and that the diagnosis of AD is made no less than 20 years after the onset of the neurodegenerative process. However, identification of those members of the elderly population who are in the early stages of clinically "silent" course of disease is currently an unrealistic task (especially on the large scale) because of the lack of reliable and specific biological markers, with the exception of identifying carriers of genetic anomalies responsible for the very rare "familial" forms of the disease, which have a predominantly young (less than 65 years old) onset.

Decreases in memory are known to be an almost obligatory feature of ageing. Identification of people whose age-related memory deterioration will progress inexorably to the stage of dementia in a few years, i.e., elderly people with a high probability of being in the clinically "silent" stage of AD (or other dementias), among the overall elderly population was addressed by developing the concept of mild cognitive impairment (MCI) [15]. The typology of the syndrome has now been developed, with identification of amnestic (mono- and multifunctional) and non-amnestic types [22]. The first of these has a greater probability of progression to AD. Up to 80% of patients with amnestic-type MCI syndrome receive diagnoses of AD within six years and the mean annual progression to AD is 10–12% [21]. Data from the same authors show that the rate for people of the same age but without MCI syndrome is 1–2%.

Not only has MCI syndrome, i.e., the presence of mild signs of memory deterioration and/or cognitive impairments without data supporting a diagnosis of dementia and after exclusion of cerebral lesions or systemic diseases which could be responsible for the development of cognitive impairment, now been defined, but quite clear operational criteria for its diagnosis have been established [15]. Cohorts of elderly people with amnestic-type MCI syndrome have been identified as the target population for clinical trials of the efficacy of methods for the preventive treatment of AD.

One potential direction in the development of preventive therapeutic approaches slowing or preventing the clinical manifestations of AD in people in risk groups for this disease consists of the use of neurotrophins or therapeutic agents with neurotrophic properties.

Cerebrolysin reproduces the effects of nerve growth factor (NGF), as evidenced by a multitude of experimental studies performed in different countries using a variety of models of neuron damage and degeneration, including a model based on implantation of β-amyloid in the hippocampus of elderly rats [16, 23] and ApoE knockout mice [18]. More detailed analysis of studies addressing the neurotrophic and neuroprotective actions of cerebrolysin have been presented by Gavrilova et al. [4, 6] and Windisch et al. [27].

A group of American authors [14] recently showed that the neurotrophic effect of cerebrolysin may be due to the presence of active neurotrophic factor peptides. Their data indicated that cerebrolysin has the activities of ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF), and insulin-like factors 1 and 2 (IGF-1, IGF-2).

[1] Data from the Russian Statistical Yearbook (2004).

TABLE 1. Comparative Characteristics of Study Patient Groups

Parameter	Group 1	Group 2
Number of patients	55	55
men	14	15
women	41	40
Mean age, years	66.9±1.1	68.4±1.1
ApoE genotype:		
ApoE4(+)	26	25
ApoE4(-)	29	30
Mean total assessments on scales and tests, points		
MMSE	28.6±0.1*	28.2±0.1
Hachinski scale	1.8±0.1	1.8±0.1
Hamilton depression scale	5.5±0.5	5.5±0.5
Clinical dementia rating (CDR)	0.5	0.5
Global deterioration scale (GDS)	3	3
Clock drawing test	9.0±0.2	9.0±0.2
Frontal dysfunction battery	13.3±0.3	13.1±0.3
Wechsler scale subtests:		
sound associations	14.0±0.5	13.9±0.5
categorial associations	15.4±0.5	15.3±0.5
Boston naming test	47.8±0.8	47.9±0.6
Forward number naming	6.2±0.1	6.0±0.1
Reverse number naming	4.4±0.1	4.4±0.2
10-word remembering (immediate)	7.2±0.2	7.3±0.2
Delayed 10-word reproduction	7.5±0.3	7.7±0.3
Mattis dementia scale subtests:		
reciprocal coordination	2.7±0.1	2.9±0.1
graphomotor test	9.4±0.2	9.5±0.1
detection of similarity	7.3±0.2	7.1±0.2
memory	22.4±0.2	22.2±0.3

Note. * Significant differences between groups ($p < 0.05$).

A series of randomized clinical trials have demonstrated both the clinical efficacy of cerebrolysin (used as courses of 20 i.v. infusions of 20–30 ml in 100 ml of isotonic saline) and its safety in patients with AD at the mild and moderate dementia stages [2, 8, 25]. These studies also showed that the therapeutic effect of cerebrolysin persisted for 2–6 months from completion of treatment [12]. A comparative clinical trial of the long-term effects of cerebrolysin (four courses over 22 months) performed in Russia showed that cerebrolysin is not only an effective agent in terms of symptomatic treatment (efficacy comparable to that of Exelon), but also that is has clear positive modifying actions on the course of the Alzheimer's-type neurodegenerative process at the mild and moderate dementia stages [5].

Existing data provided grounds for suggesting that the use of long-term courses of cerebrolysin might help to prevent or delay the clinical manifestations of AD in patients with amnestic-type MCI syndrome, who constitute a risk group for the rapid development of AD.

The aim of the present work was to undertake an open comparative trial of the efficacy and safety of prolonged (three years) courses of cerebrolysin and Cavinton (two courses per year).

These agents are regarded as medications potentially able to delay or prevent the progression of amnestic-type MCI syndrome into clinically severe dementia.

MATERIALS AND METHODS

Studies were performed using a unified method and standard tools in three study centers: the Department for the Study of Alzheimer's Disease and Associated Disorders, Scientific Center for Mental Health, Russian Academy of Medical Sciences, Moscow, the Department of Nervous Diseases, Military Medical Academy, St. Petersburg, and the Department of Neurology, Neurosurgery, and Psychiatry, Nizhnii Novgorod State Medical Academy.

The study included 110 patients: 30 each in St. Petersburg and Nizhnii Novgorod and 50 in Moscow.

Comparable therapeutic groups were formed at each center using a single method; cohorts consisted of elderly patients meeting the inclusion and exclusion criteria. Patients were selected in accordance with the following main characteristics: gender, age (less than 65, greater than 65 years old), and ApoE4 (+/–) genotype.

Inclusion criteria were: women (postmenopausal) and men aged 55–85 years; mini mental state evaluation (MMSE) scores of more than 26 points; complaints of decreased memory confirmed by the informant (usually a family member), and objective signs of mild cognitive dysfunction (at least in tests for memory and those cognitive spheres which are usually affected in AD); signs of cognitive deficit corresponding to stage 3 on the Global Deterioration Scale (GDS) [24], and assessments of 0.5 on the Clinical Dementia Rating (CDR) scale [20]; non-qualification for a diagnosis of dementia; continuation of daily activities by the patient, though there could be mild degradation of complex and instrument-assessed types of daily and/or professional activity; assessments on the modified Hachinski scale of ≤4; provision of written informed consent by the patient.

Exclusion criteria were: diagnosis of dementia (DSM-IV, ICD-10); neurological disease (innate and/or acquired metabolic encephalopathy, toxic and iatrogenic encephalopathies, Parkinson's disease, multi-infarct dementia, stroke, epilepsy, infectious diseases, demyelinating and inherited degenerative diseases of the CNS); neoplastic and/or traumatic brain lesions; systemic diseases; mental illnesses; severe organic pathology; malignant extracerebral tumors; HIV infection; diabetes mellitus in the decompensation stage or other endocrine disorders; alcoholism and/or drug dependence; drug or other toxicity; assessments of more than 18 points on the Hamilton Depression Scale; systolic blood pressure >180 mmHg; diastolic blood pressure >95 mmHg; folic acid and/or vitamin B_{12} deficiency.

Observation of these features and criteria allowed cohorts which were almost identical in terms of central values to be obtained.

In accordance with the study aims, patients were divided into two therapeutic groups.

Group 1 consisted of 55 patients who received two courses of treatment with cerebrolysin each year for three years as 20 i.v. cerebrolysin infusions of 30 ml in 100 ml of physiological saline, each course lasting four weeks.

Group 2, of equal size (55 patients), consisted of patients who received two courses of Cavinton per year for three years, of 5 mg three times daily for four weeks.

The details of these groups are presented in Table 1.

Patients' cognitive functions were assessed using a variety of scales and tests (see Table 1).

Significant differences between mean overall points scores in group 1 and 2 were identified using nonparametric statistical methods, i.e., the Wilcoxon test (for sets with any distribution of values).

The study groups showed so significant differences in mean age, gender composition or distribution of patients in terms of ApoE4(+) and ApoE4(–) genotypes at the beginning of the study (see Table 1). The groups were essentially identical in terms of the initial severity of cognitive impairments. Although patients of group 1 had significantly better assessments on the MMSE (with a difference of 0.4 points), on all other tests and scales they not only showed no significant differences as compared with group 2, but were also essentially identical in terms of most of the parameters evaluated.

RESULTS AND DISCUSSION

Totals of 46 patients in group 1 and 42 in group 2 completed three-year treatment courses; nine and 13, respectively, terminated early for non-medical reasons.

Apart from analyzing the dynamics of test results, measures of transition from one clinical stage of cognitive inadequacy to another were assessed throughout the study period (assessments on the CDR scale [20]) in patients of both groups. In group 1, only two patients (3.6%) advanced to mild dementia due to AD by the end of the study (i.e., three years from the start). In group 2, seven of 55 patients (12.7%) progressed to mild dementia and were diagnosed with AD by the end of the study.

Thus, the frequency of diagnoses of AD over the three-year period from beginning of the study was 3.5 times lower in the group receiving cerebrolysin than in the group receiving Cavinton.

Analysis of the dynamics of group mean overall test assessments in patients of group 1 (cerebrolysin) demonstrated significant improvements in measures of cognitive functioning, starting from treatment year 2 and persisting to the end of the study, in terms of the following tests: sound and categorial associations on the Wechlser scale and on two subtests of the Mattis Dementia Scale, "similarity" and "memory." The Boston card sorting and naming test showed significant improvements, starting from the first year of the study; these positive changes were seen all the way to the end of the study. By termination, there were also significant improvements in the frontal lobe dysfunction test and the clock drawing test. Only the delayed ten-word reproduction test in patients of group 1 showed significant deterioration of the initial score. Initial values on the other seven cognitive tests either did not change or showed minor improvements or deterioration (only the "reciprocal coordination" test) by the end of the study (Table 2).

In patients of group 2, significant improvements by the end of the study were seen only for the "similarity" subtest of the Mattis dementia scale. The clock drawing test showed significant improvements by the end of study year 2. Significant deterioration in measures by the end of the study were seen in two cognitive tests: the "10-word remembering test" and the "reverse number naming test." Minor deterioration in assessment were seen on four tests by the end of the study: the MMSE, the "forward number naming test," the "delayed 10-word reproduction test," and the "memory" subscale of the Mattis dementia scale. At the same time, improvements in assessments (insignificant)

TABLE 2. Dynamics of Group Mean Total Assessments (points) on Cognitive Tests in Group 1 (cerebrolysin)

Cognitive tests and scales	Years			
	before treatment	1	2	3
MMSE	28.6±0.1	28.3±0.3	28.9±0.2	28.6±0.2
Clock drawing test	9.0±0.2	9.1±0.2	9.5±0.1	9.6±0.1*
Frontal dysfunction battery	13.3±0.3	13.5±0.3	13.7±0.2	13.7±0.2*
Wechsler scale subtests:				
sound associations	14.0±0.5	14.4±0.5	15.5±0.6*	15.9±0.5*
categorial associations	15.4±0.5	15.7±0.6	16.3±0.5*	16.8±0.4*
Boston naming test	47.8±0.8	48.8±0.8*	50.3±0.7*	50.5±0.6*
Forward number naming	6.3±0.1	6.3±0.1	6.3±0.1	6.3±0.1
Reverse number naming	4.4±0.1	4.4±0.1	4.6±0.1	4.6±0.1
10-word remembering (immediate)	7.2±0.2	7.4±0.2	7.5±0.2	7.5±0.2
Delayed 10-word reproduction	7.5±0.3	7.3±0.4	8.1±0.9	6.8±0.3*
Mattis dementia scale subtests:				
reciprocal coordination	2.7±0.1	2.7±0.1	2.8±0.1	2.8±0.1
graphomotor test	9.4±0.2	9.6±0.1	9.8±0.1	9.7±0.1*
detection of similarity	7.3±0.2	7.5±0.2	7.8±0.1*	7.8±0.1*
memory	22.4±0.2	22.2±0.4	22.9±0.3*	22.8±0.3*

Note. Here and in Table 3: * Significant differences between initial and post-treatment measures ($p < 0.05$).

TABLE 3. Dynamics of Group Mean Total Assessments (points) on Cognitive Tests in Group 2 (Cavinton)

Cognitive tests and scales	Years			
	before treatment	1	2	3
MMSE	28.2 ±0.1	28.1±0.2	28.2±0.3	27.9±0.3
Clock drawing test	9.0±0.2	9.1±0.2	9.4±0.2*	9.2±0.2
Frontal dysfunction battery	13.1±0.3	13.3±0.3	13.4±0.2	13.2±0.2
Wechsler scale subtests:				
sound associations	13.9±0.5	14.6±0.5	14.8±0.5	14.6±0.5
categorial associations	15.7±0.5	15.5±0.5	16.0±0.6	16.3±0.6
Boston naming test	47.9±0.6	48.0±0.6	48.8±0.7	48.2±0.8
Forward number naming	6.0±0.1	5.9±0.1	5.9±0.2	5.7±0.2
Reverse number naming	4.4±0.2	4.2±0.1	4.0±0.1*	3.9±0.1*
10-word remembering (immediate)	7.3±0.2	7.2±0.2	7.1±0.2	6.8±0.2*
Delayed 10-word reproduction	7.7±0.3	7.1±0.3	7.8±0.3	7.3±0.4
Mattis dementia scale subtests:				
reciprocal coordination	2.9±0.1	2.9±0.1	2.8±0.1	2.8±0.1
graphomotor test	9.5±0.1	9.7±0.1	9.5±0.1	9.6±0.1
detection of similarity	7.1±0.2	7.3±0.2	7.5±0.2	7.5±0.2*
memory	22.2±0.3	22.0±0.4	22.1±0.4	21.8±0.4

were seen on six other cognitive tests by the end of the study (Table 3).

Comparison of therapeutic effects, i.e., differences between initial and post-treatment measures of cognitive functioning, between groups treated with cerebrolysin and Cavinton showed that treatment efficacy measures in group 1 demonstrated significant improvements as compared with group 2 on three of the 14 cognitive tests and scales used (the Boston naming test, the "10-word remembering test," and the "reverse number naming test") (Fig. 1).

It should be noted that the dynamics of most (nine of 14) parameters demonstrated positive treatment effects in patients receiving cerebrolysin, as indicated by improvements in these cognitive measures from initial values, and a further two tests showed no negative dynamics. At the same time, patients of group 2 (treated with Cavinton) showed progressive deterioration of cognitive functioning over the same period of time on half (seven of 14 tests) of the parameters evaluated. Improvements in final assessments on the other seven tests were smaller as compared with the therapeutic effects in patients of group 1.

Therapeutic efficacy of preventive treatment with cerebrolysin and Cavinton in relation to ApoE4(+/–) genotype. In patients with the ApoE4(+) genotype and

TABLE 4. Numbers of Patients in Groups 1 and 2 with Different ApoE4 Genotypes Progressing to Diagnoses of Alzheimer's Disease

Genotype	Group 1 (n = 26)		Group 1 (n = 25)	
	abs.	%	abs.	%
ApoE 4(+)	2	7.7	5	20.0
ApoE 4(–)	0	0	2	6.7

TABLE 5. Frequencies of Treatment Side Effects in Patients of Groups 1 and 2

Adverse events	Number of patients, abs.	
	Group 1	Group 2
Acute respiratory virus infection (ARVI)	1	0
Acute respiratory disease (ARD)	1	2
Headache	1	0
Diarrhea	0	1
Exacerbation of chronic pancreatitis	1	0
Femoral neck fracture	1	0
Arthrosis of right hip joint	0	1
Ovarian tumor, extirpation of uterus	1	0
Prostate tumor	0	1
Breast tumor	0	1
Angina	0	1
Thrombophlebitis of right leg vein	1	0
Exacerbation of gastric ulcer	1	0
Total	8	7

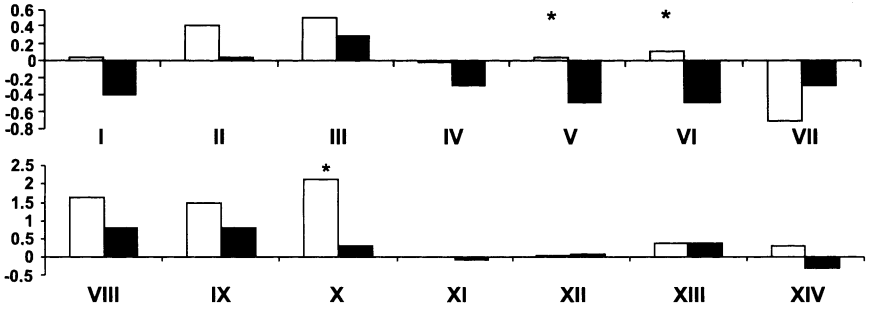

Fig. 1. Comparison of therapeutic effects in patients with MCI syndrome treated with cerebrolysin (group 1) and Cavinton (group 2). Here and in Fig. 2, therapeutic responses are compared in terms of the difference between the final and initial assessments of mean group total scores for cognitive tests. The first column in each pair shows group 1, the second group 2. The ordinate shows points. Roman numerals designate functions and tests: I) MMSE; II) frontal dysfunction battery; III) clock drawing test; IV) forward number naming; V) reverse number naming; VI) remembering 10 words; VII) delayed reproduction of 10 words; VIII) sound associations; IX) categorial associations; X) Boston test; XI) reciprocal coordination; XII) graphomotor test; XIII) similarity; XIV) memory. *Significant difference between groups ($p < 0.05$).

treated with cerebrolysin, progression of MCI syndrome to AD was 2.5 times less frequent than in patients with the same genotype but treated with Cavinton. Among patients with the ApoE4(–) genotype, only those treated with Cavinton progressed to dementia and were diagnosed with AD (Table 4).

Assessments of cognitive functions in patients with the ApoE4(+) genotype (Fig. 2) revealed significant differences in therapeutic effects in favor of cerebrolysin between groups on two tests: the "10-word remembering test" and the "Boston naming test, while overall positive effects, consisting of improvements in measures compared with initial values, were seen on the remaining nine cognitive tests, though significant intergroup differences were not seen.

Patients with the ApoE4(+) genotype treated with Cavinton showed no significant positive differences in treat-

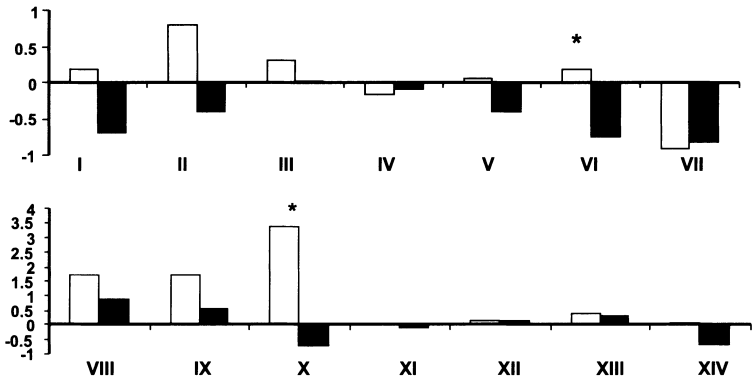

Fig. 2. Comparison of therapeutic effects in patients with the ApoE4(+) genotype receiving cerebrolysin (group 1) and Cavinton (group 2).

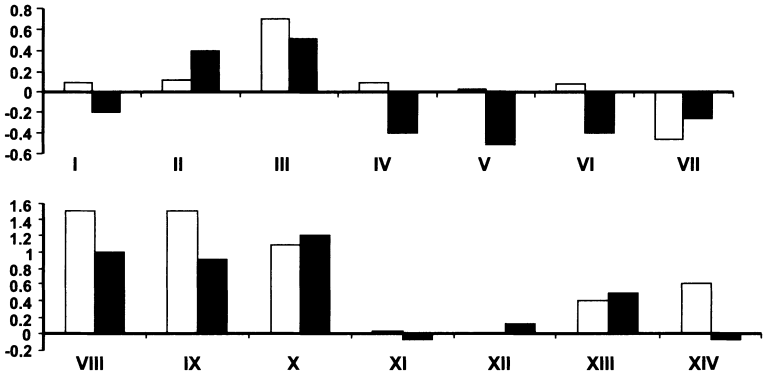

Fig. 3. Comparison of therapeutic effects in patients with the ApoE4(–) genotype receiving cerebrolysin (group 1) and Cavinton (group 2).

ment effects (on test scores) as compared with cerebrolysin, though four cognitive tests showed improvement by the end of treatment.

Thus, patients with MCI syndrome and the ApoE4(+) genotypes demonstrated significantly more marked therapeutic responses to cerebrolysin than to Cavinton; the latter produced no positive effects on most cognitive measures in this category of patients.

Group 1 patients (Fig. 3) with the ApoE4(–) genotype showed a significant difference in the treatment effect in favor of cerebrolysin as compared with group 2 patients only in terms of the dynamics of the "forward number naming test"; conversely, they showed a significant difference in favor of Cavinton on the "delayed 10-word reproduction test." Overall, 12 patients with the ApoE4(–) genotype given cerebrolysin and only seven given Cavinton showed positive treatment effects in cognitive tests.

Thus, intergroup differences in cognitive functioning test assessments in patients with the ApoE4(–) genotype were less marked than those in patients with the ApoE4(+) genotype. Overall, positive changes in cognitive functioning were seen more often in patients with the ApoE4(–) genotypes than in patients with the ApoE4(+) genotype during treatment with both cerebrolysin and Cavinton. However, more significant data on the relationship between the treatment effect and ApoE4 genotype require a larger number of observations of patients treated with cerebrolysin and Cavinton. Nonetheless, the high level of progression of MCI syndrome to dementia in patients with the ApoE4(+) genotype treated with Cavinton and the 2.5 times lower rate of this progression among those with the same genotype but treated with cerebrolysin is evidence that cerebrolysin may delay (or, perhaps, stop) the progression of cognitive deficit and the development of AD.

No significant differences were seen in the frequency and severity of treatment side effects with Cavinton and cerebrolysin (Table 5). Most side effects were mild or moderate. Serious side effects requiring hospitalization or termination of the study occurred in three patients of group 1 and two of group 2.

CONCLUSIONS

Comparative analysis of the efficacy of three-year courses of treatment with cerebrolysin and Cavinton, performed twice a year, in groups of elderly patients with MCI syndrome which were initially similar in terms of numbers, age, gender, and distributions of ApoE4(+) and ApoE4(–) genotypes, provided evidence of the undoubted advantages of treatment with cerebrolysin over Cavinton in delaying the progression of cognitive deficit and delaying or preventing its progression to the diagnostic category of AD.

A characteristic feature of the action of cerebrolysin was the fact that it had greater efficacy than Cavinton in patients with MCI syndrome and the genetic risk factor for AD – the ApoE4(+) genotype, i.e., elderly people in the risk group for AD.

The treatments used here were not significantly different in terms of the frequency and severity of side effects. The rarity of adverse events, including severe events, over three-year observation periods is evidence for the safety of the courses of treatment under comparison.

The results obtained here, evidencing the ability of cerebrolysin to slow or perhaps prevent the progression of cognitive deficit and the conversion of MCI to AD, allow prolonged courses of treatment with this medicinal agent to be recommended as preventive therapy in elderly people at increased risk of developing AD.

REFERENCES

1. Yu. B. Belousov, O. N. Mednikov, and E. S. Chikina, "Pharmacoeconomic aspects of the treatment of dementia in the Russian Federation," *Rus. Med. Zh.*, **13**, No. 20, 1354 (2005).
2. S. I. Gavrilova, I. V. Kolykhalov, N. D. Selezneva, et al., "A double-blind placebo-controlled trial of the effects of cerebrolysin on the efficacy and tolerance of subsequent cholinergic therapy in patients with Alzheimer's disease," *Sots. Klin. Psikhiat.*, **2**, 41–46 (2000).
3. S. I. Gavrilova and Ya. B. Kalyn, "Suicidal/environmental factors and the state of mental health in the elderly," *Vestn. Ros. Akad. Med. Nauk.*, **9**, 15–20 (2002).
4. S. I. Gavrilova, "Neurotrophic and neuroprotective therapy," in: *Pharmacotherapy of Alzheimer's disease* [in Russian], Puls, Moscow (2003), pp. 185–224.
5. S. I. Gavrilova, I. V. Kolykhalov, G. I. Korovaitseva, et al., "The ApoE genotype and efficacy of neurotrophic and cholinergic treatment in Alzheimer's disease," *Zh. Nevrol. Psikhiat.*, **105**, No. 4, 27–33 (2005).
6. S. I. Gavrilova, Ya. B. Fedorova, I. V. Kolykhalov, et al., "The therapeutic potential of cerebrolysin in the preventative treatment of Alzheimer's disease," *Zh. Nevrol. Psikhiat.*, **108**, No. 8, 24–28 (2008).
7. S. I. Gavrilova, "Potential for preclinical diagnosis and prevention of therapeutic interventions in Alzheimer's disease," in: *Alzheimer's Disease and Cognitive Impairments in the Elderly: Advances in Neurobiology and Medicine* [in Russian], Puls, Moscow (2008), pp. 6–32.
8. N. P. Gerasimov, "A double-blind placebo-controlled trial of the efficacy of cerebrolysin in Alzheimer's disease," *Sots. Klin. Psikhiat.*, **2**, 35–40 (2000).
9. Ya. B. Kalyn and S. I. Gavrilova, "Epidemiological and pharmacoeconomic aspects of Alzheimer's disease," in: *Alzheimer's Disease and Cognitive Impairments in the Elderly: Advances in Neurobiology and Medicine* [in Russian], Puls, Moscow (2008), pp. 275–285.
10. X. A. Alvares, M. de Olano, C. Sampedro, et al., "Cerebrolysin protect against neurodegeneration induced by β-amyloid implants in rats," *Int. J. Neuropsychopharm.*, **3**, 359 (2000).
11. X. A. Alvarez, V. R. Lombardi, L. Fernandez-Novoa, et al., "Cerebrolysin reduces microglial activation in-vivo and in-vitro: a potential mechanism of neuroprotection," *J. Neural. Transm.*, **59**, Supplement, 281–292 (2000).
12. X. A. Alvares, R. Cacabelos, M. Laredo, et al., "A 24-week, double-blind, placebo-controlled study of dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease," *Eur. J. Neurosci.*, **13**, 43–54 (2006).
13. *Alzheimer's Association/Every 72 seconds someone in America develops Alzheimer's*, Chicago, Alzheimer's Association 2007, http//www.alz.org/national/documents/Report_2007FactsAndFigures.pdf, accessed May 7, 2007.
14. Y. Chen, Yu. Tung, B. Li, et al., "Trophic factors counteract elevated FGF-2 induced inhibition of adult neurogenesis," *Neurobiol. Aging*, **28**, 1148–1162 (2007).
15. J. Golomb, A. Kluger, P. Garrard, and S. Ferris, *Clinician's Manual on Mild Cognitive Impairment*, Press Ltd, London (2001), p. 56.
16. A. Gschanes and M. Windisch, "The influence of Cerebrolysin and E021 on spatial navigation of 24-month-old rats," *J. Neural Transm.*, **53**, Supplement, 313–321 (1998).
17. L. F. Low and K. J. Anstey, "Dementia literacy: recognition and beliefs on dementia of the Australian public," *J. Alzheimer's Dementia*, **5**, 43–49 (2009).
18. E. Masliah, F. Armasolo, I. Veinberg, et al., "Cerebrolysin ameliorates performance deficits, and neuronal damage in apolipoprotein E-deficient mice," *Pharmacol. Biochem. Behav.*, **62**, 239–245 (1999).
19. K. Maslow, "How many people with dementia are hospitalized?" in: *Improving Hospital Care for Persons with Dementia*, N. M. Silverstein and K. Maslow (eds.), Springer, New York (2006), pp. 3–21.
20. J. C. Morris, "The Clinical Dementia Rating (CDR): current version and scoring rules," *Neurology*, **43**, 2412–2414 (1993).
21. R. C. Petersen, G. E. Smith, S. C. Waring, et al., "Mild cognitive impairment: clinical characterization and outcome," *Arch Neurol.*, **56**, 303–308 (1999).
22. R. C. Petersen, "Mild cognitive impairment as a diagnostic entity," *J. Int. Med.*, **256**, 183–194 (2004).
23. I. Reinprecht, A. Gschanes, M. Windisch, and G. Fachbach, "Two peptidergic drugs increase the synaptophysin immunoreactivity in brains of 24-month-old rats," *Histochem. J.*, **31**, 395–401 (1999).
24. B. Reisberg, S. H. Ferris, M. J. de Leon, et al., "The global deterioration scale (GDS). An instrument for the assessment of primary degenerative dementia," *Am. J. Psychiat.*, **139**, 1136–1139 (1982).
25. E. Ruther, R. Ritter, M. Apecechea, et al., "Efficacy of the peptidergic nootropic drug cerebrolysin in patients with senile dementia of the Alzheimer type," *Pharmacopsychiatry*, **27**, No. 1, 32–40 (1994).
26. A. Sallaw, J. Mintzez, M. Weiner, and J. Cummings, "Disease-modifying therapies in Alzheimer's disease," *J. Alzheimer's Dementia*, **4**, 65–79 (2008).
27. M. Windisch, A. Gschanes, and B. Hutter-Paier, "Neurotrophic activities and therapeutic experience with a brain derived peptide preparation," *J. Neural. Transm.*, **53**, Supplement, 289–298 (1998).