The Use of Artrofoon in the Treatment of Ankylosing Spondyloarthritis

I. V. Kudryavtseva, L. A. Ukolova, N. N. Chizhov, N. M. Braginskaya, I. A. Istranen, and O. P. Kozhevnikov

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In patients with ankylosing spondyloarthritis, artrofoon produced a more potent antiinflammatory effect than nonsteroidal antiinflammatory drugs. The study demonstrated a positive effect of artrofoon on clinical and laboratory parameters, good tolerability of the preparation, and the absence of negative effects on the hepatic and renal functions. Being added to complex therapy, artrofoon led to a decrease in the dose of nonsteroidal antiinflammatory drugs.

Key Words: *ankylosing spondyloarthritis; tumor necrosis factor-α; artrofoon*

Ankylosing spondyloarthritis (AS) is a prevalent inflammatory disease of the spine (is observed in 0.15-2.50% population); the incidence of AS is comparable to that of rheumatoid arthritis [2,11].

AS is characterized by intensive inflammatory spinal and joint pains, limited mobility, various systemic symptoms, and considerable reduction of patient's quality of life. Standard therapy used in AS including symptomatic treatment: nonsteroidal antiinflammatory drugs (NSAID) and basis antiinflammatory drugs (BAID: sulfasalazine, methotrexate, *etc*.) insufficiently control the major symptoms of the disease [2,11].

Recent studies extended our understanding of the pathogenesis of inflammatory arthropathies and spondyloarthropathies, including AS, and provided new insight into the role of pro-/antiinflammatory cytokine imbalance and TNF-α [2]. In AS, an elevated content of this cytokine is observed in iliosacral joints and blood plasma [2]. This substantiates the use of anticytokine drugs in AS.

Open placebo-controlled randomized multicenter studies of the efficiency and tolerability of anticytokine preparations (etanercept, infliximab) clearly demonstrated their efficiency in rheumatoid arthritis and AS [3-9]. However, these preparations should be administered via the parenteral route, are expensive, and have serious side effects; these drawbacks limit the use of these drugs.

Artrofoon, a novel preparation developed in Russia, is promising for long-term treatment of AS; it contains ultralow doses of antibodies to TNF-α (a mixture of homeopathic dilutions C12, C30, C200). The efficiency and good tolerability of artrofoon in patients with rheumatoid arthritis and osteoarthrosis were previously demonstrated [1,3,4], which prompted us to use this preparation in the therapy of AS.

Here we present the results of an open study of the efficiency and tolerability of artrofoon in the therapy of patients with AS.

MATERIALS AND METHODS

We performed an open comparative study of the efficiency and tolerability of artrofoon in patients with AS treated at the Municipal Rheumatologic Center.

The study included 30 patients (26 men and 4 women); AS was diagnosed using modified New York criteria. The patients were randomly divided into 3 groups (10 patients per group) comparable by patient's sex, age, and duration and clinical form of the disease (Tables 1 and 2).

Group 1 patients, in whom previous standard therapy was low effective or to whom NSAID and/

Consultative-Diagnostic Polyclinics No. 14; Municipal Rheumatological Center, Novosibirsk; Novosibirsk State Medical Academy.

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TABLE 1. Characteristics of Patients in the Studied Groups (*M*±*m*)

Parameter		Group 1	Group 2	Group 3	Total
Number of patients		10	10	10	30
Mean age, years		46.70±3.58	39.10±3.08	46.30±3.91	44.0±2.1
History, years		11.21±2.70	10.02±2.04	13.48±2.18	11.58±1.32
Men/women		9/1	8/2	9/1	26/4
AS form	axial	7	8	10	25
	peripheral	3	2	0	5
X-ray stage of AS	I	0	0	0	0
	II	3	3	1	7
	III	4	5	5	14
	IV	3	2	4	9
AS activity degree	I	3	1	1	5
	II	7	7	8	23
	III	0	2	1	2
Locomotion impairment	I	3	1	1	5
	II	6	8	9	23
	III	1	1	0	2

or common analgesics were irregularly administered, received artrofoon monotherapy. Other preparations were withdrawn 2 weeks before the start of the study. Group 2 patients received complex therapy including standard doses of NSAID and/or BAID in combination with artrofoon. Group 3 patients received only various NSAID in adequate doses.

The patients were observed and treated over 3 months, clinical and laboratory parameters were controlled before the start and after 10 days and 1 and 3 months of treatment.

TABLE 2. Incidence of Concomitant Diseases in AS Patients

Concomitant disease	Group 1	Group 2	Group 3
Arterial hypertension	1	2	2
CHD	0	1	0
Hypothyroidism	0	1	1
Type 2 diabetes mellitus	0	1	0
Ulcer disease	3	0	0
Chronic tonsillitis	1	0	0
Joint hypermobility syndrome	1	0	1
Chronic pyelonephritis	0	1	0
Total	6	6	4

We evaluated the intensity of spinal and articular pains at rest and during motions by 100-mm visual analog scale (VAS), the degree of morning stiffness by VAS (in min), the range of motions in different parts of the spine (in cm), including Schober and Thomayer tests, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI). For evaluation of the efficiency and tolerability of therapy, the laboratory tests were performed before and 3 months after the start of treatment. Common blood tests (erythrocytes, hemoglobin, ESR) were performed and the content of C-reactive protein, bilirubin, creatinine, and activities of ALT and AST in blood serum were measured.

Artrofoon was administered for 3 months according to the following scheme: 2 tablets 4 times a day for 2 weeks; then, after attaining a positive effect (starting from week 3 on average) 1 tablet 4 times a day (sublingually until complete dissolution). In two patients of groups 1 and 2, the dose of artrofoon after the 1-month course was increased to 2 tablets 4 times per day because of low efficiency of treatment.

The data were processed statistically using nonparametric methods. The reliability of differences was evaluated using Mann—Whitney *U* test. The differences were significant at reliability level of 95% ($p<0.05$).

RESULTS

Twenty-eight of 30 patients completed the study and 2 patients dropped out due to aggravation of spinal and articular pains (1 patient from groups 1 and 2).

After 10 days and 1 month, the controlled parameters remained unchanged in all groups.

After 3 months, significant differences in some parameters were revealed in groups 1 and 2, while in group 3 all parameters remained unchanged (Table 3).

The efficiency of treatment in groups 1 and 2 receiving artrofoon significantly differed from that in group 3. In group 2 patients characterized by more refractory course of the disease and more active inflammation, the positive dynamics of the studied parameters was more pronounced compared to that in groups 1 and 3 (Table 3). Better results in patients of this group can be explained by the fact that they received complex therapy (methotrexate, 7.5 mg/week or sulfasalazine, 2 g/day, NSAID).

In group 1 patients, the intensity of spinal pains during motions, morning stiffness by VAS, and BASDAI significantly decreased ($p<0.05$, Table 3).

In group 2, significant changes were obtained for greater number of the studied parameters. The intensity of spinal pains at rest and during motions, the degree of morning stiffness, BASFI, BASDAI, and ESR decreased.

Patient's and physician's satisfaction with the treatment (Tables 4 and 5) corresponded to evaluation of objective parameters. In group 1, improvement was observed in 60% patients of group1 as soon as after 1 month and more pronounced improvement was attained in 88.9% patients after 3 months. In group 2, 70 and 88.9% patients reported improvement after 1 and 3 months, respectively, which coincided with physician's opinion.

Good and excellent tolerability of artrofoon was observed (Table 6). We recorded 5 side effects, which developed usually on days 2-5 of treatment; in 2 patients the treatment was ceased. In 3 cases, transient headache, nausea, and slight aggravation of spinal and articular pains were observed on days 2-5 and disappeared on days 3-7 without special correction. The only exclusion was 2 patients, to whom NSAID were prescribed for 1 week and then artrofoon monotherapy was resumed.

In group 2 receiving combined therapy (NSAID and/or BAID+artrofoon), the dose of NSAID was reduced 40% patients.

Clinical and biochemical blood tests revealed no significant changes in all three groups, except significant decrease in ESR in group 2 after 3 months.

TABLE 3. Dynamics of Clinical and Laboratory Parameters in Patients with AS during Treatment ($M\pm m$)

Parameter	Group 1		Group 2		Group 3	
	before treatment	after 3 months	before treatment	after 3 months	before treatment	after 3 months
Spinal pain at rest	48.5±4.8	43.2±4.9	61.8±4.1	51.7±4.6*	50.0±3.8	48.0±4.3
Spinal pain during motion	56.5±4.3	45.6±4.4*	69.2±4.9	52.2±3.1*	57.5±2.9	53.5±3.1
Degree of morning stiffness	55.5±5.3	39.9±4.2*	68.5±5.4	53.3±4.6*	56.5±4.3	54.5±4.8
Thomayer symptom	31±4.1	31.1±4.9	37.3±4.4	34.0±4.7	33.4±3.7	33.2±4.1
BASFI	64±5	57.1±4.3	60.2±4.1	51.2±4.2*	71.7±4.8	66.0±5
BASDAI	6.88±0.33	5.40±0.39*	7.40±0.34	6.40±0.45	8.0±0.5	7.2±0.4
ESR	27.5±2.6	23.2±2	34.7±3.1	28.4±2.8*	27.9±2.2	26.5±2
Leukocyte count, $\times10^9$/liter	7.0±0.4	6.30±0.33	7.36±0.44	6.68±0.53	7.11±0.54	6.68±0.40
Erythrocyte count, $\times10^{12}$/liter	4.05±0.13	3.92±0.14	4.35±0.10	4.20±0.11	3.97±0.12	3.94±0.12
Hemoglobin, g/liter	127.0±3.6	126±3	129.2±2.6	126.1±2.4	124.2±3.5	121.0±3.2
ALT, U/liter	0.31±0.02	0.29±0.03	0.29±0.03	0.26±0.02	0.29±0.03	0.31±0.03
AST, U/liter	0.27±0.04	0.27±0.04	0.26±0.03	0.27±0.03	0.30±0.03	0.31±0.31
Bilirubin, μmol/liter	13.8±0.7	14.50±0.97	13.9±1.1	13.9±1.1	13.5±1.1	14.9±1
Creatinine, μmol/liter	0.08±0.01	0.09±0.01	0.07±0.01	0.09±0.01	0.07±0.02	0.05±0.01

Note. *$p<0.05$ compared to initial values.

TABLE 4. Patient's Assessment of Treatment Efficiency

Status	Group 1		Group 2		Group 3	
	after 1 month	after 3 months	after 1 month	after 3 months	after 1 month	after 3 months
Improvement	6 (60%)	8 (88.9%)	7 (70%)	8(88.9%)	3 (30%)	4 (44.4%)
Without changes	3 (30%)	1 (11.1%)	2 (20%)	1 (11.1%)	7 (70%)	6 (66.6%)
Deterioration	1(10%)	—	—	—	—	—

TABLE 5. Physician's Assessment of Treatment Efficiency

Status	Group 1		Group 2		Group 3	
	after 1 month	after 3 months	after 1 month	after 3 months	after 1 month	after 3 months
Improvement	5 (50%)	7 (77.7%)	7 (70%)	8 (88.9%)	2 (20%)	4 (44.4%)
Without changes	4 (40%)	2 (22.2%)	2 (20%)	1 (11.1%)	8 (80%)	6 (66.6%)
Deterioration	1 (10%)	—	1 (10%)	—	—	—

TABLE 6. Artrofoon Tolerability in Group 1 and Group 2 Patients (%)

Tolerability	Group 1	Group 2
Excellent and good	70	80
Satisfactory	30	20
Side reactions	30	20
Drop-outs	10	10

Thus, artrofoon produced more pronounced anti-inflammatory effects in patients with AS compared to NSAID. Artrofoon was well tolerated and significantly reduced spinal pain and morning stiffness.

The use of artrofoon as monotherapy and as a component of complex therapy in AS reduces clinical and laboratory signs of disease activity and allows lowering the dose of NSAID.

Potentiation of the effect after increasing the number of artrofoon doses in some patients with AS suggests that further studies are required for choosing optimum doses and duration of artrofoon therapy.

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