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Colostrinin®: a Proline-Rich Polypeptide (PRP) Complex Isolated from Ovine Colostrum for Treatment of Alzheimer's Disease. A Double-Blind, Placebo-Controlled Study

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Abstract. A proline-rich polypeptide (PRP) complex, subsequently called Colostrinin®, was isolated from ovine colostrum. The complex showed immunomodulatory properties in mice, rats, and chickens, inducing maturation and differentiation of thymocytes. It was recently found that Colostrinin® is a cytokine-like factor that acts as an inducer of interferon γ (IFN-γ) and other cytokines in human peripheral blood and cord blood leukocyte cultures and has psycho-immuno-enhancing activity in volunteers. These observations prompted us to study the effect of Colostrinin® on patients with Alzheimer's disease (AD). Forty six AD patients were divided into 3 groups and randomly assigned to receive orally either Colostrinin® (100 μg per tablet, every second day), commercially available bioorganic selenium (100 μg selenium per tablet, every second day) or placebo tablets. One cycle of the treatment lasted 3 weeks and was separated from the next cycle by a 2 week hiatus. Each patient received 10 cycles of treatment during the year of the clinical trial. Outcomes were assessed by psychiatrists blinded to the treatment assignment. Eight of the 15 AD patients treated with Colostrinin® improved and in the 7 others the disease had stabilized. In contrast, none of the 31 patients from the selenium or placebo groups with similar mild or moderate AD improved. The administration of selenium promoted stabilization in 13 of the 15 patients, whereas in the placebo group only 8 of the 16 patients were stabilized at the 12 month trials end-evaluation. Colostrinin® was found to be a remarkably safe drug. Mild and transient effects were anxiety, stimulation, insomnia, and tiredness. The results obtained showed that oral administration of Colostrinin® improves the outcome of AD patients with mild to moderate dementia. The results are very encouraging and deserve further research.

Key words: a proline-rich polypeptide (PRP) complex – Colostrinin®; Alzheimer's disease; therapy.

Introduction

Alzheimer's disease (AD) is one of the unsolved problems of modern medicine. The disease today represents a group of dementia of unknown etiology. For that reason, Alzheimer's disease was recently reclassified as an Alzheimer's syndrome. This term better reflects the complicated clinical and pathogenic picture[34].

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Abbreviations used: AD – Alzheimer's disease, IFN-γ – interferon gamma, TNF-α – tumor necrosis factor alpha, PRP – a proline-rich polypeptide complex, MMSE – mini-mental-state-examination.

Regardless of the scientific discussions concerning AD etiology[5, 31] characteristic changes in the brain, including plaques, tau tangles, and loss of neurons, are of the prominent feature of AD[4, 8, 33, 35]. The plaques represent amyloid β (Aβ) deposits resulting from non-physiological cleavage of the amyloid precursor protein (APP). The latter is a harmless component of the cell membrane, but, when not cleaved properly, is believed to play a key role in the pathogenesis of AD[28, 31, 33]. Insoluble Aβ forms filaments and senile plaques in the brain[33]. The non-physiological metabolism of APP most frequently occurs due to damage of the cellular membrane bilayer and exposure of APP to scavenger lysosomes[5, 25]. In the cell, phospholipids of the membrane bilayer, among them phosphatidylcholine, a precursor of the acetyl choline, are particularly affected[7, 12, 24]. AD patients show an overproduction of tau protein[8, 30, 35]. When this protein is released from the cell, it becomes heavily phosphorylated and glycated[30, 35]. In such a form, tau protein becomes less soluble and forms deposits in the white matter of the brain, causing nerve tangles, which affect the communication network and damage further neurons. These effects of tau protein occur through activation of the oxidative stress[8, 30, 35] and stimulation the Aβ formation. Since Aβ is also blamed for induction of the oxidative stress, these two proteins may operate in conjunction.

Contemporary therapies focus mainly on an alleviation of side effects caused by the lack of acetylcholine in the brain. The majority of drugs is selected from various inhibitors of cholineesterase, e.g. Tacrine[19]. However, inhibition of choline-esterase can cause perturbances in various metabolic pathways. Since AD represents failure of various brain functions, and acetylcholine inhibitors affect only one of them, they have to be classified as symptom alleviating drugs. To overcome the problems mentioned above, the search for drugs having multifunctional properties has been initiated. The post-synaptic muscarinic receptors may serve as an example. This class of drugs simultaneously enhances the action of choline and modulates the processes of amyloid depositions. Currently, several members of this family are in advanced stages of clinical trial. A group of compounds which raises hopes of becoming even more effective and certainly less toxic are the cytokines. Cytokines play a pivotal role in intercellular signalling, in the regulation of the immune system and the nervous system, as well[1, 3, 6, 9, 10]. It is worthwhile to mention that both interferon [22, 24, 27, 29] and TNF-α[1] have shown inhibitory activity on formation of β-amyloid plaques and protect neurons against Aβ peptide toxicity.

A proline-rich polypeptide complex (PRP, later called Colostrinin®), was isolated from ovine colostrum and described by JANUSZ et al. [17] Colostrinin® peptides contain a high proportion of proline residues (20–30%) and hydrophobic amino acids (about 50%). Colostrinin® induces maturation and differentiation of thymocytes and is not species-specific[16]. It also induces secretion of interferon γ (IFN-γ) and other cytokines[14]. Colostrinin® has been tentatively classified as an immunomodulator with cytokine activities[15].

Pilot studies performed in volunteers showed that Colostrinin® is bioavailable in humans after oral administration of 50–200 μg of the active substance per tablet. Studies on animals revealed that Colostrinin® is remarkably non-toxic. Moreover, Colostrinin® was found to display psychotropic activity, initially characterized as psycho-stimulation and mood enhancement[14]. The neurodegenerative processes occurring in the brains of patients with AD cause regression of the cognitive functions. Because Colostrinin® has 2 potent combined activities, immunomodulatory and psycho-enhancing, it occurred to us that it may be useful, as a natural complex of peptides with cytokine-like activities, for treatment of Alzheimer's disease. To verify this supposition, we decided to perform a double-blind placebo-controlled one-year trial, treating orally AD patients with tablets containing Colostrinin®, commercially available organic selenium preparation or a placebo. The results obtained showed that Colostrinin® improves the cognitive and behavioral abilities of AD patients.

Materials and Methods

Drugs. Colostrinin®, a new preparation containing proline-rich peptides with cytokine-like activity was purified from ovine colostrum by the method described by JANUSZ et al.[17] Colostrinin® was tested for its potency in biological assay described earlier[14]. Tablets containing 50, 100 and 200 μg of the active ingredients were prepared by admixing and pressing Colostrinin® with mannitol. Validation tests of tablets revealed that the active component present was capable of inducing the cytokines: IFN-γ and TNF-α even after two years' storage at room temperature. Selenium tablets were supplied by Power Health, Ltd., Packlington, York 404-2NR, England, commercially approved as a food additive. Each tablet contained 100 μg Se^{2+} in the form of a bio-organic yeast preparation enriched with Zn^{2+} and vitamins. Placebo tablets were formed from mannitol without active compounds.

Bioavailability assay. The direct assay to measure

circulating nanogram amounts of Colostrinin® peptides is not available as yet. The peptide complex was found to be a very weak immunogen, which excluded the preparation of antibodies. Besides, Colostrinin® is poor in Tyrosine residues and preparation of ^{125}I-labeled derivatives for radioimmunoassays was unsuccessful. Therefore, an indirect bioassay elaborated by INGLOT et al.[13] was used. This assay measures the development and disappearance of tachyphylaxis (hyporeactivity) to IFN-γ by the ovine Colostrinin®.

The volunteers were treated orally with Colostrinin® tablets containing 50, 100 or 200 μg of active peptide complex daily or every second day for 3 weeks. The individuals donated 10 ml of venous blood weekly, before and after administration of Colostrinin®. The production of IFN-γ by the blood cell cultures was assayed as described by INGLOT et al.[13]. The volunteers treated with Colostrinin® developed tachyphylaxis to selected IFN-γ inducers, including the Colostrinin® complex within 2–3 weeks. The hyporeactivity state (shown as a loss of the ability of blood cell cultures to respond properly to IFN-γ inducers) disappeared spontaneously after 2 weeks of hiatus.

All participants of the trials signed agreements before entering the study.

Patients. Forty six patients with AD were included in this study. All were outpatients who were under the care of the Lower Silesian Association of Families with Alzheimer's Disease in Wrocław, Poland. Seven of the patients had been hospitalized for a short time only. None of the AD patients was at the time of entry under chronic or sporadic immunomodulatory treatment. The examinations at entry included psychiatric and neurological tests, blood and urine morphological and chemical analyses, electro-encephalographic (EEC) and computer tomographic (CT) scans of the brain. Final diagnosis was made by Dr. Jerzy Leszek, a senior psychiatrist with expertise in dementia diagnosis. All patients under study met the DSM-III-R and NINCDS--ADRDA criteria for probable AD[23]. Patients were excluded if they would not agree to take medicine or respond to the test questions and/or if they had life--threatening diseases other than AD.

Randomization and treatment. To evaluate the safety and efficacy of Colostrinin®, a double-blind placebo-controlled trial was conducted. AD patients were assigned at random to 1 of 3 parallel groups, A, B, and C.

Group A consisted of 15 patients who received every second day one tablet containing 100 μg of Colostrinin®. They were instructed to dissolve it in saliva in the mouth between meals.

Group B consisted of 15 patients who received the selenium (100 μg) tablets in the same way as the patients from the group A.

Group C consisted of 16 patients who received placebo tablets, prepared in the same way as tablets containing Colostrinin®.

One cycle of the treatment lasted 3 weeks and it was always separated from the next cycle by a 2-week hiatus without treatment. The "3 + 2 protocol" of the drug administration was devised to avoid the development of long-term tolerance to IFN-γ and other cytokine induction and overstimulation of the immune and/or nervous system, and to promote homeostasis. Over a one-year period each patient received 10 cycles of treatment.

The primary efficacy outcome was assessed by the mini-mental-state-examination (MMSE)[7] and each patient was evaluated 5 times. After one year of treatment, the code was broken and the results were analyzed.

The MMSE tests were carried out by the departmental psychologists, blinded to the treatment assigned to the patients. The efficacy outcomes included subjective evaluation of the psycho-social functioning of the AD patients provided by the patients' caregivers. They provided detailed information concerning the degree of independence by describing patients' ability to cope with everyday tasks. A vivid description of changes in their daily performance, mood, appetite, day and night sleep patterns and general behavior was reported. Both the psychologist's and caregiver's evaluations constituted the basis for the psychiatrist's assessment.

The study was conducted according to the guidelines of the regional ethics committee for conducting research on humans. Each of the AD patients or their relatives or caregivers signed an agreement to participate in the study.

Statistics. Statistical analyses were performed using Student's *t*-test

Results

Volunteers and bioavailability

To establish the therapeutic dosis, studies were first initiated on 5 healthy volunteers recruited among research personnel who received through orally one tablet containing 100 μg of the Colostrinin® per day for a period of 3 weeks. The volunteers were carefully monitored for signs of adverse reactions. They were also monitored for changes in cognitive functions, particularly early memory. To test bioavailability of Colostrinin® they donated blood at the beginning of the

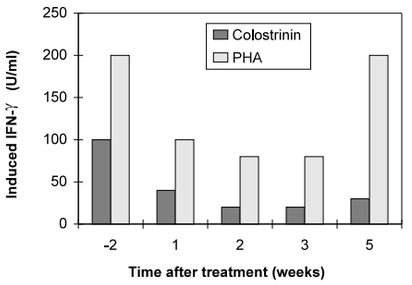

Fig. 1. Induction of the tachyphylaxis phenomenon in the blood of a volunteer (SDJ) participating in the first clinical study. This phenomenon occurred 3 times during 3 cycles of Colostrinin® application. The volunteer received 100 μg per oral route every second day following 2 weeks hiatus

study and at weekly intervals. All volunteers reported memory improvement, changes in clarity of thinking and improvement of mood. The bioavailability assays revealed that each volunteer developed classical tachyphylaxis after 3 weeks of treatment with Colostrinin®. After the 2-week hiatus, volunteers' cells again responded to IFN-γ inducers (Fig. 1). Some of the volunteers repeated the Colostrinin® treatment cycles several times. They observed appearance and regression of the tachyphylaxis phenomenon in each treatment cycle.

Then, preliminary studies on Alzheimer's patients were performed. The first group of patients received 50 μg of Colostrinin® per day, second 100 μg, and the third 200 μg per day. The fourth group received 100 μg Colostrinin® every second day. All treatments were carried out over a period of 3 weeks. All patients were monitored for the appearance of toxic or adverse reactions. Changes in cognitive functions and the appearance of tachyphylaxis were also assessed. All volunteers, regardless of Colostrinin® dose, tolerated treatment very well. None of them reported signs of toxicity. In the group of patients treated with 200 μg of Colostrinin® per day, a strong stimulation was observed manifested by an increase of biological activity, logorrhea, excitation and a diminished requirement for sleep. These signs were transient and subsided after termination of the treatment. The group receiving 100 μg of Colostrinin® per day showed changes in mood similar to these of the previous group but the intensity of the adverse symptoms was lower. The group of patients receiving 50 μg of Colostrinin® per day did not report any changes in their behavior and, especially, in mood. The group of patients receiving 50 μg of Colostrinin per day exhibited tachyphylaxis later than in the case of patients receiving 100 or 200 μg daily of the preparation. The tachyphylaxis phenomenon was more profound in patients obtaining 100 or 200 μg of Colostrinin®. The best results were obtained when the patients were treated with 100 μg of Colostrinin® every second day. So for the placebo-controlled double-blind trial, patients were treated every second day for 3 weeks with 100 μg of Colostrinin® followed by a 2-week hiatus.

Enrollment and characteristics of the AD patients

During the blinded 12 month phase of the study, 15 patients were randomly assigned to Colostrinin® (group A), 15 to selenium (group B), and 16 patients (group C) were treated with placebo. The patients were well-matched regarding the age and sex distribution (Table 1). They also showed similar duration of the disease and general characteristics of AD. However, their disease advancement, measured by MMSE scores, was not uniform. For this reason, the evaluation of the efficacy of therapy was carried out using a matched controls method. In each of the groups, A, B, and C, the patients were divided into subgroups according to the MMSE scores: subgroup 1 – scores 17–24 (mild advancement of the disease), subgroup 2 – scores 12–16 (moderate advancement of the disease), subgroup 3 – scores 11 and below (severe advancement of the disease). Using this strategy, the size of the assessed subgroups diminished but a higher precision of evaluation was achieved.

Outcome of the blinded phase of the study

To evaluate the efficacy of Colostrinin®, MMSE scoring was assessed before treatment and several times during the treatment for each of the patients assigned to either the Colostrinin®, selenium or placebo group (Table 2 and Fig. 2). There were statistically significant differences in outcome between the 3 study groups. The results obtained were supported by assessment of the social functioning of the AD patients in their homes.

The efficacy of Colostrinin® treatment depended upon the stage of advancement of the disease (Table 2). Patients who at the beginning of the trial were at early stages of disease (mild advancement of the disease) responded to the Colostrinin® treatment better than the patients in a very advanced period of the disease (Table 2, A vs C). The patients showed an improvement or, at least, stabilization of the health status. This is in contrast with results obtained with selenium (Table 2, B), and particularly with the placebo (Table 2, C), where no improvement, at the best only stabilization, was observed.

Patients who were treated with Colostrinin® showed better social functioning connected with enhanced mood, drive and cognitive abilities.

Table 1. General characteristics of AD patients enrolled in double-blind placebo-controlled study

Clinical data	Groups		
	Colostrinin® n = 15	selenium n = 15	placebo n = 16
Duration of disease before treatment, years (mean, range)	3.5 (1.5–6.5)	4.0 (2.0–5.9)	3.9 (2.8–7.5)
Sex			
female	12	12	10
age (mean, range)	68.5 (45–83)	69.8 (50–82)	68.9 (61–75)
male	3	3	6
age (mean, range)	73 (72–74)	71.7 (69–76)	66.7 (59–76)
Education			
primary school	5	4	3
high school	7	9	11
university	2	2	1
not specified	1	0	1
Concomitant diseases			
arterial hypertension	7	7	3
transient ischemic attacks	1	0	0
type II diabetes	3	4	2
obesity	7	9	6
chronic bronchitis	2	3	2
chronic peripheral arterial diseases	2	1	0
mixed (diabetes + obesity)	10	13	8

n – the number of patients.

Table 2. Changes in the MMSE score during the one-year treatment with Colostrinin® (A), organic selenium preparation (B), or placebo (C) patients being initially at different stages of the Alzheimer's disease

Subgroup	MMSE scores	Number of patients	Evaluation					P
			1	2	3	4	5	
Colostrinin								
1	17–24	7	19.5 ± 2.7	22.1 ± 3.9	20.9 ± 3.4	22.7 ± 3.0	24.3 ± 3.0	0.02
2	12–16	7	14.3 ± 1.3	15.3 ± 1.8	15.4 ± 2.6	16.0 ± 2.8	16.7 ± 2.8	NS
3	≤ 11	1	11.0	10.0	10.0	11.0	12.0	–
Selenium								
1	17–24	3	19.0 ± 1.4	16.3 ± 2.5	16.3 ± 2.9	18.0 ± 2.2	17.0 ± 3.0	NS
2	12–16	8	12.6 ± 1.1	11.7 ± 0.8	12.2 ± 1.6	11.6 ± 3.6	10.6 ± 3.6	NS
3	≤ 11	4	7.0 ± 2.3	7.2 ± 2.5	6.2 ± 2.2	6.0 ± 2.4	5.7 ± 1.4	NS
Placebo								
1	17–24	4	20.3 ± 2.3	19.5 ± 2.3	16.8 ± 3.1	14.3 ± 4.7	13.0 ± 4.1	0.02
2	12–16	3	12.3 ± 0.5	11.0 ± 0.8	9.0 ± 2.8	8.7 ± 4.2	5.5 ± 2.0	0.005
3	≤ 11	9	8.7 ± 2.1	8.9 ± 2.5	7.1 ± 2.5	7.0 ± 2.2	6.0 ± 2.0	0.03

The patients in each group were divided into 3 subgroups according to the initial MMSE scores before treatment into mild (17–24), moderate (12–16) and severe (≤ 11). Evaluation 1 describes the initial MMSE score of patients before treatment and evaluations 2–5 present MMSE scores obtained at various times during the treatment. The results concerning improvement for Colostrinin® group vs selenium or placebo are significantly different: $p = 0.002$ by Student's t-test. The results concerning stabilization for selenium vs placebo group also are significantly different: $p = 0.001$ by Student's t-test. p – probability of observed data. In all cases significance was only ascribed to p values < 0.05. NS – not significant.

The results obtained are even better expressed when presented in the form of diagrams in Fig. 2, which show changes in MMSE scores obtained for patients treated with Colostrinin® vs patients treated with selenium or a placebo.

The cumulative results presented in Table 3 show that 50% of patients treated with Colostrinin® showed improvement and 50% stabilization of the health status. In the case of patients treated with selenium, 90% showed stabilization. In the case of placebo-treated patients, 50% showed stabilization and 50% deterioration of their health. The results presented in Table 3 also indicate beneficial effects of Colostrinin® in the treatment of AD patients.

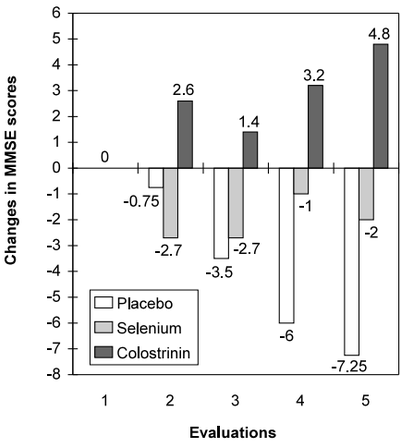

Fig. 2. Comparison of efficacy of treatment of AD patients with Colostrinin® vs patients treated with placebo, selenium, and selenium vs placebo. The patients showed MMSE scores between 17 and 24. The number of patients in the Colostrinin® group was 7, in the placebo group 4, and in the selenium group 3. The values presented are differences in MMSE scores between the initial MMSE scores (0) and the scores obtained during the consecutive measurements (2–5) during the one-year trial (see Table 2)

Table 3. Cumulative results of the double-blind placebo-controlled study at 12 months evaluation

Group	Classification of AD patients	Number of patients	Outcome		
			improvement	stabilization	deterioration
Colostrinin®	mild	7	4	3	0
	moderate	7	4	3	0
	severe	1	0	1	0
	total	15	8 (54%)	7 (46%)	0
Selenium	mild	3	0	3	0
	moderate	8	1	6	1
	severe	4	0	4	0
	total	15	1 (7%)	13 (87%)	1 (6%)
Placebo	mild	4	0	2	2
	moderate	3	0	1	2
	severe	9	0	5	4
	total	16	0	8 (50%)	8 (50%)

The initial classification of AD patients was based on MMSE score: ≥ 17 – mild; 12–16 – moderate; ≤ 11 – severe. Improvement: increasing MMSE score and subjective improvement of social functioning (amelioration of fresh memory, mood, drive, apetite, and social behavior. Stabilization: stabilized MMSE score on higher or lower level (± 2). Deterioration: progressive decline of MMSE score, subjective slow or rapid deterioration.

During the trial, 4 of the 46 patients died. There were 2 deaths in the placebo and 2 in the selenium

Table 4. Behavioral disturbances observed during the Colostrinin® – immunotherapy of AD patients

Symptom	Colostrinin® n = 15	Selenium n = 15	Placebo n = 16
Anxiety	5	1	0
Sleep disturbance			
insomnia	6	2	1
somnolence	1	0	0
Speech flow	6	0	0
Psychosis	2	0	5
Psychomotor dysfunction	2	2	0
Tiredness, fatigue	3	0	0
Gastro-intestinal disturbance	1	0	0
Fever	0	1	1
Rash	1	0	1

The number of AD patients with the indicated behavioral disturbances is shown.
n – the number of patients in each group.

group. Two patients died as a result of stroke, one of pneumonia, and one death was associated with the very rapid progression of the disease.

Side-effects

Colostrinin® is practically non-toxic. The side-effects were rather mild and transient and were mainly observed at the beginning of the treatment. About 30% of the AD patients showed anxiety, insomnia and speech flow disturbances. The results are presented in Table 4. In the selenium or placebo groups, no discernible side-effects were observed, except for a relatively high number of patients with psychosis in the placebo group.

Discussion

Double-blind placebo-controlled studies were designed to assess the effect of Colostrinin® in treatment of AD patients. Although the patient groups were relatively small, one feature becomes immediately prominent. Colostrinin®, consisting of a natural mixture of peptides with cytokine activities was remarkably non-toxic to the patients. Adverse reactions, if any observed in AD patients who received Colostrinin® were transient, remarkably mild, and difficult to detect in already intoxicated patients. For that reason, reported reactions need to be analyzed with caution. For example, in about 30% of patients, caregivers reported transient speech flow disturbances and insomnia (Table 4). Others reported that patients were tired. All these complaints occurred in a mild form and after a short period of time subsided. This impression is in accordance with earlier observations made on volunteers and patients used for dose-finding studies. Another prominent effect was that all patients responded to Colostrinin® therapy. This effect persisted to the end of the trial, i.e. for one year. Of course, the treated groups were too small to draw definite conclusion, but statistical analysis of a comparison between Colostrinin® treated patients with the selenium and placebo groups indicates that Colostrinin® is an effective drug for AD treatment. The kinetics of the progression of AD in the placebo and selenium patients seems to depend upon the stage of the disease. Patients with a severe form of AD dementia progressed less rapidly than patients who entered the clinical study at the early stages of disease.

Colostrinin® therapy was found to be more effective in patients at the initial stages of disease. The first sign of improvement was seen within a relatively short period of time (3–6 months). Improvements occurred also at the late stages of disease, but were less prominent. The above observation needs further confirmation on a larger group of patients. Colostrinin®, given to the AD patients through the oral route in dose of 100 μg every second day in cycle 3 + 2, was found to be remarkably safe and effective. No initial or late side-effects were observed. There were no signs of cumulative toxicity, either (Table 4). Furthermore, generated data confirm that the doses and schedule of Colostrinin® deliveries were selected correctly. Finally, the fact that there were no deaths in the group treated with Colostrinin®, and 4 deaths in control groups should be mentioned. Based on available information, however, it is too early to speculate about the effects of the Colostrinin® therapy on life extension, although the majority of the treated patients were at the statistical limit of their life-span and death in this group is to be expected. It is also too early to draw definite conclusion concerning the effect of Colostrinin® on the elective functions measured by MMSE scores. Nevertheless, it became clear that AD patients improved by making better use of their immediate memory. Even some of those patients who were withdrawn at the beginning line responded by improving communication skills with family members or caregivers.

The fact that Colostrinin® can improve memory is of itself a quite remarkable achievement. This fact needs to be evaluated in view of the fact that it was achieved in patients with a neurodegenerative disorder considered as a progressive, non-reversible process. This fact may raise disbelief among skeptics, especially as it is difficult to explain the mechanism of how it happended. However, recent discoveries, which have revealed that brain neurons can regenerate throughout human life, provide a basis for the formulation of a hypothesis concerning Colostrinin's® mode of action[11, 21].

Assuming that Colostrinin® represents a naturally occurring complex of cytokine-like peptides specifically formed for the development of the communication network, its role in AD treatment may be pivotal. Such an interpretation of Colostrinin's® activity allows us to assume that the cytokines present in colostrum initiate cascade reactions which, among other things, might correct metabolic abnormalities occurring in patients with AD such as: cell membrane damage[25], excessive production, or modification of the post-translation process that causes the Aβ accumulation in the brain blood vessels[4, 5, 28, 31, 33, 34], and plaque formation[28, 33]. Colostrinin® peptides may also modulate tau protein formation[31, 32], its glycation or phosphorylation[30]. They might also normalize or control the oxidative stress [30, 35] and stimulate the growth of new brain nerves[11, 20]. If Colos-

trinin® corrects only a part of the above-listed malfunctions, its application for the treatment of AD might become a vital therapy. Right now there is no definitive proof for this. However, several lines of evidence suggest that the cytokines present in Colostrinin® may indeed be responsible for the induction of the beneficial changes in AD patients. The immunomodulatory properties of Colostrinin® [14, 15, 16] may induce changes which may improve brain functions[26]. The ability of Colostrinin® preparations to induce cytokine secretion, e.g. IFN-γ, correlates well with observations that IFN-γ inhibits formation of β-amyloid deposits and might have a beneficial effects on AD patients[22, 24, 27, 29]. The present there are not very many known compounds which can affect the cognitive functions of patients with AD[26]. Therefore, Colostrinin® needs to be considered as a unique entity that deserves further studies.

Several of these questions could be answered, for example, brain tissue of Colostrinin® patients be made available. Until now there is no such brain tissue available. The only tool that can help, although not a perfect one, is a study on animals, especially the rat model. This model is generally accepted for study of a drug's effects on an animal's memory. Recent experiments carried out with Colostrinin® in the rat model revealed that Colostrinin® can improve memory of rats, increase their capabilities to acquire memory and accellerate the speed of memorization of new information[26]. This means that Colostrinin® induces similar changes in rats as those seen in patients with AD. Another fact, which remains indisputable, is that Colostrinin® treatment does not induce either acute nor chronic toxicity. Patients on Colostrinin® remain longer in a state of disease arrest than do control groups. These positive effects on patients with AD, also have beneficial effects on their caregivers, who are subjected to heavy stress and frequently require professional help to handle the existing situations[2, 18]. In conclusion, Colostrinin® treatment may represent a totally new approach to the therapy of AD.

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