Efficiency and Safety of Long-Term Artrofoon Treatment in Rheumatoid Arthritis

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In patients with rheumatoid arthritis, prolongation of artrofoon therapy to 2 years led to maintenance of the positive clinical effect attained after 6-month treatment. Moreover, significant improvement was observed by some parameters (integral pain intensity, swelling index, Ritchie articular index, morning stiffness, and articular score). No side effects related to artrofoon treatment were observed throughout the treatment period in the main group. The results indicate high efficiency and good tolerability of the preparation and attest to advisability of its long-term use.

Key Words: *rheumatoid arthritis; proinflammatory cytokines; tumor necrosis factor-a; artrofoon*

Disturbances in the cytokine network regulation characterized by excessive synthesis of proinflammatory cytokines are important elements in the pathogenesis of rheumatoid arthritis (RA). An important role in chronic transformation of the immunopathological process and development of destructive changes in joints is played by TNF-α [5]. These data provided the basis for the use of biological methods of therapy, primarily, application of TNF-α antagonists blocking biological activity of this cytokine in the circulation and at the cellular level [3]. At the same time, parenteral route of administration under clinical setting, the risk of serious side effects, and high price limit the use of this therapy.

A series of recent clinical studies demonstrated high efficiency of artrofoon, a preparation containing ultralow doses of antibodies to TNF-α, in patients with RA. The preparation produces a potent effect on the main symptoms of articular inflammation; moreover, the positive clinical and laboratory dynamics is associated with reduced production of some proinflammatory cytokines [1,2].

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Here we evaluated the efficiency and safety of long-term artrofoon therapy in patients with RA.

MATERIALS AND METHODS

This study was a continuation of an open comparative randomized trial carried out in Volgograd State Medical University and enrolling 60 patients (30 patients received artrofoon and 30 patients received diclofenac) with documented RA verified according to criteria of American Rheumatologic Association [6]. Artrofoon treatment was continued after completion of a 6-month course. Now we have the results of a 1.5-year observation of 20 patients; of them the treatment was ceased in 13 patients (2 years of therapy), while other patients still receive the preparation.

The artrofoon group (n=30) included 28 women and 2 men aging 29-69 years. History of the disease varied from 1 to 25 years (mean 7.9 years). Clinical variant of RA was characterized by polyarthritis with clear-cut symmetry, predominant involvement of hand joints, and symptoms typical of RA: morning stiffness, exudation in 2-3 metacarpophalangeal joints, amyotrophy in the zone of involved joints, and ulnar deviation of the hand in the majority of patients. Clinical and

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anatomic variant of RA in the form of polyarthritis was diagnosed in 22 patients; oligoarthritis was diagnosed in only 6 patients. Twenty-two patients had moderate inflammation (II degree) and 8 patients had severe inflammation (III degree, maximum). Seropositive and seronegative variants of RA were observed in 16 and 14 patients, respectively. Steinbrocker X-ray stage varied from I to IV. X-Ray examination revealed stage I RA (paraarticular osteoporosis) in 2 patients, stage II RA (narrowing of the joint cleft and solitary usures) was observed in 15 patients, stage III RA (narrowing of the joint cleft and multiple usures) and stage IV RA (the same plus ankyloses) were found in 11 and 2 patients, respectively. Analysis of the clinical course of the disease and data of X-ray examination revealed slowly and rapidly progressing RA in 24 and 6 patients, respectively. Functional insufficiency of the first, second, and third degree was diagnosed in 5, 20 and 5 patients, respectively.

All patients received nonsteroidal antiinflammatory drugs before the study; these drugs were withdrawn 2 weeks before the start of artrofoon treatment. Only 6 patients received basis therapy: 5 patients were treated with methotreaxate and 1 patient received placvenil. Artrofoon was administered in a dose of 2 tablets 4 times a day.

The efficiency of artrofoon was evaluated during dynamic observation by the data of examination performed 6, 12, 18, and 24 months after the start of treatment. Reduction of inflammation in involved joints and significant decrease in clinical and laboratory signs of inflammation served as the criteria of treatment efficiency. The following parameters were taken into account: integral intensity of joint pains, duration of morning stiffness, joint score (absolute number of involved joints), Ritchie articular index, swelling index, number of swelled joints, Lee functional index, ESR, and the content of C-reactive protein (CRP) [4]. The efficiency of treatment was also evaluated according to criteria of European Antirheumatic Society (DAS) including assessment of pain during palpation (Ritchie articular index), number of swelled joints, and ESR.

The means and standard deviations were calculated, parametric Student *t* test for dependent variables and nonparametric Wilcoxon *U* test were used.

RESULTS

After artrofoon therapy for 6 months we observed significant improvement in the following parameters: integral pain intensity (by 44.3%), morning stiffness (by 37.2%), Ritchie index (by 27.3%), swelling index (by 42.3%), joint score (by 24.2%), Lee functional index (by 13.6%), ESR and CRP (by 34.1%; Table 1). After 6 months, moderate response to artrofoon treatment according to DAS criteria was observed in 50% patients (Fig. 1).

Prolongation of artrofoon treatment to 1-2 years demonstrated stability of the attained parameters and led to further improvement of the clinical picture. The therapeutic effect of artrofoon increased with increasing the duration of treatment (Table 1).

A tendency towards improvement of the majority of clinical and laboratory parameters was observed during a period from 6 month to 2 years, or these parameters remained at the level attained by the 6th month of treatment; no negative dynamics was noted. At the same time, some parameters (morning stiffness, joint score, and CRP content) significantly improved after 2 years of artrofoon treatment (compared

TABLE 1. Dynamics of Clinical and Laboratory Parameters in Patients with RA Treated with Artrofoon (*M*±*m*)

Parameter	Initial (*n*=30)	After 6 months (*n*=30)	After 12 months (*n*=20)	After 18 months (*n*=20)	After 24 months (*n*=13)
Integral intensity of pain, score	2.00±0.08	1.10±0.06***	1.3±0.1***	1.1±0.1**	1.08±0.08**
Morning stiffness, min	161.30±12.16	101.30±7.54***	85.5±7.7***	76.90±8.58***	68.85±7.36**
Ritchie joint index, score	18.70±1.09	13.60±1.03***	12.00±1.04***	11.50±1.28***	11.08±1.25**
Joint score	20.30±1.43	15.40±1.24***	12.30±1.18***	11.70±1.48***	10.08±1.24**
Swelling index, score	12.8±1.6	7.40±0.97***	5.80±0.91**	6.70±0.92**	5.83±0.89*
Lee functional index, score	16.70±0.91	14.40±0.85***	15.10±1.07***	15.10±1.25**	15.54±1.32
Number of swelled joints	7.10±0.91	8.70±4.15	9.40±5.07	3.70±0.41**	3.83±0.41
ESR, mm/h	32.50±2.45	28.20±1.87*	26.1±2.1**	30.10±2.89	28.92±3.19
CRP, mg/liter	13.20±0.91	9.00±0.83**	9.40±1.01*	8.10±0.73*	8.80±0.87*

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to initial values.

to 6-month course). Evaluation of the efficiency of therapy according to DAS criteria, a moderate response to 12- 18-, and 24-month artrofoon treatment was observed in 60, 64.3, and 69.2% patients, respectively. The response was absent in 40, 35.7, and 30.8% patients, respectively (Fig. 1).

Thus, the positive effect of artrofoon in RA patients attained during 6-month therapy was preserved during further treatment. After the 2-year course, a significant decrease in the major clinical symptoms (integral pain intensity, swelling index, Ritchie index, duration of morning stiffness, joint score) and positive dynamics according to DAS criteria were noted.

No side effects related to artrofoon treatment were observed throughout the treatment period in the main group.

The results indicate high efficiency and good tolerability of the preparation and attest to advisability of its long-term use.

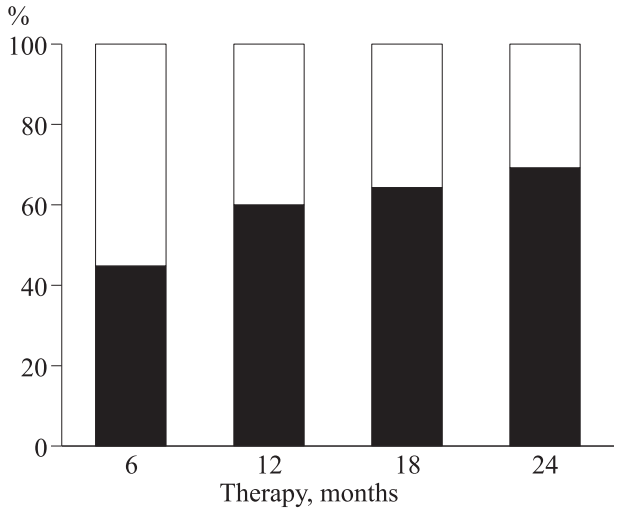

Fig. 1. Percent of patients with positive response to artrofoon according to DAS criteria. Dark bars: moderate response; light bars: no response.

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