Efficiency and Tolerability of Artrofoon (Ultralow Doses and Antibodies to TNF-α) in Osteoarthrosis

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 148, Suppl. 1, pp. 109-112, September, 2009
Original article submitted August 1, 2008

Antiinflammatory and analgesic effects of artrofoon in osteoarthritis and the absence of side effects were demonstrated. The maximum antiinflammatory effect was attained by the end of the 3rd month of artrofoon treatment. The effect persisted from 6 months to 2 years against the background of maintaining therapy with artroofoon.

Key Words: *osteoarthrosis; tumor necrosis factor; artrofoon; nonsteroidal antiinflammatory drugs*

Osteoarthrosis is a chronic degenerative and inflammatory disease of the musculoskeletal system characterized by involvement of all articular components (cartilage, subchondral bone, synovium, ligaments, synovial bursae, muscles, *etc.*); this is why this pathology is called osteoarthritis disease [5,7,8].

In recent years, OA is considered as an inflammatory disease (osteoarthritis) and an important role in the progression of this pathology is allocated to hyperproduction of antiinflammatory cytokines. It was demonstrated that processes mediated by TNF-α and IL-1 are of particular importance. It is known that TNF-α has a receptor on chondrocytes, activates inflammation and tissue alteration in OA, stimulates the synthesis of prostaglandins, platelet-activating factor, superoxide radicals, metalloproteinases, and induces the synthesis of other proinflammatory cytokines (IL-1, IL-6, IL-8, *etc.*) TNF-α stimulates fibroblast proliferation and inhibits the synthesis of collagen and proteoglycans, *i.e.* produces a destructive effect in OA [5,8,12]. Therefore, it is reasonable to use TNF-α antagonists in the therapy of OA.

Artrofoon contains affinity-purified antibodies to human TNF-α in ultralow doses (a mixture of homeopathic dilutions C12, C30, and C200). The preparation reduces the level of TNF-α in biological fluids of the body, regulates the balance between pro- and antiinflammatory cytokines, and is characterized by antiinflammatory and analgesic activities and unique safety [2-4,6,9-11]. Previous studies demonstrated the efficiency of this preparation in some inflammatory and degenerative-inflammatory diseases (rheumatoid and psoriatic arthritis, OA, and chronic hepatitis) [1-4,9-11].

However, there are no data on the efficiency, tolerability and safety of long-term (up to 2 years) course treatment with artrofoon in patients with OA.

We carried out an open randomized controlled study of artrofoon in patients with OA and evaluated clinical efficiency and tolerability of long-term (from 6 months to 2 years) continuous treatment with artrofoon in various doses in patients with OA.

MATERIALS AND METHODS

The study included 70 female patients aging 64.1±1.9 years with signs of documented OA (stage II-III gonarthrosis); the history of the disease was 6.50±1.27 years; of these patients, functional classes I, II, III were diagnosed in 11, 41, and 18 patients, respectively. Fifty-one patients had X-ray stage II and 19 had stage III OA. OA was diagnosed using common criteria [7,8]. A necessary inclusion criterion was the presence of clinical signs of reactive synovitis and

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0007-4888/09/1483-0470

pain syndrome severity >40 mm by visual analog scale (VAS).

Group 1 patients (n=20) received artrofoon (8 sublingual tablets per day, 2 tablets 4 times a day) for 6 months; group 2 patients (n=10) received combined therapy (artrofoon, 8 tablets per day+nonsteroidal antiinflammatory drug, NSAID). Group 3 (n=10) comprised patients receiving NSAID monotherapy (diclofenac, voltaren, nimesil, movalis). The treatment dose of NSAID was equivalent to 100 mg diclofenac. Group 4 patients (n=10) received artrofoon in a dose of 8 tablets per day for the first 3 months and then 4 tablets per day for the next 3 months. In group 6 patients (n=10), artrofoon treatment in a dose of 8 tablets per day for 3 months was followed by complete drug withdrawal. If patient's state worsened, the treatment was resumed in the same dose. Group 6 patients (n=10) received artrofoon in a dose of 4 tablets per day for 6 months. We also formed a special group comprising 53 patients, who continued artrofoon monotherapy in a maintaining dose of 2-4 tablets per day after successful treatment with artrofoon for 6 months. These patients received artrofoon for 2 years (continuously or with short intervals). This group included patients of groups 1, 2, 4, 5, and 6.

The patients of all groups were comparable by their age and history and form of the disease. The efficiency of treatment was evaluated by the parameters of articular syndrome (pain intensity by VAS and in points and pain during palpation in points), duration of morning stiffness (min), knee joint circumference (cm), Lecene and Likert tests, time spent for 20-m walk, and clinical and laboratory data. The presence of synovitis in knee joints was verified by ultrasonography. The dynamics of patient's state was analyzed after 10-14 days, and 1, 3, 6, and 24 months.

RESULTS

On days 2-5 of artrofoon treatment, a slight aggravation of the pathological process and pain syndrome in the joint was noted. Moderate exacerbation of the pain syndrome was observed primarily in patients receiving artrofoon in a dose of 8 tablets per day. Joint pains in these patients became more intensive despite simultaneous treatment with NSAID (group 2). At later terms, the pain and stiffness decreased; the effect of exacerbation disappeared on days 10-14 of artrofoon therapy. Appreciable decrease in the severity of pain syndrome was observed on days 20-30 and became significant on day 30 of artrofoon therapy. The most pronounced clinical improvement was attained by the 3rd month of treatment (Fig. 1, Table 1). We observed a decrease in pain intensity evaluated by VAS scale (p<0.01), pain intensity score (p<0.01), joint tenderness (p<0.01), and Lecene index (p<0.01), which attested to improvement of the function of the joint apparatus. In most patients, pain at rest disappeared and pain during movements considerably decreased (p<0.05) by the 3rd month of treatment. The circumference of the knee joints also decreased, which attested to a decrease in the severity of synovitis and periartricular changes and confirmed the antiinflammatory effect of artrofoon. Ultrasonic examination in dynamics also confirmed disappearance or alleviation of exudative changes. Treatment with artrofoon (8 tablets per day) decreased the time spent for 20-m walk (p<0.05). Erythrocyte sedimentation rate tended to decrease by the end of 3-month treatment (Table 1).

In group 1, the tendency to clinical improvement was noted earlier (starting from days 10-14 of treatment), but by the end of 3-month course clinical parameters did not attain the values observed in group 1 (Fig. 1).

The general effect of treatment was maximum in groups 1 and 2 by the 3rd month and remained unchanged during further treatment with artrofoon in the same dose (Fig. 1, Table 1).

In group 4 patients, the positive result of treatment were still observed after switching to the lower dose (Fig. 1). The results of monotherapy with NSAID were less pronounced (months 3 and 6, Fig 1). Artrofoon withdrawal after 3-month course led to exacerbation of the joint process within 1-3 months.

The efficiency of therapy in group 6 patients was lower than in patients receiving NSAID (Fig. 1).

Administration of the maintaining doses of artrofoon (2-4 tablets per day, monotherapy, continuously or with short intervals) after completion of the 6-month course maintained the positive effect of therapy over

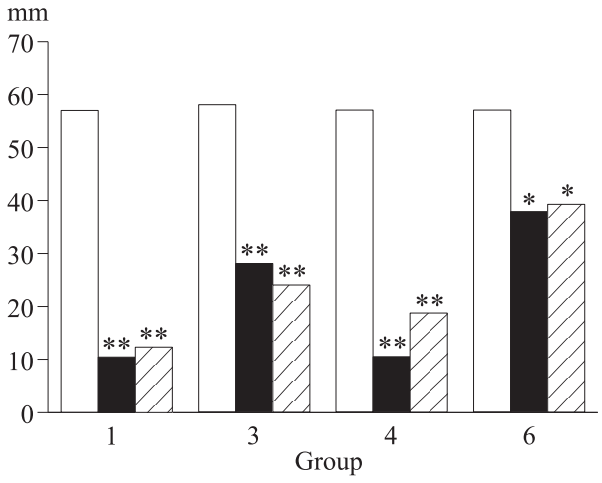

Fig. 1. Pain intensity assessed by VAS in the dynamics of therapy with artrofoon and NSAID. *p<0.05, **p<0.01 compared to initial values. Light bars: before treatment, dark bars: after 3 months, shaded bars: after 3 months.

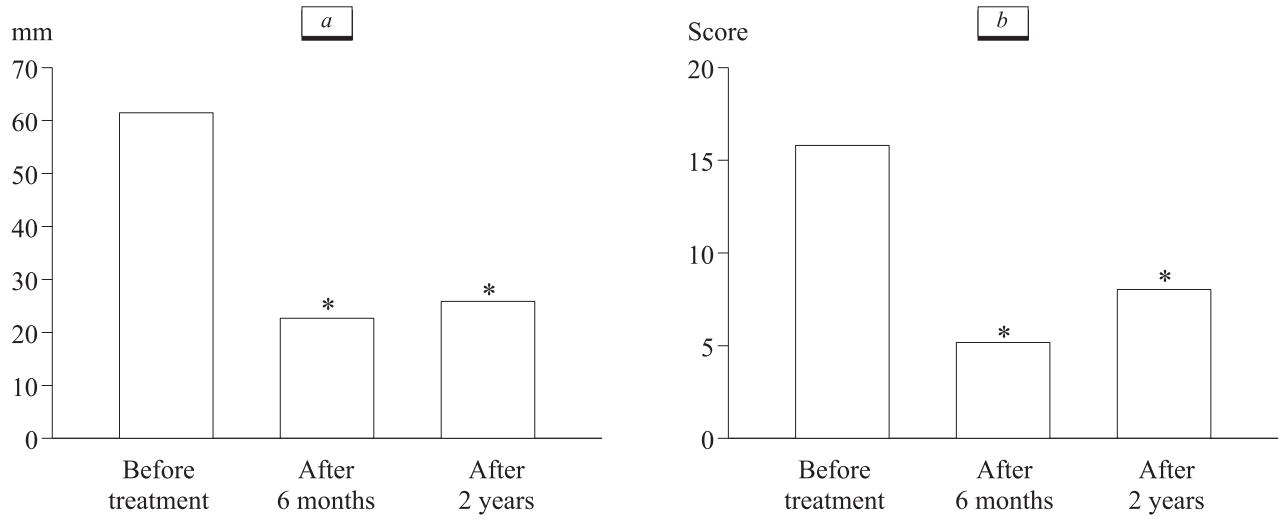

Fig. 2. Pain intensity assessed by VAS (*a*) and Lecene index (*b*) in the dynamics of 2-year maintaining therapy with artrofoon. *$p<0.001$ compared to initial values.

2 years ($p<0.01$ compared to values before treatment; Fig. 2). No exacerbation of the disease was noted during this period, which prevented considerable impairment of functional activity of patients (Fig. 2, *b*). Lecene index and knee joint circumference remained unchanged during the observation period (6 months to 2 years). Ultrasonic examination performed during therapy confirmed the absence of synovitis relapses.

Side effects were recorded in 3 patients receiving combined therapy (group 2), in 4 and 5 patients receiving NSAID monotherapy for 3 and 6 months, respectively. These were primarily drug-related gastropathies requiring temporal or complete NSAID withdrawal.

No side effects of artrofoon were recorded (even during long-term treatment), except short-term aggravation during the first few days of treatment. Laboratory parameters reflecting the function of the liver, kidney, *etc*. also did not differ from the normal (Table 1). Two patients stopped treatment with artrofoon for reasons not related to the treatment. Three patients in group 2 were able to stop NSAID and switched to artrofoon monotherapy.

Thus, artrofoon in a dose of 8 tablets per day produced pronounced analgesic and antiinflammatory effects surpassing those of NSAID. Artrofoon belongs to a group of slowly-acting antiinflammatory preparations, its effect developed over 1-3 months. Artrofoon in the maintaining dose of 2-4 tablets per day was effective over 2 years and was well tolerated.

TABLE 1. Dynamics of Clinical and Laboratory Parameters in OA Patients Treated with Artrofoon in a Dose of 8 Tablets per Day (*M*±*m*)

Parameter	Before treatment	After 3 months	After 6 months
Pain at rest, score	2.68±0.24	0.3±0.1**	0.40±0.12**
Pain during motions, score	2.74±0.21	0.88±0.08*	0.97±0.10*
Pain during palpation, score	2.71±0.31	0.23±0.12**	0.27±0.18**
Morning stiffness, min	21.4±3.1	5.80±2.73*	6.40±2.91*
Leukocytes	6.5±1.1	6.30±0.91	6.36±0.88
Hemoglobin, g/liter	128.0±4.2	126.0±5.4	126.0±6.1
ESR, mm/h	15.2±3.4	8.4±1.7	8.8±1.9
ALT	28.1±4.1	30.1±4.2	27.6±4.6
AST	24.7±2.7	27.6±3.8	28.1±3.4
Urea, mmol/liter	5.1±1.4	6.3±0.9	6.50±0.84

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

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