Efficiency of Potentiated Antibodies to Tumor Necrosis Factor-α (Artrofoon) in the Therapy of Patients with Rheumatoid Arthritis

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Antiinflammatory activity of a new preparation Artrofoon (antibodies against tumor necrosis factor-α in ultralow doses) and nonsteroid antiinflammatory drug diclofenac in patients with rheumatoid arthritis was compared in an open randomized trial. The course of treatment with Artrofoon more significantly improved clinical and laboratory signs in patients with the articular form of rheumatoid arthritis than diclofenac.

Key Words: *rheumatoid arthritis; antibodies to tumor necrosis factor-α; ultralow doses; Artrofoon*

Rheumatoid arthritis (RA) is an urgent problem of modern rheumatology. The incidence of RA in able-bodied men of various counties is 0.3-1.5%. RA is a chronic progressive disease most common in young people. Published data show that 3 and 5 years after onset the disease causes disability in 38 and 50% patients, respectively [1,2].

RA is a systemic disease of the connective tissue. The major pathogenetic phenomenon of RA is immune inflammation associated with immune dysregulation. RA is accompanied by the inhibition of T suppressor cells and activation of T helper lymphocytes. These changes contribute to stimulation of B lymphocytes, uncontrolled production of autoantibodies, imbalance between secretion of cytokines with proinflammatory and antiinflammatory properties, and intensive synthesis of proinflammatory macrophageal cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1, interleukin-6, and interleukin-8 [5].

The role of TNF-α in the development of immune inflammation attracts much recent attention. The biological effects of TNF-α are realized via type 1 transmembrane receptors expressed on leukocytes, endothelium, and fibroblasts. TNF-α binds to these receptors and regulates secretion of proinflammatory cytokines and inflammatory mediators. TNF-α stimulates the synthesis of prostaglandins, platelet-activating factor, and superoxide radicals of metalloproteinases, induces secretion of proinflammatory cytokines, and stimulates the growth of new vessels (neoangiogenesis) and proliferation of fibroblasts that play an important role in the pathogenesis of RA. RA is accompanied by uncontrolled overproduction of TNF-α [2,3,5].

New methods for the therapy of patients with RA are developed taking into account the pathogenetic mechanisms of this disease. Antiinflammatory drugs play a major role in the therapy of patients with RA. However, the progressive and self-maintaining course of rheumatoid inflammation requires continuous treatment with nonsteroid antiinflammatory preparations (NAIP) and, more rarely, with glucocorticosteroids (GCS). Long-term treatment with NAIP and GCS causes various side effects. The most common and severe complication of treatment is NAIP- and GCS-associated gastropathy. Published data show that gastroduodenal complications of antiinflammatory therapy are the main cause of death in patients with RA. The search for new medicinal preparations highly competitive with NAIP in antiinflammatory activity and not causing side effects is an urgent problem.

Preparations of antibodies against TNF-α blocking the effect of this proinflammatory cytokine hold much promise for the therapy of patients with RA. Remicade (Infliximab) containing monoclonal antibodies against TNF-α was first approved for the use in medical practice. Studies performed primarily in foreign countries revealed high antiinflammatory activity and immunomodulatory effect of Remicade during RA. The use of this preparation in medical practice was substantiated [6,7]. However, the course of treatment with Remi-

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cade suggests repeated intravenous injections at 4-8-week intervals (5-6 procedures), which may produce allergic reactions. It should be emphasized that Remicade causes serious side effects, including development of opportunistic infections, lymphoproliferative processes, and lupus-like syndrome, formation of delayed-type hypersensitivity, and production of antichimeric antibodies. Moreover, there are numerous contraindications for treatment with this preparation.

A new preparation Artrofoon containing antibodies against TNF-α in ultralow doses holds promise for antiinflammatory therapy of patients with RA. Antibodies against TNF-α were subjected to potentiation to enhance their biological activity. Published data show that potentiated antibodies modify the antigen. They regulate activity of the corresponding antigens that act as biologically active substances. Previous experiments on animals with immune inflammation revealed the antiinflammatory effect of affinely purified antibodies against TNF-α in homeopathic dilution.

Artrofoon was approved by the Russian Pharmacological Committee (March 28, 2001) for the use in medical practice as an antiinflammatory and analgetic drug. However, there are no data on the efficiency and safety of this preparation during the therapy of patients with RA.

Here we studied therapeutic efficiency and safety of Artrofoon in patients with RA.

MATERIALS AND METHODS

We examined 30 patients with RA that were under rheumatologist's supervision at the Clinics of Faculty Therapy (Volgograd Medical Academy). The diagnosis of RA was verified by criteria of the American Association for Rheumatology. Observations were performed on patients with classic or reliable RA. The patients with possible RA were not examined.

We examined 28 women and 2 men (29-60 years). The duration of RA was 5-22 years. The clinical variant of RA was characterized by polyarthritis with symmetric damage (primarily to the joints of the hands) and other signs of the disease: morning stiffness, exudation in the metacarpophalangeal joints II-III, amyotrophy in damaged joints, and ulnar deviation of the hands (in most patients).

Clinical and laboratory signs of the inflammatory process corresponded to degrees II-III. Roentgenologic signs corresponded to stages 1-3 of the disease (by Schteinbroker). Most patients had stage 2-3 RA characterized by narrowing of the joint space and presence of usuras. Rheumatoid factor was detected in the blood from 11 patients (seropositive RA); 19 patients had seronegative RA.

Before examination the patients perorally or rectally received NAIP. NAIP were withdrawn from treatment 2 days before the start of Artrofoon therapy. Previously, 12 patients parenterally received GCS (Kenalog and Diprospan, intraarticularly or paravertebrally). Three months before examination these preparations were withdrawn. We verified the diagnosis of RA, estimated its clinical variant, severity, and stage of the process, and excluded associated disease. The patients were subjected to clinical examination that included standard laboratory tests (analysis of the blood and urine, rheumatologic tests, and assay of functional parameters in the liver and kidneys) and instrumental observations (roentgenography of thoracic organs and joints, ultrasonography of abdominal organs, and electrocardiography).

The patients were divided into 2 groups. The main group included 15 patients that sublingually received 2 tablets of Artrofoon for 6 months (4 times a day). Control patients were treated with diclofenac in a daily dose of 100 mg.

The efficiency of therapy was estimated by clinical and laboratory criteria recommended by the Russian Ministry of Health for tests of antirheumatic drugs. We determined the severity of exacerbation (increase in the degree of arthralgias, exudation, and morning stiffness and formation of damage to other joints), development of undesirable effects, and their relationship with intake of the preparation. Tolerability of Artrofoon was evaluated.

We estimated the arithmetic mean and confidence interval. The results were analyzed by Student's *t* test.

RESULTS

Patients of the main and control group did not differ in the initial severity of clinical symptoms and laboratory signs. Therefore, the severity of RA and joint inflammation was comparable in these patients (Table 1).

Average values of 6 of 8 clinical symptoms changed in patients receiving Artrofoon. The articular score and number of swollen joints insignificantly decreased. The functional index of Li underwent less pronounced changes. The severity of pain syndrome, duration of morning stiffness, Ritchie index, index of swelling, and diameter of damaged joints decreased.

C-reactive protein (CRP) concentration was the only laboratory sign that underwent considerable changes. The erythrocyte sedimentation rate (ESR) and plasma globulin content tended to decrease. Albumin content in proteinogram increased. Rheumatoid factor (RF) titer remained unchanged.

Initial parameters in control patients did not differ from those in patients of the main group (Table 1). Six-month therapy had no effect on clinical and labo-

TABLE 1. Clinical and Laboratory Signs in Patients Receiving Artrofoon and Diclofenac (*M*±*m*)

Parameter	Main group		Control group	
	initial	after 6 months	initial	after 6 months
Total severity of pain, points	1.73±0.12	1.01±0.09* (13, 86.7)	1.68±0.16	1.45±0.21 (6, 40)
Duration of morning stiffness, min	150.66±18.00	88.00±13.43* (14, 93.3)	144.66±15.93	113.32±16.15 (7, 46.6)
Ritchie articular index, points	18.93±2.10	13.1±1.8** (12, 80)	24.47±2.44	21.02±2.61 (5, 33.3)
Articular score (abs. number)	20.66±2.10	16.46±2.07 (11, 73.3)	21.34±2.19	18.36±2.09 (4, 26.7)
Swelling index, points	16.8±2.7	10.01±1.69** (11, 73.3)	17.65±2.29	15.78±2.43 (4, 26.7)
Li functional index	17.00±1.73	14.27±1.38 (7, 46.6)	20.43±3.01	18.12±2.97 (3, 20)
Number of swollen joints (abs. number)	9.93±1.77	5.93±1.14 (9, 60)	11.08±2.17	9.39±2.44 (3, 20)
Diameter of swollen joints (difference)	0.96±0.25	0.38±0.10** (9, 60)	1.34±0.18	1.23±0.17 (2, 13.3)
Leukocytes	6.44±0.44	6.32±0.27 (2, 13.3)	6.42±0.41	5.89±0.50 (1, 6.7)
ESR	333.60±3.99	28.33±2.53 (6, 40)	31.87±3.55	32.80±4.13 (3, 20)
Albumins	44.59±1.40	46.0±0.7 (2, 13.3)	46.06±1.23	48.13±1.19 (4, 26.7)
Globulins	55.20±1.44	54.0±0.7 (2, 13.3*)	53.83±1.24	51.77±1.18 (4, 26.7)
CRP	133±0.22	0.530±0.135* (12, 80)	1.12±0.22	0.77±0.24 (4, 26.7)
RF (titer, geometric mean)	0.63±0.20	0.60±0.19 (1, 6.7)	0.67±0.19	0.67±0.19 (0, 0)

Note. *p<0.01 and **p<0.05 compared to the initial value. Number of patients with positive changes is shown in brackets (abs. number, %).

ratory signs. The average duration of morning stiffness and, to a lesser degree, severity of other clinical symptoms tended to decrease (statistically insignificant). We evaluated the number of patients in the main and control groups characterized by considerable changes in test parameters (compared to the initial level, Table 1).

Signs of NAIP-associated gastropathy were revealed in 4 control patients (26.7%), which required treatment with antisecretory drugs. Laboratory signs of Artrofoon-produced hepato- and nephrotoxicity were not observed in patients of the main group.

There were no patients with exacerbation of the disease that required a decrease in the dose of Artrofoon or its temporal withdrawal. In 2 patients the severity of pain in the joints slightly increased on day 3 of treatment. However, joint pain was reduced on days 4-5 without decreasing the dose of Artrofoon. The preparation did not cause other side effects.

After therapy with Artrofoon major clinical symptoms were improved more significantly than in control patients. The severity of joint pain and morning stiffness, articular score, and functional index decreased in a greater number of patients from the main group (compared to the control). The differences in laboratory signs were less pronounced. However, ESR and CRP content in patients of the main group decreased more frequently than in the control. Positive changes in test parameters depended on the duration of Artrofoon therapy. The severity of joint pain decreased in 2 (13.3%), 9 (60%), and 13 (86.7%) of 15 patients re-

ceiving Artrofoon for 1, 3, and 6 months, respectively. Other clinical signs of the disease underwent similar changes (Fig. 1).

Ten (66.7%) and five patients (33.3%) considered the results of Artrofoon therapy as good and satisfactory, respectively. According to evaluation of physicians, Artrofoon produced good and satisfactory effects in 9 (60%) and 6 patients (40%), respectively. It should be emphasized that none of the patients evaluated Artrofoon therapy as excellent. However, none of the patients suffered from aggravation of the symptoms or considered that Artrofoon is ineffective.

Artrofoon most significantly affected clinical signs associated the inflammatory process. Pain that accompanies RA has the inflammatory origin and correlates with the severity of pathological changes. A decrease in the severity of joint inflammation is followed by the reduction of arthralgia. The articular score decreased in patients of the main group, which indicates that the severity of rheumatoid inflammation was reduced.

The duration of morning stiffness associated with synovitis, intraarticular exudation, and inflammation of the periarticular apparatus underwent similar changes. Shortening of morning stiffness may be related to a decrease in the severity of inflammation in periarticular soft tissues. These changes probably contribute to a decrease in the index of swelling, diameter of damaged joints, Ritchie index, and number of swollen joints.

The articular score and functional index of Li changed less significant. These parameters reflect not only the severity of inflammation, but also irreversible organic and functional changes in the joints. It is unlikely that antiinflammatory therapy may affect these changes in patients with long-term disease.

The therapeutic effect of Artrofoon depended on the duration of treatment. Positive changes were observed only by the 3rd month of therapy and became most pronounced after 5-6 months.

Our results indicate that Artrofoon possesses antiinflammatory properties and relieves the major symptoms of inflammation during RA. Clinical tests showed that Artrofoon surpasses diclofenac in antiinflammatory activity. The effective daily dose of Artrofoon given sublingually is 8 tablets (4 treatments). The therapy should be performed for no less than 3 months. The persistent positive effect is achieved after 6-month therapy with Artrofoon. Artrofoon does not cause side effects that would require its withdrawal or treatment with other medicinal preparations. Artrofoon holds promise for antiinflammatory therapy of patients with the articular form of RA.

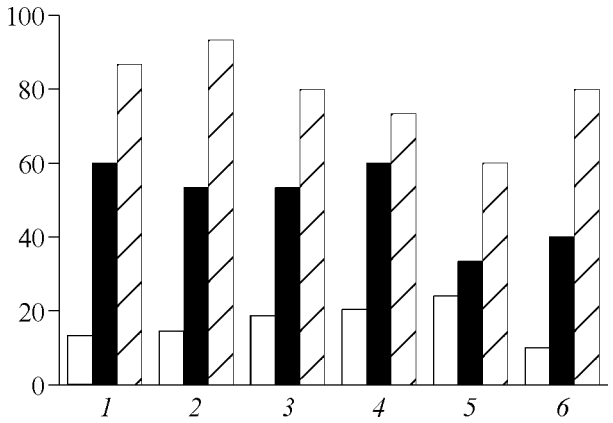

Fig. 1. Dependence of positive changes in clinical and laboratory signs on the duration of Artrofoon therapy. Light bars: 1 month. Dark bars: 3 months. Shaded bars: 6 months. Total severity of pain (*1*), duration of morning stiffness (*2*), Ritchie articular index (*3*), swelling index (*4*), diameter of swollen joints (*5*), and C-reactive protein content (*6*). Ordinate: ratio of patients with positive changes.

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