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

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We studied the efficiency and safety of a new homeopathic preparation Artrofoon containing affinely purified antibodies to tumor necrosis factor-α in the therapy of patients with rheumatoid arthritis. Artrofoon produced a positive antiinflammatory effect on the course of rheumatoid arthritis. This preparation reduced the severity of arthralgia (indexes of Li and Ritchie) and morning stiffness and decreased the erythrocyte sedimentation rate and contents of rheumatoid factor and C-reactive protein. One-month therapy improved the state of patients. Artrofoon was well tolerable. The preparation did not cause the ulcerogenic and nephrotoxic effects. Artrofoon holds much promise for combination therapy of patients with rheumatoid arthritis (including severe articular-and-visceral forms) and complications after treatment with nonsteroid antiinflammatory preparations.

Key Words: *rheumatoid arthritis; secondary AA amyloidosis; tumor necrosis factor-α; tumor necrosis factor-α inhibitor*

Rheumatoid arthritis (RA) is a common disease whose incidence reaches 1%. Difficulties in the therapy of this disorder are related to a variety of its clinical variants, unknown etiology, and multifactor pathogenesis.

RA is a systemic immunoinflammatory disease with primary damage to the synovial tissue of joints. The development of synovitis in patients with RA is associated with the action of autoreactive T lymphocytes. They initiate inflammation and destructive processes in the joints via recruitment and stimulation of macrophages, B lymphocytes, fibroblast-like synoviocytes, and endothelial cells [1,2]. These cells secrete various inflammatory mediators (arachidonic acid metabolites, chemokines, adhesive molecules, cytokines, and growth factors) and matrix-degrading enzymes (metalloproteases, aggrecanase, and cysteine proteases) that play a role in the pathogenesis of chronic inflammation. These substances enhance proliferation and transformation of synoviocytes and promote growth of the hyperplastic synovial tissue into adjacent regions, which contributes to destruction of the articular cartilage in subchondral bone, tendons, and ligaments [8]. Destructive changes in the articular cartilage are the early manifestation of RA. Modern therapy of patients with RA suggests effective and early suppression of synovitis for the prevention or attenuation of destructive processes in the joint.

In recent years the therapy of patients with rheumatoid synovitis includes modulation of proinflammatory cytokine activity, *e.g.*, inhibition of tumor necrosis factor-α (TNF-α). Under normal conditions this macrophageal cytokine regulates the interaction between immune cells. Experimental and clinical observations indicate that TNF-α plays an important role in the pathogenesis of RA [5].

TNF-α causes inflammation and tissue damage in patients with RA. This agent affects other proinflammatory cytokines (*e.g.*, interleukin-1 (IL-1), IL-6, and IL-8) and granulocyte/macrophage colony-stimulating factor, mobilizes inflammatory cells via the regulation of adhesive molecules on endothelial cells or co-stimulatory influence, activate various cells, and stimulates secretion of matrix metalloproteinases and production of oxygen radicals by neutrophils, macrophages, and chondrocytes [3].

TNF-α is produced in a form of the transmembrane precursor protein. Cleavage with convertase results in its conversion into the soluble form, which binds to p55 (TNF-RI) or p75 receptors (TNF-RII) on the cell surface and produces various biological effects. The extracellular domain of TNF-α receptors may undergo cleavage with convertase with the formation of soluble TNF-S that act as natural inhibitors of this cytokine [1].

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Pharmacological inhibitors of TNF-α synthesized from monoclonal antibodies to TNF-α (Infliximab) and TNF-α receptors (Etanercept) are used for the therapy of patients with moderate and severe RA. These preparations are administered parenterally in combination with methotrexate. However, they cause side effects. The search for new pharmaceutics blocking TNF-α in patients with RA is an urgent problem.

Artrofoon containing antibodies to TNF-α and synthesized at the "Materia Medica Holding" Research-and-Production Company underwent an open clinical trial in patients with RA.

Here we evaluated the efficiency and safety of this preparation in patients with complicated RA.

MATERIALS AND METHODS

The preparation Artrofoon containing ultralow doses of antibodies to TNF-α was synthesized by the homeopathic technology. We examined 12 patients with severe complicated RA (4 men and 8 women, 38-68 years, 52.4±2.7 years) admitted to the Hospital of Nephrology, Internal Diseases, and Occupational Diseases (I. M. Sechenov Moscow Medical Academy). The diagnosis was made by American Rheumatologic Association criteria for RA.

The stage and severity of RA was determined by the duration of morning stiffness (min), indexes of Li (functional state of joints, points) and Ritchie (pain and swelling, points), roentgenologic signs of damage to the joints, and laboratory parameters (erythrocyte sedimentation rate, ESR; rheumatoid factor content; and hyper- or hypoproteinemia).

Three of 12 patients had adult-onset Still syndrome. Two of these patients (1 man and 1 woman) were hospitalized with fever (38.5-39.0°C) persisting for 4 and 9 months. The diagnosis was made for the first at the hospital. In 1 woman the diagnosis of RA was made 4 years ago. In this patient fever (39-40°C) persisted for the past 1.5 years, which was accompanied by the increase in ESR (70 mm/h) and severe joint-and-muscle pain syndrome. In 7 patients with RA and 2 patients with peripheral ankylosing spondylitis, the disease ran a mild or severe course for 4-22 years before the start of Artrofoon therapy (14.40± 2.03 years) and caused visceral complications. Three patients with RA had fibrosing alveolitis (FA). In these patients periodic exacerbations of FA did not necessarily proceed in the acute stage of joint syndrome. In 4 patients with RA and 2 patients with severe joint syndrome the disease was complicated by AA amyloidosis with primary damage to the kidneys. During observations nephrotic syndrome, moderate proteinuria, and early symptoms of renal failure were found in 5, 1, and 2 patients, respectively. Patients with long duration of the disease received standard drugs. However, the therapy was low effective or badly tolerable. Before the start of observations 6 patients with AA amyloidosis were treated with methotrexate (5.0-7.5 mg/week) and colchicine (0.5-2.0 mg/day) for no less than 6 months. Supportive therapy of 3 patients with FA included prednisolone in a daily dose of 5.0-7.5 mg. The patients with persistent pain in the joints received not only standard drugs, but also nonsteroid antiinflammatory preparations (NAIP).

One of 3 patients with adult-onset Still syndrome received Delagil for 2 weeks before the start of observations, which did not affect the severity of fever. Two patients with adult-onset Still syndrome did not receive standard therapy. One woman had RA for 4 years that was accompanied by prolonged fever. Since previous treatment with standard preparations were ineffective or caused side effects, this patient received only antipyretics and NAIP. Monotherapy with Artrofoon was prescribed to 2 patients not receiving standard preparations. Other patients received combination therapy with standard preparations and Artrofoon. NAIP were withdrawn 2 days before the start of Artrofoon therapy.

The patients received Artrofoon sublingually up to complete dissolution. Four tablets of Artrofoon were given at equal intervals in the morning. If the therapy was low effective over the first 10 days, the dose of Artrofoon increased to 6-8 tablets. After achieving persistent changes, the daily dose of Artrofoon was reduced to 1-2 tablets (supportive therapy). The course of treatment lasted 6 months.

RESULTS

Artrofoon therapy was effective in 8 of 12 patients with RA (66%). Positive changes were observed in 2 of 3 patients with adult-onset Still syndrome and 6 of 9 patients with articular-and-visceral form of the disease (2 patients with FA and 4 patients with amyloidosis). The severity of RA decreased on day 10 of treatment. Artrofoon therapy improved the state of patients after 1-2 months.

Over the first 10 days of therapy body temperature returned to normal in 2 patients with adult-onset Still syndrome, including 1 woman with prolonged fever (1.5 years) refractory to various preparations. In this patient monotherapy with Artrofoon in a daily dose of 8 tablets reduced fever. The severity of pain and swelling in the joints decreased by 30.4 and 22.5%, respectively (30-70 and 15-50%, respectively, Ritchie index). The degree of morning stiffness decreased by 30% (0-60%), while the volume of movements in the joints increased by 20% (0-40%, Li index). It should be emphasized that NAIP were com-

pletely withdrawn. The demands for NAIP therapy were considered as a criterion for low efficiency of Artrofoon.

In 4 patients the severity of pain in the joints increased on days 4-5 of treatment. However, joint pain persisted for no more than 10-18 h and did not require Artrofoon withdrawal.

One-month therapy with Artrofoon progressively relived the symptoms of arthritis. The Ritchie index characterizing pain and swelling decreased by 62 and 57%, respectively (up to 85-100%). The degree of morning stiffness decreased by 65%; in some patients this symptom disappeared. The Li index reflecting functional activity in the joints was improved by 36% (up to 67%). Symptomatic improvement in patients with RA was accompanied by the decrease in ESR. These changes were especially pronounced in 2 patients with adult-onset Still syndrome (from 60 to 15 mm/h and from 70 to 25 mm/h) and less significant in patients with renal damage and nephrotic syndrome. The content of C-reactive protein in the plasma decreased by 30%; in 3 patients this compound was undetectable. Rheumatoid factor (RF) level decreased by 25%.

Erosive changes in the joints were determined roentgenographically by the end of treatment. A direct relationship was found between the effect of Artrofoon on main symptoms of RA and dose of the preparation. One-month therapy with Artrofoon produced the excellent, good, and satisfactory effect in 1, 5, and 2 patients, respectively (as evaluated by patients and physicians). In 5 of these patients the positive effect of Artrofoon was achieved after the increase in its daily dose from 4 to 8 tablets over the first 10 days of treatment. Two patients demonstrated a good response to Artrofoon in a daily dose of 4 tablets. A decrease in the dose of this preparation after 1-month therapy was followed by exacerbation of joint syndrome and increase in the Ritchie index to an initial level. Increasing the dose of Artrofoon to 6-8 tablets produced a decrease in the Ritchie index. In 1 patient with adult-onset Still syndrome and fever persisting for 1.5 years before the start of therapy, the decrease in a daily dose of Artrofoon from 6-8 to 4 tablets caused 2 exacerbations of the disease (increase in body temperature, stiffness, and pain in the joints).

Physicians evaluated the results of 1-2-month therapy with Artrofoon as unsatisfactory in 4 patients. However, the preparation was actually ineffective only in 1 of 3 patients with adult-onset Still syndrome receiving Artrofoon monotherapy. Treatment of 3 patients with Artrofoon in a daily dose of 4 tablets initially relived joint syndrome and reduced pain by 30, 20, and 33%, respectively (Ritchie index). In 2 patients functional activity of the joints was improved by 25 and 34%, respectively (Li index). However, further therapy with Artrofoon in this dose did not produce the positive effect. Periodic treatment with NAIP in a lower dose was prescribed. Our observations indicate that Artrofoon therapy was not absolutely ineffective in these patients.

Published data show that the effect of parenteral antibodies to TNF-α (Infliximab) is more pronounced after administration of the preparation in high doses [5]. However, the appearance of antibodies to Infliximab may reduce its effect. In some instances Infliximab withdrawal is accompanied by exacerbation of RA.

Artrofoon is well tolerable and does not produce the ulcerogenic, bronchospastic, and nephrotoxic effects. By contrast, in 2 patients with FA the severity of dyspnea decreased after Artrofoon therapy. In 6 patients with RA complicated by AA amyloidosis functions of the kidneys remained unchanged after treatment with Artrofoon. In 1 of 2 patients with renal insufficiency creatinine content decreased from 2.2 to 1.7 mg/l after 2-week therapy with Artrofoon. These changes were probably related to withdrawal of NAIP, which may produce adverse effects on the tubulointerstitial apparatus in the kidneys with the development of tubulointerstitial nephritis. In 2 patients with renal amyloidosis urine protein content decreased by 50%, while blood albumin level tended to increase. It was probably associated with the anti-amyloid effect of colchicine and attenuation of changes in the tubulointerstitial apparatus after NAIP withdrawal.

These observations indicate that Artrofoon containing ultralow doses of the active substance holds much promise for the therapy of patients with RA. The advantages of this preparation are simplicity of treatment, well tolerability, and absence of ulcerogenic and nephrotoxic activities. Artrofoon may be used for the therapy of patients with severe visceral forms of RA, including those complicated by AA amyloidosis.

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