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Peptide Bioregulators: A New Class of Geroprotectors, Report 2. The Results of Clinical Trials

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Abstract—This paper reviews the results of long-term studies by the authors on the clinical efficacy of peptide bioregulators (Timalin, Thymogen, Vilon, Epithalamin, Prostatilen, Cortexin, and Retinalamin) for the prevention of diseases and treatment of people of all ages. Particular attention is paid to analysis of the use of peptide bioregulators as geroprotectors.

Keywords: peptide bioregulators, geroprotectors, age-related pathology, aging
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INTRODUCTION

It was demonstrated in the previous report that peptide bioregulators have a broad range of actions and exhibit properties inherent to geroprotectors. Their influence covers all defense systems of the organism: innate and adaptive immunity, hemostasis, the kinin–kallikrein system, lipid peroxidation, and antiradical protection. Moreover, they possess potent antistressor effects [62]. E.I. Chazov [78] believes that the protective systems of the body are those targets at which the search for new effective drugs should be directed. Similar views were held by I.P. Ashmarin [3], who pointed out that the study of short peptides is a promising direction in clinical medicine.

This report presents the results of clinical use of peptide bioregulators, including in elderly and senile aged persons. The review includes literature references, in which there are indications of ethical principles imposed by the World Medical Association Declaration of Helsinki (1964, 2000 ed.).

TIMALIN

Timalin is a polypeptide preparation isolated from the thymus of animals [31, 32, 37]. The drug restores the immune reactivity (regulates the amount and ratio of T- and B-lymphocytes and their subpopulations, stimulates the cellular immune response, and enhances phagocytosis), stimulates regeneration and haemopoesis in the case of their suppression, and improves the process of cellular metabolism. The drug increases the average lifespan [62]. Timalin was allowed by the USSR Ministry of Health for medical use by order no. 1108 of November 10, 1982 (Registration number 82/1108/8).

For the first time, Timalin was applied in clinical practice in 150 patients with chronic purulent-inflammatory diseases accompanied by significant inhibition of T-cell immunity and tissue regeneration processes. Administration of Timalin fully restored the number and functional activity of T-lymphocytes and contributed to the reduction of B-lymphocytes to the norm, which correlated with the improvement of the patients and the activation of reparative processes [53, 55]. Subsequently, Timalin was used in more than 550 patients with a variety of acute and chronic diseases of bones and soft tissues. Pronounced clinical and immune effects characterized by the recovery of cellular and humoral immunity to the norm, as well as the processes of regeneration, were observed in 79% of patients. An increased number of T-lymphocytes, enhancement of blast-transformation reaction, and leukocyte migration inhibition in the presence of concanavalin A and phytohemagglutinin, as well as a delayed hypersensitivity reaction to tuberculin, were observed in most of these patients [55], which indicates increased function of the T-system of immunity.

Application of Timalin for 4–6 days in patients with erysipelas led to an improved state: symptoms of infection disappeared and temperature normalized 3–4 days earlier than in the control group receiving conventional treatment. Regardless of the form of the disease, pain, swelling, and erythema disappeared 3–4 days earlier. Periods of ESR normalization were

reduced by 4–5 days, and the length of the hospital stay decreased by 5–6 days. At the same time, the content of T- and B-lymphocytes and the state of the hemostasis system normalized in the patients. It should be noted that during application of Timalin relapses of erysipelas were observed in no cases, while without its use the cases of repeat diseases reached more than 10, the number of patients [41].

Application of Timalin for 5–10 days for the treatment of adults and children with meningococcal disease led to normalization of the parameters of cellular and humoral immunity, cerebrospinal fluid, and hemogram and coagulogram, and the C-reactive protein content. Clinically, patients quickly passed intoxication and stopped vomiting; the temperature normalized, and hemorrhagic rash disappeared; and no meningeal syndromes were found. In the group of patients treated with Timalin, in no case were complications observed and or residual effects, while complications were found in six patients among the 28 patients who did not receive the drug [22]. Good results were obtained in the treatment of patients with typhoid fever: after applying Timalin the fever disappeared, on average, 8 days before in these patients, the number of relapses decreased 3.7-fold, and the hospital stay decreased, on average, by 5 days [4].

The results of clinical studies show the efficacy of Timalin application in obstetric practice. For example, in women with pregnancy when receiving Timalin at 10 mg for 3–4 days experienced the activation of the immune system leading to an increase in the number of T- and B-lymphocytes and decreased levels of IgG and IgM. Clinically the effect of Timalin on pregnancy past the due date was that 56% of women themselves started their labor, and the overall duration of labor was on, average, 2 hours less than in the control group. Using Timalin led to a significant reduction in the frequency of fetus asphyxia during labor by 2.4 times and pathological blood loss 1.5 times less than in the control group. In pregnant women who received Timalin, no postnatal septic diseases were recorded, and hypogalactia occurred 1.3 times less than in the control group [16, 22]. During anemia in pregnant women, the introduction of Timalin at 10 mg intramuscularly for 5–7 days resulted in an increase in the content of reticulocytes 2.7 times (1.5 times in the control group with conventional therapy) [13].

Using Timalin in children with medium-acute pneumonia at the age from one month to three years resulted in an increase in the number of T-lymphocytes, on average, by two times. Simultaneously, a decrease in the concentration of IgG and a rise in IgA were observed [24]. In this group of children, the duration of infection decreased, appetite recovered faster, coughing disappeared earlier, and temperature normalized. The length of hospital stay of children receiving Timalin decreased by 31.4% as compared with the control group.

Positive results were obtained in the treatment of infants with severe and very severe acute pneumonia forms: the number of T- and B-lymphocytes normalized, whereas IgG levels remained elevated at 1.5, and IgA—almost 3 times. Therapy using Timalin in these children was effective in all cases without exception: good results were observed in 80% of the cases, in 20% of cases it was satisfactory. Duration of hospital stay in the control group (receiving no drug) was, on average, 30 days, while it was 20 days in children who received Timalin from the early days of the disease [22].

The results of applying Timalin for five days in 85 children with bronchial asthma depended on the form, degree of severity, and duration of the disease. Thus, a positive effect was shown between attacks in 91% of children with atopic bronchial asthma when Timalin was used: persistent improvement of the disease was revealed for 77% of children, short-term improvement for 13.3%; when Timalin was applied during an attack of bronchial asthma sustained improvement was noted in 81% of children, while short-term improvement occurred in 14.2%. In mild disease improvement occurred in all children [22, 43]. It should be pointed out that parameters of cellular and humoral immunity, completed phagocytosis, coagulation, and fibrinolysis normalized to a large extent two weeks after application of Timalin in children with bronchial asthma. At the same time, the content of IgE increased, although no new phenomena of allergization occurred.

Timalin was used under extreme conditions of Transbaikalia for the prevention of acute respiratory infections and exacerbation of chronic nonspecific pulmonary disease (CNPD) in 180 children aged 3–6 years and 150 adults. The drug was administered intramuscularly to children at 2–2.5 mg one time a day for 2–3 days and to adults at 5 mg for 3 days. In the first 6 months among children receiving Timalin, the number of cases of acute respiratory infections decreased by more than four times; over one year it decreased by 2.5 times in comparison with the control group. It should be noted that the children who were administered Timalin endured the acute respiratory disease considerably easier. They had no significant signs of infection or high temperature, and there were no complications. In adults, after application of Timalin, acute conditions of CNPD were noted three times less during the year than among patients in the control group [14].

The study of Timalin efficacy in antiepidemic practice showed that even a single injection of 5 mg of the preparation to patients provided reduction in infectious diseases in the first 1.5–2 months by 1.6 times and labor loss by 2.2 times [12]. The incidence of pneumonia and acute respiratory disease decreased

most significantly (3.5–4 times). By increasing the Timalin dose to 10 mg during vaccination against influenza or meningococcal infection, the effect was significantly higher, the share of diseased decreased by 6.5 and the multiplicity of incidences decreased 9.3 times [22].

Timalin was used in cancer patients of the breast, body of the uterus, lung, stomach, and other areas [56]. The majority of patients were subjected to radiation or chemotherapy according to standard schemes. Before the application of Timalin, all patients were divided into three groups. Group 1 ($n = 20$) consisted of patients with persistent leukopenia developed after radiation or chemotherapy. Application of known leucopoiesis stimulants proved to be ineffective. The second group consisted of 28 patients who had not previously been able to undertake a full course of chemotherapy because of the rapid decline in the number of leukocytes and lymphocytes in the blood. The third group included 38 patients with a sharply decreased number of leukocytes and lymphocytes after chemotherapy. In this category Timalin was used to restore leucopoiesis. Patients in first group were administered Timalin at 10 mg daily for 10–15 days (100–150 mg per course); Group 2 received 10 mg 2 times a day for 15–20 days (300–400 mg per course); third group was administered 10–20 mg for 5–10 days (100–200 mg per course). Patients in group 2 received simultaneously chemotherapeutic agents according to standard schemes.

The amount of lymphocytes, mainly due to T-lymphocytes, increased in the blood of patients in group 1 as a result of treatment using Timalin. At the same time, the total content of leukocytes also increased. Only four patients showed an insignificant rise in the number of these cells. During simultaneous application of Timalin and chemotherapy in patients of group 2, no significant reduction in the number of leukocytes and lymphocytes was observed in the blood. A pronounced protective effect of this preparation with respect to these cells was detected. Clinically, patients showed reduced symptoms of toxicity, which were sharply marked during previous cycles of chemotherapy. Only four patients refused further chemotherapy due to toxicity and weakness. In general, the clinical efficacy of Timalin in the 2nd group of patients was 82.7%. After treatment with the preparation, a significant increase in the number of leukocytes and T- and B-lymphocytes was found in patients of the third group. Almost all values were within the physiological norm. Patients experienced an improved state of health, symptoms of toxicity disappeared, muscle tone increased, and appetite improved. Thus, application of Timalin after chemotherapy proved to be highly effective (clinical improvement was noted in 91.3% of cases).

Timalin was also used in 159 cancer patients treated with radiation therapy (Hodgkin's disease 37, lung cancer 80, and breast cancer 42). Patients with Hodgkin's disease were irradiated by a radical program. The 1st group comprised five people in which the introduction of Timalin was started 2–4 days after irradiation. The drug was administered daily by intramuscular injection at 10 mg 2 times a day for 5 days. The 2nd group included 9 patients who received Timalin in the middle of the course of radiation therapy at 10 mg once daily for 10 days. Eighteen people with similar disease severity and radiation therapy comprised the control group. The third group consisted of five patients who received Timalin late after completing radiation therapy (after 1–3 months). This drug was administered to patients at 10–20 mg daily for 5–10 days. A separate group included 8 patients with Hodgkin's disease, who suffered from infectious (virus) complication during or after radiotherapy—herpes zoster; therefore, they were also prescribed Timalin. Thirteen patients with herpes zoster that arose during radiotherapy made up the control group.

Radiation therapy of 71 patients with lung cancer at stages I–III was carried out as a part of combination therapy. Timalin was used in 38 patients. Twenty-nine subjects received the drug after radiotherapy at 10 mg intramuscularly 1–2 times a day for 3 days prior to surgery and then for 10 days thereafter. Thirty-three patients with the same diagnosis made up the control group. Immunological examination of blood was performed after radiotherapy and 12–14 days after the operation. Nine patients received Timalin during postoperative irradiation in the first and the last ten-day period of radiation therapy at 10 mg intramuscularly 1–2 times a day (200–400 mg per course). Immunological study was carried out before and after radiotherapy.

Radiation therapy in 42 patients with breast cancer at stages II–III was also performed as a stage in the combined treatment. Timalin was used in 26 patients. Twelve people received Timalin after radiotherapy termination once at 5–10 mg intramuscularly for 5–10 days (50–100 mg per treatment). Seven patients received the drug in the middle course (at 10 mg for 5–10 days) and the last 5–10 days (at 10 mg) of preoperative radiotherapy. Immunological research was conducted before and after radiotherapy. Seven patients were prescribed Timalin late after radiotherapy (after 2–6 months) due to persistent leukopenia and lymphopenia, which are not amenable to correction with other drugs. Timalin was administered intramuscularly daily at 5–10 mg for 10 days.

Total irradiation of the lymph node basins led to a sharp decline in all indicators of immunity. Thus, the total number of lymphocytes in the blood decreased by 6.1 times, E-rosette-forming cells decreased 12.6, EA

rosette forming cells decreased 12.7, $CD4^+$ lymphocytes decreased 30.0, and $CD8^+$ lymphocytes decreased 8 times. Application of Timalin facilitated a significant increase in the number of lymphocytes and T-cells as well as the index of $CD4^+/CD8^+$, which indicates restoration of the T-lymphocyte subpopulations ratios. Introduction of Timalin into patients with Hodgkin's disease during radiation therapy (group 2) not only prevented a decrease in the number of lymphocytes in the blood, but also contributed to their significant increase by 1.5 times. At the same time, the amount of lymphocytes decreased 2.2 times in control patients. Application of Timalin in patients with Hodgkin's disease late after irradiation (group 3) facilitated a significant rise in the number of lymphocytes by 1.3 times. It should be noted that the earlier introduction of other drugs to these patients was ineffective.

The results of Timalin application in patients with Hodgkin's disease are of substantial interest, in which radiotherapy was complicated by the occurrence of herpes zoster. When treated with Timalin, the duration of primary lesion development on the skin and the mucosa in patients was 4.9 ± 0.6 days, while in the control group it was 11.8 ± 2.1 days. The duration of herpes infection in patients receiving Timalin was 14.2 ± 2.3 days, while it was 18.7 ± 2.7 days in the control group. Thus, the use of Timalin in patients with Hodgkin's disease and herpes zoster reduces significantly the duration of the infection.

The application of Timalin in cancer patients was associated with an improved state of health after operations, normalization of body temperature, and increased muscle tone. Only in one patient out of 29 did a complication appear after surgery—small focal pneumonia (duration was 12 days), whereas in the control group infectious complications occurred in 5 of 33 patients with a duration of the disease up to 22 days.

The use of Timalin in cancer patients during radiation therapy allowed the complete planned course of radiation therapy. In 5 of the 18 control patients (2 with lung cancer and 3 with breast cancer), radiation therapy was interrupted in the middle of radiation treatment in connection with the development of complications (leukopenia, deterioration of health).

The introduction of Timalin into cancer patients facilitated a significant increase in the quantity of lymphocytes, T-lymphocytes, and "active" T-lymphocytes in the blood. Furthermore, in patients with breast cancer, the functional activity of T-cells improved after immunocorrection and the intensity of cellular immunity reactions recovered.

Introduction of Timalin into patients with breast cancer at late stages after irradiation led to a significant increase in the number of leucocytes in the blood by 1.3 times. Indicators of cellular immunity after the preparation practically normalized.

As a result of the study, it was found that radiation and chemotherapy resulted in a significant reduction in the immunity parameters in cancer patients. Application of Timalin reduced the incidence of infectious complications, promoted their more rapid elimination, and restored the body's immune reactivity [56].

Timalin was used for the prevention of various diseases associated with immune deficiencies. With this aim, the drug was administered to a group of people aged 70–88 years with frequent exacerbations of purulent-inflammatory diseases and acute respiratory viral infections (ARVI) for the correction of immune reactivity. After the course application of Timalin, these patients had an increased functional activity of T-lymphocytes and the basic coagulation indicators normalized or tended to normalize. It should be noted that in the future these people were much less hurt by ARVI, chronic processes did not exacerbate, and the muscle tone was much higher than before treatment [56].

O.V. Korkushko et al. [18] conducted a longitudinal clinical trial to study the geroprotective action of Timalin in people with manifestations of accelerated aging. The study involved 106 patients with coronary artery disease, the mean age was 69 ± 2 years, 58 of which received Timalin at 10 mg intramuscularly every 2–3 days, five injections per course, and the intervals between courses were 5–6 months. In addition, each patient showed more than three signs of accelerating aging (disorders in the lipid spectrum of the blood, decreased carbohydrate tolerance, impairments of the genital glands and a detoxifying function of the liver, osteoporosis, and decreased mental and physical performance). During the survey period of 30 months, patients received six courses of treatment with Timalin. As early as after the first course, the capacity of threshold physical loading increased by 14%, levels of the maximum oxygen consumption during threshold physical load increased in 53% of patients (this occurred in only 7% of cases in the control group who received conventional treatment). At the same time, the intensity of the tissue respiration was observed to heighten and oxygen delivery to peripheral tissues improved. In the majority of patients with dyslipidemia, the cholesterol level and atherogenic index decreased. It is important to note that in patients with normal values of the atherogenic index the drug had no effect on the lipid spectrum profile. Indicators of carbohydrate tolerance normalized only in 46% of patients (only in 14% of patients in the control group). Simultaneously, the concentration of circulating immune complexes (CIC) significantly decreased under the influence of Timalin in patients with initially higher parameters, which is important to reduce the risk of vascular wall damage in patients with coronary

artery disease. It should be noted that no patient had a worsened subjective state over the survey period (in the control group, 50% of patients did), new cases of coronary heart disease and hypertension were not registered, quality of life improved, and mortality in patients who received Timalin amounted to 6.6% (in the control group, it was 13.6%). At the same time, there was considerably reduced functional age of the cardiovascular system at 6.5 ± 2.7 years indicating the expressed geroprotective effect of Timalin.

Clinical studies involving several thousand patients (including by the program of the Main Military Medical Directorate of the Ministry of Defense of the Russian Federation) testify to the high efficiency of Timalin in adults and children for both treatment and prevention of diseases accompanied by secondary immunodeficiencies [25, 30, 57]. In addition, Timalin can be used as a geroprotector to improve the quality of life of the elderly and enlarge the period of healthy longevity.

THYMOGEN

Thymogen is a glutamyl-tryptophan synthetic dipeptide preparation [33, 65, 81]. The drug regulates the reaction of cellular, humoral immunity, and nonspecific resistance of the organism, stimulates regeneration processes in the case of their suppression, and improves the processes of cellular metabolism. The drug enhances the lymphoid cell differentiation processes, inducing the expression of differentiation antigens on lymphocytes and normalizes the number of T-helper cells, T-suppressors, and their ratios [62]. Thymogen was allowed by the USSR Ministry of Health for clinical use by order no. 250 of June 19, 1990 (Registration number 90/250/1).

Thymogen was used in patients with chronic liver diseases and a good effect was produced in 2/3 patients. They showed decreased signs of hepatocellular deficiency, weakness and headache disappeared, sleep normalized, pain in the right hypochondrium weakened, and the activity of aminotransferases and the bilirubin content in the blood decreased [34, 56].

Thymogen was used for 5 days in 65 patients with virus hepatitis A and typhoid and paratyphoid fevers, as well as mixed infections, both in the acute and reconvalescent periods. The positive effects of the drug were reported in all these states: more rapid (4–7 days) reduction of jaundice was observed in patients with viral mixed hepatitis A and appetite and liver function normalized, which led to reduced length of treatment by 7–10 days. In some patients with viral hepatitis A + typhoid and paratyphoid fevers, after treatment with Thymogen the pigment crisis occurred much faster followed by earlier recovery and normalization of the biochemical parameters [34].

V.Kh. Khavinson et al. [34] used Thymogen intramuscularly or intranasally for five days in patients with active and regressing forms of leprosy; in patients with neurotrophic ulcers, Thymogen was used as a local prick of ulcer lesions. During treatment with the drug, therapy using antibiotics and hormonal agents was discontinued. After completion of treatment, no clinical and morphological changes were noted in a group of patients with leprosy in the active stage. Meanwhile, as early as after a month the first signs of regression appeared, the intensity of skin lesions decreased, and they tended to reduce their size. Histopathological study confirmed the general trend towards improvement, but a clear dependence of the rate of rise of changes on the type of leprosy and the activity of the process was noted. After three months, the most pronounced signs of regression of cutaneous signs in all patients were registered, a significant reduction in infiltration, leprosy, plaques, and papules. Six months after therapy, significant signs of regression were found. Subcutaneous infiltrates almost completely disappeared in the patients, the area of spots decreased sharply, and the amount of clarification zones of skin elements increased significantly.

E.A. Zhuk and V.A. Galenok [15] used Thymogen for the treatment of diabetes mellitus (DM) type 1 for elimination of clinical signs of secondary immunodeficiency: patients were administered intramuscularly at 100 μg of the drug for 5–7 days and later it was administered at an interval of 7–10 days for 2 months. The effectiveness of therapy by clinical signs was 94.4% of cases, according to the laboratory parameters, it was 83.3%. The authors recommended repeating courses of the therapy every 2–3 months with analysis of the immunograms.

Thymogen was used in children with chronic persistent hepatitis B for three days. The treatment was carried out again after ten days. This improved the overall health, appetite increased, and pigment metabolism normalized. Positive changes in the immunogram were observed approximately in 2/3 patients, and lactate dehydrogenase decreased to normal levels. However, the maximum effect when using Thymogen was observed in patients with no manifestation of the autoimmune component. These patients did not show any recurrence for 6 months (the survey period) [34].

It is known that the cause of infertility can be in the immunobiological incompatibility of couples. To eliminate these disorders, Thymogen was prescribed at 100 μg to men and at 50 μg to women once every three days (10 injections for the course). As a result of the treatment, the functional state of the immune system normalized, which allowed continuing the next stage of treatment of immunobiological incompatibility of couples. The therapy resulted in pregnancy in 33 of 80 women who received Thymogen [80]. Good results

were obtained when Thymogen was used in more than 100 women with anemia of pregnancy. After treatment with the preparation, the content of reticulocytes increased 3.1 times in women, the parameters of adaptive and innate immunity normalized, and the intensity of intravascular blood coagulation decreased. Children born from mothers who received Thymogen suffered from hypoxia less during delivery and asphyxia at birth and had a higher Apgar score [13, 34].

The efficacy of intranasal application of Thymogen in adults (including the elderly) and children was established for the prevention of influenza and acute respiratory viral infections: the incidence decreased 3–4 times, and the number of toxic forms of influenza decreased more than 30-fold [22, 34].

Thus, the results of clinical study indicate a high efficiency of Thymogen in diseases of different genesis, including elderly and senile patients [22, 66]. In the overwhelming majority of cases, not only the clinical aspect of the disease improved but also the number of relapses decreased and the hospital stay significantly shortened.

VILON

Vilon is a synthetic dipeptide, lysil-glutamic acid preparation; it stimulates the regeneration of tissues, the synthesis of tissue-specific proteins and the proliferative and metabolic activities of cells, accelerates wound healing, activates functions of cells of connective tissue, endothelial cells, macrophages, and leukocytes in the focus of damage, and has antioxidant, immunostimulating, and antistress properties [62, 72]. Vilon was recommended for clinical study (permission to conduct clinical trials, number 4 of the Department of State Control of Medicines and Medical Technology of the Ministry of Health, Russian Federation dated February 19, 2002).

Administration of Vilon to patients with different forms of pulmonary tuberculosis, which was accompanied by bacterioexcretion and decay of tissue, stimulated healing of cavities. Simultaneously, the number of lymphocytes bearing markers $CD4^+$ increased in the peripheral blood and that of $CD8^+$ decreased. The healing process of cavities was observed to be enhanced in patients with tuberculosis, and after a long application of Vilon, the immune parameters improved and periods of treatment shortened [77].

The inclusion of Vilon in the complex therapy of patients with erysipelas led to significant improvement in the treatment results. Thus, the symptoms of intoxication disappeared 1.5 days earlier and body temperature returned to normal, pain and signs of inflammation disappeared 2–3 days earlier, the ESR normalized 4 days faster than in patients in the control group, and the number of purulent-inflammatory complications decreased. After treatment with Vilon, the content of individual subpopulations of T-lymphocytes and B-lymphocytes, as well as IgG and IgM, normalized and only the IgA concentrations remained elevated [22]. Simultaneously, the concentrations of IL-1α and IL-1β reached normal levels, while the levels of IL-8 and TNFα remained slightly elevated.

The use of Vilon in 150 patients with diabetes mellitus type 1, including 30 patients older than 50 years, led to the normalization of adaptive immunity and phagocytic activity of leucocytes, vascular-platelet hemostasis, and coagulation homeostasis and contributed to reduced glucose level in the blood. In addition, before treatment with Vilon, the insulin concentration in the blood was 24.4 ± 2.3 μUnits, after conventional therapy in patients in the control group it was 30.6 ± 5.9 μUnits, and in patients after administration of Vilon, it was 43.3 ± 4.0 μUnits. A significant proportion of patients with diabetes who received Vilon was able to decrease the dose of insulin by an average of 9 units. Among patients who received Vilon during the year, no repeat hospitalizations were observed associated with decompensation of carbohydrate metabolism. It should be noted that the inclusion of Vilon in the complex therapy of patients older than 50 years also showed good results: in 6 of 30 patients the insulin dose was reduced by 3–8 units [22, 26, 88].

The use of Vilon in patients with diffuse toxic goiter not only contributed to a more rapid normalization of the blood levels of pituitary TSH and thyroid hormone levels, but also decreased the content of autoantibodies to thyroid gland tissues and its hormones. In this case, the length of stay of patients in the hospital decreased by an average of two days [8].

Vilon was used in 56 people with wounded limb osteomyelitis after necrsequestrectomy to stimulate the innate immune system and accelerate the repair processes. Administration of the drug contributed to clinical improvement of the patients and normalization of phagocytosis and stimulation of regeneration and reduced the duration of therapy [39].

In a double-blind, randomized study of Vilon, 63 surgical patients were attended, including 33 patients aged 18–77 with acute purulent-inflammatory disease of the maxillofacial area and 30 patients aged 24–45 years with moderate or severe dysplasia of the epithelium or preinvasive carcinoma (carcinoma in situ) of cervical cancer. Patients were divided into control and main groups that were identical by sex, age, and stage of disease. All patients which received conventional treatment, and patients of the main group were additionally treated with Vilon at a dose of 10 μg intramuscularly once daily for 7 or 10 days [46]. The results of the study showed that prescription of therapeutic measures using Vilon in surgical patients in addition to conventional complex treatment accelerated tissue

regeneration and recovery of body functions. The introduction of the drug into patients was accompanied by a statistically significant shift of several hematological, immune indices, indicating the activation mechanisms of sanogenesis, favorably affected the course of infectious-inflammatory process, and shortened periods and improved the quality of rehabilitation of the patients without causing unwanted side effects.

Inclusion of Vilon in the complex treatment of patients with inoperable cancer of the stomach, esophagus, and the lung allowed not only improving the quality of life of patients, but also significantly extended the period of their lives [44]. L.S. Yas'kevich et al. [82] surveyed 57 patients with colorectal cancer (80.6% were over 50 years, including 47.3% who were over 60 years old) who after radical surgical dissection or during the generalization of the process were administered Vilon daily at a dose of 1 mg for 10 days, the courses were repeated three times at intervals of 1 month. All the patients who received three courses of Vilon lived one year without recurrence of the disease, and the two-year survival rate was 85.8% (in the control group it was 37%), while no tumor process generalization was noted, the incidence of complications and side effects of chemotherapy was decreased.

Vilon was administered to more than 250 people aged 65–87 with chronic periodontitis accompanying diabetes type 2, atherosclerosis, and other diseases of the cardiovascular system, at a dose of 10–20 μg daily submucous 5–10 days. This improved the parameters of the immunogram, phagocytic activity of leukocytes, the complement system, lipid peroxidation processes, and antioxidant protection in the blood and saliva, and the intensity of disseminated intravascular coagulation decreased. However, these changes were expressed to a lesser degree than in young people with chronic periodontitis [23, 42]. The use of Vilon in treatment of the elderly with generalized chronic periodontitis leads to a reduction in the duration of pathological process by reducing the depth of periodontal pockets, which is expressed in the reduction of the Ramfjord index by 1.2 points and the index of the papillary marginal alveolary index by 10 times. This is confirmed by the approach of the results of the treatment of older patients using Vilon to that of the surveyed individuals in the control group with a practically healthy paradentium [6].

These data suggest that the dipeptide Vilon has a geroprotective property due to enhancing the reparative processes in tissues and can be recommended as a stimulant of regeneration of tissues during purulent-inflammatory diseases and postoperative complication, trophic disorders, cancer, and cases involving impairment of reparative processes, primarily in elderly and senile aged people.

EPITHALAMIN

Epithalamin is a polypeptide drug isolated from the epithalame-epiphyseal region of the brain of animals [64, 69, 73]. It regulates metabolism in the epiphysis gland, enhances the sensitivity of the hypothalamus to endogenic hormonal influences, contributes to normalization of the function of the anterior pituitary and the content of gonadotropic hormones, normalizes melatonin content in the blood, has antioxidant properties, and increases the body's resistance to stress influences. The drug increases the average lifespan [62]. Epithalamin was allowed by USSR Ministry of Health for medical use by order no. 250 of June 19, 1990 (Registration number 90/250/6).

Application of Epithalamin in patients with diabetes mellitus type 1 led to decreased glycemia, glycosuria, and the glycosylated hemoglobin level in the blood. In addition, in patients with manifestation of hypertension disease, arterial pressure normalized and diastolic function of the heart muscle improved [79]. T.S. Shutak et al. observed 46 elderly patients with diabetes mellitus type 2, which in addition to conventional therapy were administered Epithalamin 10 mg intramuscularly each day for 10 days. It was established that Epithalamin at the course prescription caused a long-term normalizing effect on carbohydrate metabolism, which is modulated by nature and decreases as disease compensation is achieved. Furthermore, the use of Epithalamin resulted in the normalization of the blood atherogenic lipid fraction content and reduced the initially high arterial blood pressure [60].

Epithalamin was used in obstetric practice for the treatment of late toxicosis, miscarriage, and post-due pregnancy in more than 200 women. At late gestosis disorders in cellular and humoral immunity decreased substantially, and indicators of blood coagulation and fibrinolysis normalized. A positive effect of Epithalamin was observed in 76.6% [22]. Good results were obtained by combined use of Epithalamin and Timalin for 3–5 days in women with pregnancy that went past the due date. This significantly improved the parameters of an immunogram and coagulation. Furthermore, the incidence of complications in childbirth decreased, 70% of women started labor themselves, and complications of childbirth were extremely rare: untimely breaking of the waters was observed 1.9 times more rarely, labor weakness was noted 2.2 times less often, and fetal asphyxia in labor occurred 2.8 times less often than in the control group; there was no pathological blood loss during delivery [13].

In patients with psoriasis, Epithalamin was used as monotherapy and in combination with Timalin. In monotherapy using Epithalamin, cellular and humoral immunity and coagulogram normalized. All this contributed to faster recovery of patients (hospital

stay decreased on average by 4–5 days) and a longer remission (up to 1.5 years). However, the best results were obtained in the combined treatment of patients with psoriasis using Timalin and Epithalamin (5 mg of each preparation together in a day, a course of 10 injections). In this case, by clinical aspects, recovery occurred in 60%, and significant improvement in 40% of patients with increasing remission to 1.5 years or more [22].

Due to the fact, that Epithalamin promotes restoration of cellular immunity and hormonal regulation and has an anticancer effect, the drug was applied in 260 cancer patients, mainly with hormone-dependent forms of cancer (breast cancer, cancer of body of the uterus or cervix uteri, ovaries, and other areas) [56]. Epithalamin was administered intramuscularly by different courses simultaneously or after radiation or chemotherapy. Patients after applying Epithalamin showed a steady increase in the number of leukocytes, lymphocytes, T-lymphocytes, including T-helper cells, which allowed a further full course of chemotherapy. During treatment with Epithalamin, the general condition and appetite improved and muscle tone increased. Twenty-five percent of the patients of them failed to achieve improvement of the immunity parameters, but during the second part of the course the number of leukocytes, lymphocytes, and their subpopulations increased in the blood of the subjects. Application of Epithalamin in conjunction with the course of chemotherapy prevented a decrease in the number leucocytes, lymphocytes, and their subpopulations during chemotherapy. Clinically, decreased symptoms of toxicity were noted in most patients in this group allowing sufficiently easy bearing of a full course of chemotherapy in 76% of patients. Patients after treatment with Epithalamin given after a course of chemotherapy showed an increase in the number of leukocytes, lymphocytes, and their subpopulations (especially T-helper cells). After 30 days indicators of immunograms almost reached the norm. Most of the patients reported significant improvement. Toxicity symptoms, weakness, and apathy disappeared, muscle tone increased, sleep improved, and body temperature normalized. It should be noted that the use of Epithalamin together with antibiotics contributed to rapid elimination of infections that occurred after chemotherapy.

A group of patients received from 10 to 30 courses (2–3 courses per year) of Epithalamin after radical mastectomy and a full course of radiation and chemotherapy. Almost all investigated parameters of the immunogram remained within the normal range or were slightly reduced. Clinical examination revealed that all of them felt right and worked in their specialty. Recurrence and metastasis were not detected in most examined. It should be noted that some of the patients in this group received Epithalamin strictly systematically over 18–20 years. These patients had no complaints about the progression of the disease during follow-up.

The use of Epithalamin in inoperable patients showed that the drug contributed to reduced toxicity and body temperature in case of fever. It should be particularly noted that Epithalamin reduced or eliminated pain syndrome, and this often made it possible to eliminate narcotic drugs. Unfortunately, the improvement of these patients did not last long, which required a repeat course of Epithalamin therapy. Nevertheless, the use of the drug improved the general condition of patients, and in some cases extended their lives. Finally, a proportion of patients who had undergone surgery for malignancies, as well as inoperable patients treated with a course of radiation or chemotherapy, received Epithalamin every 3–4 months. This prevented relapses of the disease and improved treatment outcomes.

The antitumor effect of Epithalamin was studied in 89 patients aged 33–75 with breast cancer, who were subjected to chemotherapy at the first stage of complex treatment. Theblood cells of patients were treated extracorporeally with Epithalamin at a dose of 10 mg followed by reinfusion. On the remaining days of treatment, the drug was administered intramuscularly at 10 mg once daily. Simultaneous introduction of cytotoxic drugs with Epithalamin allowed achieving a marked clinical effect in the form of partial and complete regression of the tumor and lymph nodes in 87.5% versus 68.0% of cases in the control group ($p < 0.05$) and to avoid cases of disease progression. Furthermore, the use of Epithalamin allowed significantly reducing the frequency and severity of leukopenia and improved the immune status of the patients. Overall, two-year survival in patients of the main group was 100%, while in the control group, it was 89.8% ($p < 0.05$).

The clinic of the Institute of Gerontology, National Academy of Sciences of Ukraine, carried out a longitudinal study (over 15 years) involving 46 elderly patients with coronary artery disease and accelerated aging of the cardiovascular system (CVS), who received 6 courses of Epithalamin injection intramuscularly at a dose of 10 mg after every 2–3 days for 30 months (5 injections in the course), the interval between courses was 5–6 months [18]. It was established that under the influence of Epithalamin the quality of life improved significantly determined by the method LEIPAD. Thus, as early as even under the influence of the first 3 courses of Epithalamin, the functional age of CVS decreased by 3.2 ± 1.5 years, while the actual age increased by 3 years (the increase in the functional age of CVS in the control group was shown to be at 7.2 ± 3.5 years). The vast majority of patients showed heightened physical performance (by 10 ± 4 W compared with the baseline level), glucose tolerance

increased, lipid spectrum parameters normalized at their initial disorder, indices of functional age of CNS decreased, and indicators of the immune system normalized, including the CIC concentration in the blood. The modulating effect of Epithalamin on the function of the reproductive system is important to note: in men with an initially low concentration of testosterone in the blood, the levels of the hormone after a course of Epithalamin increased to normal, and at the baseline the increased value of this parameter decreased to normal values. Patients treated with Epithalamin showed incidences of CVS disease resulting in deaths two times less, and they had colds 2 times less frequently. After 12 years, despite the same basic therapy, the mortality rate in patients treated with Epithalamin was 37.5% less than in the control group.

It is known that the recovery of the hormonal function of epiphysis and the associated level of melatonin secretion in the elderly is one of the main ways to prevent accelerated aging and age-related pathology. It turned out that the introduction of Epithalamin every 3 days for a month increases the concentration of melatonin in the elderly in the evening [17, 19].

The results of long-term clinical studies on the treatment of elderly patients and senile aged patients showed a significant geroprotective efficiency of Epithalamin, including the prevention and treatment of age-associated pathology.

CORTEXIN

Cortexin is a preparation of polypeptide nature isolated from the cerebral cortex of animals [35, 38, 63]. The drug has tissue-specific action on the cerebral cortex, cerebroprotective, nootropic, and anticonvulsant effects, reduces the toxic effects of neurotropic substances, improves learning and memory processes, stimulates reparative processes in the brain, and accelerates the recovery of its functions after stress effects [62]. Cortexin was allowed for medical use by the Ministry of Health of the Russian Federation, order no. 136 of April 19, 1999 (Registration number 99/136/14).

Clinical studies of the efficacy of Cortexin were performed using patients of all ages. Thus, the inclusion of Cortexin in complex treatment of 95 patients with traumatic brain injury increased the effectiveness of the therapy, which was reflected in a significant increase in the cerebral blood flow, normalization of EEG parameters, and rapid relief of subjective measures [47].

Forty-eight patients with epilepsy received Cortexin in addition to conventional methods of treatment [11]. It was found that the drug is highly effective in the treatment of the "GABA-deficient" variant of epilepsy, epilepsy with generalized seizures, and focal seizures with psycho-pathological phenomena, in traumatic etiology of the disease, duration of epilepsy up to 5 years, the presence of coarse impairments in the bioelectrical brain activity, and atrophic processes in the cortex and subcortical structures, including the temporal lobe. Use of Cortexin in this group of patients intramuscularly at 10 mg once daily for 10 days provided the cessation of seizures during the year, improvement of the subjective condition of the patients, and normalization of EEG and stimulated GABA-ergic structures of the brain five times more effectively than during the conventional treatment, including cerebrolysin.

A comprehensive clinical trial was conducted in 58 elderly and senile patients with organic mental disorders of various genesis—Alzheimer's disease, Pick's disease, a consequence of cerebral arteriosclerosis, traumatic brain injury, and neuroinfections [47]. Patients with symptoms of neurosis were able to achieve full recovery of productive mental activity, and in patients with more severe disorders Cortexin had a stimulating effect, which resulted in improved functional, quantitative indicators of memory and thinking. It is important to note improvements in the EEG parameters: slow-wave activity decrease in the frontal leads (δ-and υ-rhythms) by 1.56- to 3.2-fold and an increase in the activity of the α-rhythm 1.43 times compared with the control group patients.

In the treatment of 76 patients with neurological consequences of neuroborreliosis, Cortexin was used at a dose of 10 mg intramuscularly once daily for 10 days. Regression of the subjective symptoms of patients was accompanied by reduction in objective disorders, the function of the oculomotor nerve, and reflex reactions were the most rapidly restored followed by restoration of intellectual–mental brain function. There was also a significant normalization of the EEG, which was reflected in the integral indicator of the degree of bioelectrical brain activity disorders: 63% of the EEG became normal or with mild impairments (in the control group, it was 25%), and the number of coarse disorders of the EEG also decreased significantly [47].

In the treatment of 120 children with different residual organic syndromes, which are a consequence of traumatic brain injury, neuroinfections, and other acquired encephalopathies, as well as perinatal brain lesions in the late recovery period, Cortexin was used intramuscularly at a dose of 0.5 mg per 1 g of weight of the child's body every day for 10 days [47]. It was established that a clinically good result from treatment was obtained in 70.2% of children, and satisfactory results were noted in 22.4%; there was a significant improvement in the EEG parameters characterizing the overall brain processes: reduction of the index of pathological slow activity in all regions of the brain,

reducing hypersynchronous υ-potentials both at rest and during functional loads with hyperventilation and breath-holding, as well as a clear improvement of psychophysiological indicators (according to the corrective test) and biochemical parameters (content of brain fractions of creatinine phosphokinase in the serum).

Cortexin was used for the treatment of 70 neonates with hypoxic-generic traumatic brain injury in the form of subarachnoid or intraventricular hemorrhage (birth trauma) and 76 children aged 1–15 with acute serous or purulent meningoencephalitis of undifferentiated etiology in severe form [40]. Due to birth injury in all children after application of Cortexin, hydrocephalus was compensated (in the control group, it was 67%) and spasms were eliminated (in the control group, it was 78%), 83% of patients had a positive trend in the treatment of muscular hypotonia, and 95% of children who were prescribed Cortexin recovered function of the eye muscles. During meningoencephalitis all children receiving Cortexin managed to compensate for intracranial hypertension (in the control group, 77% of children) and to achieve a significant reduction in muscle tone and increase in the volume of movements (in the control group, it was 22%).

Application of Cortexin to treat 100 newborn infants with hypoxic-ischemic lesions of the central nervous system led to compensation of the pathological process: there was a lack of growth in the head circumference, arresting syndrome of vomiting and posseting, normalization of head position of the newborn relative to the axis of the spine, no signs of edema of the brain were revealed according to neurosonography data, and the number and size of cystic cavities decreased in 30% of children. It is important to note that the elimination of neurological deficit was achieved by applying Cortexin already on the 6th day of treatment and did not require the prescription of additional agents [20, 47].

The high efficacy of Cortexin was shown in the treatment of 206 children and adolescents with attention deficit disorder and hyperactivity: in 71.9% of the children clinical improvement was observed, in particular in 100% of children with prevalence of attention disorders, which was accompanied by an increase of the α-rhythm power in the EEG in the occipital regions and normalization of ratios of υ-rhythm and the β-1-rhythm [21]. A large number of studies were conducted to identify the effectiveness of Cortexin for the correction of the functional state of the central nervous system in extreme situations. In particular, the use of Cortexin was found to be effective for increasing statokinetic human resistance during the survey of healthy men 22–24 years old, who were administered Cortexin intranasally at 5 mg 2 times a day for 10 days [9], as well as in improving performance and reducing feelings of fatigue during examination of 50 operators of the aerospace profile, who were administered Cortexin at a dose of 10 mg intramuscularly for 5 days [45].

The efficacy of intranasal Cortexin application was established by the method of intranasal electrophoresis in 54 healthy individuals of different ages with symptoms of fatigue and cerebrasthenia: all the patients had a marked effect of the drug on the psychoemotional state, the functions of attention, perception, memory, and thinking, and the functional state of the central nervous system and professional performance [45].

Numerous clinical studies indicate a geroprotective effect of Cortexin. For example, a study of the efficiency of the drug in 250 patients 50–70 years old with encephalopathy of various genesis was carried out: with intellectual and mental disorders on the basis of cerebral atherosclerosis, after old stroke, vascular encephalopathy, and neurasthenia, who were administered intramuscularly Cortexin at 10 mg 1 time per day for 10 days [47]. After the course of the drug, clear normalization of reactive EEG indices and increased power of bioelectrical activity of the cerebral cortex in the α- and β-diapasons were observed indicating an increase in the reserve capacities of the CNS, balance of excitation and inhibition in the cerebral cortex, and the activation of the excitatory process and the general condition of patients. The most significant positive changes were observed in the left hemisphere of the brain, which is responsible for higher intellectual functions and increases the accuracy and coordination of simple psychophysiological functions.

A multicenter, randomized, prospective, double-blind, placebo-controlled study of the Cortexin efficacy in the acute and early recovery period of hemispheric ischemic stroke was carried out involving 272 patients 30–80 years old who were administered the drug intramuscularly at a dose of 10 mg 2 times/day (morning and afternoon) for 10 days with the same course again in 10 days [48]. The results of the study in seven specialized centers for the treatment of vascular disease proved the high efficacy of repeated courses of Cortexin in acute stroke, which was expressed in a more rapid, compared with the control group, restoration of daily activities and cognitive functions of the patient.

N.V. Govorin [10] mentions a unique case of treatment of Alzheimer's disease using Cortexin. The patient had a typical course of the disease, showed signs of severe progredience, and 3 years after the manifestation in the patient progressive amnesia, spatial agnosia, phenomenon of aphasia, acalculia, and apraxia were determined. In addition, the disease was accompanied by severe choreiform hyperkinesia, violent grimaces, oral and grasping automatisms, swallowing disorders, increasing cachexia, and utter help-

lessness. The patient received four courses of Cortexin at 10 mg intramuscularly for 10 days with intervals between courses of 1–1.5 months, which led to the rapid recovery of swallowing and stabilization of the patient's condition and significantly reduced the rate of progression.

The results of numerous clinical studies indicate the high efficiency of Cortexin to treat a wide range of neurological diseases and pathological conditions in adults and children, as well as in healthy people of various ages, including older people with symptoms of fatigue and cerebrasthenia, when exposed to different extreme factors. It is important to note that the geroprotective effect of the drug has been proved, which is most effective for the treatment of elderly and senile patients with impaired function of the brain of different genesis and for prevention of pathological conditions associated with increased intellectual and psycho-emotional stress, including elderly and senile people.

RETINALAMIN

Retinalamin is a preparation of polypeptide nature isolated from the retina of animals [68, 71]. The drug has a tissue-specific effect on the retina and a stimulating effect on the photoreceptors and cellular elements of the retina, helps to improve the functional interaction between the pigment epithelium and photoreceptor outer segments with dystrophic changes, and accelerates the recovery of the light sensitivity of the retina [62]. Retinalamin was allowed for medical use by the Ministry of Health of the Russian Federation by order no. 212 of June 1, 1999 (Registration number 99/212/7).

The efficacy of Retinalamin was established in clinical studies for treating degenerative–dystrophic diseases of the retina of different genesis. Thus, the use of Retinalamin during diabetic retinopathy accompanied by diffuse macular edema or laser photocoagulation prior to therapy in patients 65–78 years old led to an improvement in central vision up to 1.5 times more frequently than in patients without prior Retinalamin introduction and improvement in visual acuity occurred already in the 2nd week and remained at this level throughout the survey period (2 months), while in patients who received only laser treatment, visual acuity improvement was recorded after only 4 weeks, and by the end of the 2nd month vision had returned to baseline in 70% of patients. In addition, patients treated with Retinalamin had decreased retinal reaction to laser treatment, which was reflected in a decreased macular edema zone. This improved the efficiency of laser treatment and contributed to long-term remission [76]. During electroretinography in patients with diabetic retinopathy treated with Retinalamin, the activity rate of the 1st neuron was closer to the norm and a significant increase in the activity of the 2nd neuron by 45.0% and reduced latency time by 19.3% were observed in the preproliferative stage. During the proliferative stage of the disease, a significant increase in activity at 15% of the 1st and at 36% of the 2nd neuron was shown with a decrease at 17.9% of the latency time of the 2nd neuron, which indicates improved metabolic processes in the retina [50, 52, 58, 59, 67, 87].

Integrated use of peptide bioregulators (Retinalamin, Cortexin) significantly increased the effectiveness of multistage ophthalmic treatment of patients with traumatic injuries, including gunshot wounds of the eye [58]. This had an effect on the damaged structures of the organ that enhanced visual acuity by an average of 0.3–0.5, almost completely restored frequency and contrast retinal sensitivity in the low and medium spatial frequencies, and significantly reduced the rehabilitation period.

Retinalamin proved to be effective in involutional central chorioretinal dystrophy (ICCD) [27, 28]. The study involved 112 patients 28–87 years of age, who were subjected to sub-Tenon injection once of 5 mg Retinalamin and 10 mg Cortexin during the surgical treatment in addition to conventional therapy. Within a few days after drug administration, an increase in visual acuity was noted in 98.5% of patients (in the control group, 35%), expansion of visual fields, and improved dark and color adaptation, and visual contrast perimetry were observed. It is noted that the increase in visual function was due to an improved ophthalmoscopic picture of the fundus: in 95.3% of cases partial or complete gemarragy resorption, and decreased vascular permeability were recorded. According to the results of fluorescein angiography, a decrease in dye transudation from vessels and signs of bleeding and narrowing areas of focal ischemia were identified, which led to diminution in edema in the macular area. The electro-physiological studies showed improved conduction of impulses between neurons of the visual analyzer, indicating improvement in the metabolism of the retina. In addition, S.V. Trofimov and O.Z. Fikhman [51] noted a significant improvement in the physical status of patients with ICCD due to significant improvements in the antioxidant defense system. There was a significant increase in overall antioxidant and antiradical activity of the blood serum, decreased content of lipid peroxidation products (primary conjugated hydroperoxides and Schiff bases), and increased activity of SOD and glutathione peroxidase; i.e., the balance between prooxidant and antioxidant systems was restored. At the same time, 70.4% of patients reported improved quality of life on a specially developed scale assessing the quality of life of elderly patients with visual impairment.

Retinalamin was used in patients with peripheral retinal pigment abiotrophy at 5 mg parabulbarly daily for 10 days, repeating similar courses twice a year for 7 years [61]. A significant increase in the thresholds of light sensitivity, decreased electrosensitivity thresholds of the retina, the normalization of the Arden index of the ratio between the light and dark potentials, and increase in the average amplitude of the wave B on the electroretinogram were established; visual acuity increased by a few tenths of conventional units in 62.5% of patients. It is important to note that regular use of Retinalamin helped to stabilize the disease process: deterioration of visual functions was marked in no patients.

Retinalamin at 5 mg parabulbarly and Cortexin at 10 mg intramuscularly were used for 10 days for the treatment of patients 61–82 years of age with senile macular degeneration of the retina, which resulted in a significant improvement in the picture of the fundus in 71.1% of patients expressed in the disappearance of hemorrhages and reduction of the macular edema zone. Acuity improved from 79.5% of patients (including in 46.4% at 0.2–0.4), and central scotomas decreased by 77.9% [85, 86].

S.V. Kharintseva conducted research on the effectiveness of Retinalamin application in the treatment of diabetic retinopathy, macular degeneration, thrombosis of arteries and veins of the retina (the central artery of the retina (CAR)), and circulatory disorders of the disk of the optic nerve in more than 700 patients, of whom 72% were patients of elderly and senile ages [74–76]. Under the influence of Retinalamin in patients with macular degeneration and preproliferative and proliferative diabetic retinopathy, the content of proinflammatory cytokines in the tear fluid was close to normal ranges. The therapy with Retinalamin and Cortexin in all examined patients showed a significant increase in antioxidant activity in the blood and in tears. This significantly increased visual acuity, which even 10 years later was 2.5 times higher in patients who received Retinalamin than in the control group. In patients with post-thrombotic retinopathy who received no bioregulators, visual acuity decreased by 57% over 10 years of follow up due to the development of atrophic processes in the macular region and progressive clouding of the lens. Visual acuity remained virtually unchanged in patients treated twice a year with courses of Retinalamin. There were 77 patients with acute disorders in the CAR and its branches. Decreased visual acuity in the control group was due to the development of secondary optic atrophy. The number of nerve fibers in the optic nerve decreased by 30–56% according to optical coherence tomography. Patients treated with Retinalamin and Cortexin for three years in courses twice a year showed no reduced visual function, and the decrease in the number of nerve fibers was only 23–27%.

Results from clinical studies indicate a geroprotective effect of Retinalamin and prospects and reasonability of its application for the treatment of patients of elderly and senile age with degenerative–dystrophy diseases of the retina, as well as for the prevention of complications of eye injuries, diabetes, and other diseases [29].

PROSTATILEN (SAMPROST)

Prostatilen (Samprost) is a preparation of polypeptide nature derived from the prostate gland of animals [36, 70]. The drug reduces edema and leukocyte infiltration and thrombosis of the venules of the prostate gland, normalizes the secretory function of epithelial cells, increases the amount of lecithin granules in the acini secret, and stimulates the muscle tone of the bladder [62]. Prostatilen was allowed for medical application by the Ministry of Health of the Russian Federation by order no. 329 of December 17, 1992 (Registration number 92/329/7).

Clinical studies showed the high efficiency of Prostatilen for the treatment of patients with acute exacerbation of chronic prostatitis and benign prostatic hyperplasia (BPH), which affects more than 70% of men older than 50 years. Thus, 307 patients 18–70 years old with exacerbation of chronic prostatitis were prescribed the drug at a dose of 5 or 10 mg intramuscularly daily for 10 days. Within 6 months follow-up, 55.4% of patients had stable disappearance of pain and dysuria and sexual function improved [49]. It is important to note that of the 230 patients who complained of sexual dysfunction, 102 pointed to its full recovery and 96 people noted its improvement. Patients with stage I–II disease displayed full recovery of urination parameters, and a noticeable increase in the urine stream was observed in patients with stage III. In this case, the size and consistency of the prostate by palpation and ultrasonography normalized, and the number of leucocytes in the urine, semen, and prostate secretion decreased. It should be emphasized that the use of Prostatilen was accompanied by a significant reduction or complete disappearance of microorganisms in prostatic secretions due to the stimulation of humoral immunity and increased phagocytosis.

The most common manifestation of chronic prostatitis is a disorder of urination. Studies have shown that the inclusion of Prostatilen in complex treatment of patients with chronic prostatitis contributes to the disappearance or improvement of dysuria in 95% of patients [5, 7]. The authors also showed an increase in the sperm count from 78.5 to 98.9% and a decrease in the number of pathological forms of sperm cells from 44.9 to 36.7%. Important for the treatment of patients with chronic prostatitis is the presence of immunomodulatory properties in Prostatilen: the number of T-lymphocytes increased 13% and the content of IgG

1.7 times, and the B-cell count and functional activity of natural killer cells normalized in patients during the course of application of the preparation. Microcirculation in the prostate gland was established to improve under the influence of Prostatilen, especially because of increased venous outflow (according to rheography) [2].

Clinical improvement was observed in 53.5% of patients with BPH stage I–II with a minimal amount of residual urine (to 100 mL) [2]. The authors conducted a study of the effectiveness of Prostatilen in patients with BPH in the preoperative period to reduce the incidence of postoperative coagulopathy. Patients were prescribed Prostatilen at 5 mg intramuscularly once a day for 5 days prior to surgery. The results of coagulation studies after surgery showed reduced clotting time of the whole blood and the plasma recalcification time, an increase in the platelet count and the fibrinogen content, shortening of clotting time, and a decrease in the fibrinolytic activity of whole blood of patients treated with Prostatilen as compared with the control group. These positive changes in coagulogram were accompanied by shortening of the postoperative period.

S.Kh. Al'-Shukri et al. [1, 2] used Prostatilen at a dose of 5 mg/day every day for 5 days for the treatment of patients with chronic primary and secondary pyelonephritis. Improvement in the subjective condition of the patients was accompanied by a decrease in the degree of leukocyturia (it remained in only 7.1% of patients with primary pyelonephritis and 28% of patients with secondary pyelonephritis), return of the erythrocyte sedimentation rate to normal levels, and a reduced content of ceruloplasmin and C-reactive protein in the blood serum. An important fact is the revealed immunomodulatory effect of Prostatilen: the ratio $CD4^+/CD8^+$, which was decreased in patients with primary pyelonephritis to 1.02 ± 0.11, reached 1.52 ± 0.21 ($p < 0.05$) after the course of the drug treatment, and the ratio $CD4^+/CD8^+$ increased from 1.06 ± 0.12 to 1.39 ± 0.18 ($p < 0.05$) in patients with secondary pyelonephritis. An increase in the leukocyte migration inhibition rate in the presence of concanavalin A was marked indicating an increase in the functional activity of T-lymphocytes, and an increased content of B-lymphocytes and the normalization of ratios of B-cell subpopulations were observed. In addition, in patients with pyelonephritis, under the influence of Prostatilen there was a decrease in the severity of hypercoagulation of blood characteristic of this disease.

There is no doubt that in its properties Prostatilen that normalizes the function of the urogenital system in men can be attributed to geroprotectors aimed at improving the quality of life of men at elderly and senile ages.

CONCLUSIONS

This review summarizes some of the results of clinical study of a new class of drugs—peptide bioregulators created by a team of scientists under the direction of V.Kh. Khavinson indicating their high efficacy in the treatment of various diseases, including age-related pathology [54, 83, 84]. Timalin, Epithalamin, Prostatilen, Cortexin, Retinalamin, and Thymogen have been used for 30 years in clinical practice; more than 15 million people have received the agents during this time, while there was no evidence of side effects of the drugs or complications after their application. Hence, long-term experience of experimental and clinical studies have demonstrated the prospects of the use of these drugs—peptide geroprotectors based on extracts from animal tissues or their synthetic analogues, which can significantly enhance the effectiveness of treatment of many pathologies, including age-related pathologies, increase the vital resource of the organism, and improve the quality of life, especially in people of older age groups.

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