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Pathogenetic treatment of large joint osteoarthritis at the clinic for sports medicine

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The paper discusses the etiology, pathogenesis, pathomorphology and pathophysiology of osteoarthritis of large joints from the perspective of evidence-based medicine. The processes occurring in the tissues of the joints during the development of the pathological process at various stages are described in detail; the features of diagnosis and treatment in sports medicine are described in detail. The characteristic of drugs used to treat osteoarthritis is described, with a description of the positive effect and negative effect on particular organs and systems. A preparation *Alflutop* was comprehensively analysed regarding its effectiveness in terms of safety and impact on the development of the pathological process. It was shown that Alflutop is a drug of choice in the treatment of joint destruction.

Keywords: osteoarthrosis, etiology, pathogenesis, pathomorphology, treatment, *Alflutop*

Osteoarthritis (osteoarthritis, OA) is a chronic progressive joint disease with a predominant pathological change in the cartilage tissue and subchondral bone with compensatory marginal outgrowth (osteophytosis). A broader interpretation of the pathological process, among other things, includes pathomorphological and functional disorders of other joint structures (capsule, ligament, synovial membrane) and periarticular soft tissues [1, 2, 3, 4, 5].

Epidemiology

OA is an undoubtable leader among the diseases of the locomotor system. Eighty percent of all patients with joint diseases are individuals who suffer from OA.

It is generally accepted that OA onset occurs between the age of 40-50 and older in 50 % of patients [7, 8, 2, 9]; more than 60 % of the population over the age of 65 suffers from OA [7]. Gonarthrosis is considered the most common OA type; coxarthrosis is a somewhat less frequent OA type [8]. In Russia, OA of large joints affects more than 12–15 % of the population [3, 6, 10, 11]. Neurological consultations find that every fifth patient suffers from OA; in the therapeutic and surgical consultations every fourth and third patient, respectively, complains of pain in large joints associated with OA [9]. Among rheumatology patients, more than 75 % are patients with OA [7, 9, 12]. The main reason for the widespread prevalence of OA is late diagnosis of pathological changes in joint tissues, since the clinical symptoms of the disease are detected later than radiological ones [3, 13], which sharply reduces the effectiveness of conservative treatment of OA [9] and is logically confirmed by the widespread prevalence of arthroplasty operations. Thus, the rate of large joint arthroplasties in Europe is 0.5–0.7 per 1000 people. In Russia, such operations are the most common in the practice of surgical interventions on the joints [7].

OA is an important social and economic issue. In the USA, the total expenditures on treating patients with OA are about one trillion dollars a year, exceeding the amount allocated for the treatment of cancer and cardiovascular diseases [9]. In the global statistics, OA takes the second ranking place among the causes of disability [6]; for example, the risk of disability due to gonarthrosis is comparable to a similar risk of cardiovascular system diseases [3]. In the outcome stage of the disease, more than a quarter of patients with OA experience difficulties in domestic self-care [6, 14, 15], in 10 % of the population over 55 years of age OA appears to have disabling symptoms [2, 3, 16, 17] and logically increases the risk of mortality in the presence of severe pain [15].

Relevance of osteoarthrosis in sport medicine

Most authors agree that obligate risk factors for development of OA include specific professional activities, static and dynamic mechanical overload of joints, sports injuries and metabolic disorders [1, 3, 14, 18]. The variety of risk factors allows us to interpret OA as a heterogeneous nosology, in which individual nosological units are similar in their

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pathophysiological, pathomorphological and clinical features, primarily associated with an imbalance of pro- and anti-inflammatory agents [8], catabolic and anabolic processes [14]. Hereditary predisposition to OA remains a debatable topic. Thus, the most obvious hereditary factors are seen in the development of OA in small joints of the hand [7], while the genes associated with the development of gonarthrosis have a pronounced polymorphism and cumulative effect in the development and progression of this disease [9]. In addition to the above, the risk factors for OA traditionally include the female sex, abnormalities of the musculoskeletal system, endocrine and other systemic pathological processes [7].

It is unambiguously permissible to extrapolate these risk factors for OA to sports medicine with a number of precisions. Higher dynamic loads in athletes lead to a logically greater decrease in the concentration of proteoglycans in the superficial zone of the cartilage, which results in a faster reversible softening and remodeling of the subchondral bone [8]. The facts that exacerbate the influence of sports on the OA development also include physical fatigue, irrational or inadequate treatment of injuries, which leads to chronic diseases of the musculoskeletal system, which make up 13.8 % of the total morbidity in athletes and are the main reason for the completion of a sports career [10].

The study on injuries in athletes in the Perm Territory identified a high number of athletes who had persistent pain after an injury, as well as a large number of athletes with impaired functional activity of the injured area [19]. Thus, in 41.9 % of cases, athletes reported persistent (more than for two months) pain in the injured area and impaired function of the injured area was recorded in 8.7 % of respondents. No doubt that the chronicity of the inflammatory process, poor function of the injured area of the musculoskeletal system is an etiological factor in the development of secondary post-traumatic OA in athletes [6].

A particular feature of a number of specific sports loads is strengthening of anaerobic mechanisms of energy supply, which, in turn, reduces to a greater extent the severity of anaerobic anabolic and reparative processes in cartilage tissue [8], that has an initially low recovery potential [7].

Inflammatory diseases of serous bursas (bursitis of various localizations), post-traumatic OA of the knee and ankle joints often complicated by reactive synovitis, lesions of the periarticular tissues (tendovaginitis, sclerotizing and exudative types of tendonitis, ligamentous calcinitis prevail in the structure of the pathology incidence of large joints in athletes [10].

Sport medicine focuses on the most relevant type of OA which is gonarthrosis that occurs in more than half of athletes in playing sports since it significantly reduces the tolerance of most physical activities and the quality of life of athletes due to impaired functional activity of the lower limb [20, 21, 22], which, in turn, portends the end of a sports career [20, 23].

A typical disease of a large joint which is more common in athletes than in general population not involved in sports is OA of the temporomandibular joint [24, 25, 26, 27] that develops as a result of displacement, defects and deformations of the articular disc, sprains and ruptures of the articular ligaments in athletes of martial arts.

The main goal of OA therapy in sports medicine may be formulated as short-term relief of pain, prevention of OA progression, and the athlete's fastest return to regular professional training and competition activities [10, 28, 29, 30, 31, 32].

Unlike OA in professional athletes, degenerative damage to the cartilage of large joints in amateur athletes acquires its own characteristics. Current trends to adhere to a healthy lifestyle and the desire for aesthetic improvement of the body exacerbate the course of OA in patients with obesity and metabolic syndrome [33, 34], which is associated with a higher mechanical load on the affected joints and more frequent microtrauma in the process of doing sports exercises, especially if they are performed improperly [9, 35, 36, 37, 38, 39]. Obesity in this case clearly contributes to the development of OA, since leptins and adipokines proved to be participants in the pathogenesis of OA, and infrapatellar fat was reported in a number of studies as a donor of cytokines, tumor necrosis factor, arachidonic acid and prostaglandin E [3, 40] . A similar adverse effect of excessive motor activity and sports occurs in elderly people who have high expectations maintaining the level of habitual physical activity but developed OA [9].

Features of osteoarthrosis course in the clinical practice of sports medicine

The generally accepted earliest symptoms of OA are stiffness in the joint, which occurs in the morning and disappears after the start of movement in a few

minutes, restriction of passive movements, muscle weakness, coupled with a decrease in proprioception and a feeling of "looseness" in the joint [9]. According to the recommendations of NICE (2014), subjective symptoms of the disease such as patient' complaints of mechanical pain and morning stiffness (if any) for no more than 30 minutes are enough to diagnose OA [7]. Mild lateral deformity of the foot and disorders patella gliding can be added to subjective symptoms of gonarthrosis [41, 42].

Pain due to OA has a diffuse character; it can occur due to mild swelling of soft tissues in the joint area, crepitus during limb movement. A distinctive feature of joint pain in athletes is its occurrence or intensification during professional activities, especially among athletes involved in cyclic sports [4, 9, 43]. The source of pain in OA is the nociceptors of the synovial membrane, ligaments, muscles [6, 9] of the subchondral bone, the increase in the mineral density of which (subchondral sclerosis) is proportional to the intensity of the pain [6, 44, 45]. Irritation of the nociceptor apparatus of the muscles leads to the closure of the "vicious circle" and typical signs of myofascial pain syndrome [6].

In chronic pain, there is a greater disturbance of the myostatic balance and, as a consequence, postural deficiency [16–19] and muscle atrophy. Chronic irritation of sensory fibers and somatosensory pathways of the central nervous system provides an actual pain syndrome with neuropathic traits. In this case, patients with OA complain of phenomena that are atypical for OA such as allodynia and hyperalgesia, demonstrate pain reactions inadequate to the irritant force [9, 46].

Pathogenetic "targets" of rational pharmacotherapy in osteoarthrosis

To consider the possibilities of adequate treatment of OA, it seems necessary to consider a number of information about the pathomorphogenesis of the disease.

The cartilage tissue matrix consists of proteoglycans, molecules in which the axial protein is bound to one or more chains of glycosaminoglycans (GAGs). Depending on the saturation with sulfate groups, two types of GAG are distinguished: non-sulfated (hyaluronic acid, chondroitin) and sulfated (chondroitin sulfate, keratan sulfate). The main function of the GAG, along with collagen fibers, is to ensure cartilage resistance to mechanical stress.

Chondroitin sulfates are the most common GAGs in the human body; they are found in tendons, skin, artery walls, and the cornea. In the cartilage, chondroitin sulfates are a structural component of aggrecan, the main proteoglycan of the cartilage matrix. According to the structural features of the molecule, two main types of chondroitin sulfate are distinguished – chondrotin 4- and 6-sulfate, respectively, which differ in the position of the sulfate group. Keratan sulfates differ in carbohydrate content and are also found everywhere, for example, keratan sulfate I is found in the cornea, keratan sulfate II is found in cartilage and bone tissues, keratan sulfate III is part of the cartilage matrix. Dermatan sulfate is present in the tissues of the cardiovascular system, intercellular substance of cartilage, intervertebral discs and menisci [3].

At OA onset, the synthesis of GAG and collagen type II by chondrocytes decreases; collagen types I, III and X, on the contrary, begin to be produced in larger quantities. In addition to collagen, chondrocytes begin to produce a number of enzymes (cytokine-regulated metalloproteinases [3], inducible nitrogen synthetase, cyclooxygenase-2) and pro-inflammatory agents (interleukins, tumor necrosis factor), which leads to the destruction of the cartilage tissue (including chondrocytic cell pool, initially small [47, 48],) and the spread of the inflammatory process to the periarticular tissues [14, 49, 50, 51, 52]. Microscopic disorders of the cartilage tissue result in decrease in the amount of hyaluronic acid, which affects the viscous and shock-absorbing properties of the synovial fluid [47, 53, 54].

In addition to the direct suffering of the cartilage, synovitis is prognostically important in the pathogenesis of OA, which is ubiquitous in the OA, and its intensity is a predictor of the outcome of the disease [3, 55, 56].

Diagnosis of osteoarthrosis in sports medicine

The "gold" standard for the diagnosis of OA is radiography of the affected joint. But taking into account modern requirements for the treatment of OA in the early stages [2], it seems necessary to consider dynamic approaches to objectification of OA using an example of diagnosing gonarthrosis [9].

Clinical and radiological criteria of the American College of Rheumatology (ACR) are used for the

diagnosis of gonarthrosis, including clinical and radiological characteristics, namely, pain in the knee joint and the presence of at least one of three criteria: age older than 50 years, stiffness up to 30 minutes and crepitus of the joint, structural changes (osteophytes) and narrowing of the joint space (Kellgren II in standard radiographs). However, ACR criteria provide only 91 % sensitivity and 86 % specificity of the method [47, 57] for moderate and terminal GA. Thus, the proposed criteria cannot be used in the early stages of OA of the knee joints, when the proposed radiological symptoms are absent [58, 59, 60]. Thus, the magnetic resonance diagnosis of gonarthrosis seems promising. In clinical practice, two MRI systems for assessing morphological changes in early OA are used: BLOKS [61] and WORMS [62]. The diagnosis of early gonarthrosis is established if at least two of the four criteria are present: morphological condition of cartilage of grades III–VI according to WORMS, regional degeneration of cartilage of the 2–3rd class according to BLOKS, damage to the menisci of the 3–4th class according to BLOKS, damage to the bone marrow in the subchondral zone of grades II-III according to WORMS. More information about the state of articular tissues is provided by techniques performed on tomographic systems with an inductance of 3 Tesla – the content of glycosaminoglycans can be estimated using delayed amplification with gadolinium (dGEMRIC) — and the presence of such sequences as T2 mode or diffusion-weighted images [9].

The merit of arthroscopic diagnostics is the ability to directly visualize joint tissues and the possibility of performing simultaneous surgical interventions. The International Cartilage Repair Society (ICRS) system is used for endoscopic evaluation. The criteria for early gonarthrosis according to ICRS are [46]: changes in cartilage of grades I-IV according to ICRS in two joint compartments or grades II-IV in one compartment with edema and softening of the cartilage when examined with a hook [9].

Combined systems of MRI and endoscopic study in early gonarthrosis were proposed by F. Luyten et al. [41] and include at least 2 episodes of pain over 10 days in the year, radiographic grade according to Kellgren-Lawrence at least 2 and one of two morphological characteristics: cartilage damage of grades I–IV according to ICRS in two joint compartments or grades II–IV in one associated with edema and softening of the cartilage and signs of degeneration of the cartilage and / or menisci and / or the presence of zones of damage to the bone marrow in the subchondral bone, detected by MRI [9].

Ultrasonic diagnosis of cartilage tissue condition is less commonly used to detect gonarthrosis, but it allows one to evaluate the collagen frame of the cartilage tissue in the affected joint [63, 64]. The use of ultrasound with a frequency of more than 10 MHz is promising, which enables to estimate the amount of proteoglycans in the intercellular matrix. However, it is also difficult in the early stages of OA [65].

Biochemical diagnosis of gonarthrosis is a dynamically developing direction; however, to date, a highly specific marker of the disease has not yet been identified. Promising studies reported that fragments of the C-terminal telopeptide of type II collagen (uCTX-II) can be used as a prognostic criterion, while oligomeric cartilage matrix protein (COMP) may indicate the presence and progression of gonarthrosis [66, 67].

The information presented above demonstrates current trends in the diagnosis of OA towards the earliest detection of the pathological process. Given the fact of informational insufficiency of radiography and the promising risks and complications of arthroscopic examination, it is recommendable to use MRI scanning of large joints in athletes with clinical signs of OA in a clinical setting for sports medicine.

Pathogenetic rationale for the use of *Alflutop* in the treatment of osteoarthrosis in athletes

The objectives of medication therapy are pain relief and inflammation subsidence, reduction in recurrences and prevention of other joint involvement in the process, decrease of disease progression, prevention of disability and improvement of patient's quality of life [2, 39, 68, 69, 70].

Medical preparations used in the treatment of OA are traditionally divided into two main groups: symptom-modifying (painkillers and non-steroidal anti-inflammatory drugs: NSAIDs) and structurally-modifying drugs of slow action.

Paracetamol and cyclooxygenase-2 inhibitors, regardless of their selectivity, glucocorticoids and opioid analgesics are traditionally referred to the first group of drugs [14]. Most recommendations from clinical communities (the European Anti-

Rheumatic League - EULAR, the American College of Rheumatology - ACR), the International Society for the Study of OA - OARSI) agree on the need for prescribing paracetamol and NSAIDs in OA [3, 71, 72]. They should be used by short courses for the treatment of OA, taking into account the chondronegative effect of non-selective cyclooxygenase-2 inhibitors and the prospectively high risk of complications by using selective cyclooxygenase-2 inhibitors [3, 18, 73] associated with their hepato- and nephrotoxicity, as well as risks of erosive and ulcerative lesions of the gastric mucosa, cardiovascular complications due to their intake [3, 6, 74, 75, 76, 77].

Regarding paracetamol, the latest meta-analysis showed that most of the randomized clinical trials of paracetamol as a treatment means for chronic pain continued no more than six months, and significant beneficial efficacy was recorded with respect to function, but not pain [3, 78]. In addition, a sufficient amount of information has been accumulated (18,880 studies involving about 700,000 patients) about a wide range of adverse events with long-term use of paracetamol [79].

The second group of drugs for treating OA is SYSADOA (symptomatic slow acting drugs for osteoarthritis), which partly reduce, including the severity of symptoms typical of OA, but their main effect is to slow down its progression [6, 69]. A distinctive feature of SYSADOA is a slow onset of the therapeutic effect (after 2-3 months), which, however, persists for 2–4 months after cessation of administration [6]. Typical representatives of SYSADOA are glucosamine sulfate, chondroitin sulfate (in combination and as monotherapy [7]), hyaluronic acid, diaceriin, unsaponifiable avocado and soy compounds [14].

Thus, the paradigm of OA therapy consists of the tasks to reduce the severity of disease symptoms and the pathogenetic correction of the pathophysiological process [20], which is generally described by the requirement for the use of the "disease-modifying" [24, 80] approach in the treatment of OA [14]. The European Society for the Clinical and Economic Aspects of Osteoporosis and OA (ESCEO) [81], on the basis of an analysis of the proposals of various expert groups, came to a consensus in the administration of NSAIDs, according to which a cautious approach to NSAIDs and high efficiency of SYSADOA therapy have been designated. Thereby, the experts emphasized that SYSADOA should be prescribed already at the first OA stages while and NSAIDs are indicated for patients with insufficient symptom-modifying effect produced with SYSADOA [3].

The latest revision of the ESCEO therapy algorithm (2016) recommends starting OA treatment with SYSADOA, and use paracetamol and NSAIDs for a short time if necessary [3].

Among the SYSADOA preparations, much more experience has been gained with the use of chondroitin sulfate and glucosamine sulfate, the injection of which allows for a faster symptom-modifying effect [3].

Pathogenetic treatment of osteoarthrosis in athletes from the perspective of clinical efficacy

Alflutop is an original anti-arthritic drug for parenteral administration that contains sterile purified (delipidized and deproteinized) standardized and stabilized biologically active extract (0.01 ml) of four marine fish (Severomorsk sprat – Sprattus sprattus sprattus, Black Sea merlang – Odontogadus merlangus euxinus Black Sea pod - Alosa tanaica nordmanni, Black Sea anchovy - Engraulis encrasicholus ponticus), developed in 1993 by Biotehnos S.A. (Romania) [2, 3, 8, 14, 47, 82].

The chemical composition of *Alflutop* is represented by the GAG as proteoglycans and glycoproteins (hyaluronic acid, chondroitin 6-sulfate, chondroitin 4-sulfate, dermatan sulfate, keratan sulfate), low molecular weight polypeptides (with a small molecular weight of less than 50 kDa [6], free amino acids, myoinositol , glycero phospholipids, (containing nitrogen, sulfur, phosphorus) and microelements (Na, K, Fe, Ca, Mg, Cu, Mn, Zn) [2, 6, 8, 47].

The advantage of *Alflutop* is its natural biological origin and the xenospecific features of the chemical structure of the chondroitin sulfate molecule, namely, different degrees of sulfation, the position of sulfate groups, the magnitude of the ionic charge and molecular weight. So, chondroitin sulfate obtained from marine organisms (primarily from cartilage and bone of fish) contains a small proportion of sulfate groups in the fourth position and has a high negative charge, which gives it an affinity to human tissues. Chondroitin sulfate obtained synthetically, on the contrary, contains tri- and tetrasulfate groups, which is not specific for living organisms [3].

The mechanism of *Alflutop* action is associated with a decrease in the release of interleukins 6 and 8 [3, 7, 47], which induce cell infiltration in inflammatory processes [82]. Besides, the use of *Alflutop* significantly (by 56 %) reduces the production of VEGF (vascular endothelial growth factor) [3, 7, 82, 83, 84], which leads to a decrease in the severity of neoangiogenesis and autocrine stimulation of chondrocytes.

It was shown that the use of *Alflutop* has a beneficial effect on the proliferation and modulation of the extracellular protein TGF-β, the most important modulator of cartilage homeostasis [3], the balanced pool of which ensures, in turn, cell regeneration of cartilage tissue [3, 47, 53] that has a beneficial effect on the course of OA against the background of intensification of bonds between cells and the extracellular matrix by overexpression of α2β1 integrins [3]. The proliferative status of chondrocytes increases due to *Alflutop* stimulation of DNA synthesis [3] and mitosis of the primary chondrocyte cycle, respectively [47]. The regenerative effect of *Alflutop* has been confirmed by its effect on the increased synthesis of aggrecan and hyaluronan (activation of the expression of hyaluronan synthase mRNA – HAS-1), as well as activation of the main transcriptional regulator necessary for the formation of articular cartilage [47, 85].

The antioxidant effect of *Alflutop* is associated with an increase in the activity of SOD [47] and catalase [13, 14], which prevents the destructive effect of oxidative stress on the cartilage tissue [47, 53, 86] and reduces the severity of inflammatory reactions [53, 85, 86]. In addition, the antioxidant effect of *Alflutop* is associated with a decrease in the content of intracellular peroxidanion, hydrogen peroxide and omega-3 fatty acids [24, 47, 53].

Alflutop has a dose-dependent effect on the inhibition of hyaluronidase [3, 87, 88, 89, 90, 91, 92] and other proteases responsible for the degradation of the nuclear protein of aggrecan.

According to the results of more than 20 clinical trials, *Alflutop* showed high efficiency in the treatment of gonarthrosis, coxarthrosis, osteochondrosis, spondylosis, arthrosis of small joints of the hands and feet, chronic lumbalgia, chronic arthritis, post-traumatic complications of the joints of the lower extremities, periarthritis, traumatic dystosis, sports injuries of the spine, postoperative complications following treatment of intervertebral disc extrusions, in the recovery period after surgical interventions on the musculoskeletal system [82].

Summarizing the results of the 20-year studying the effect of *Alflutop* in OA and the outcomes of clinical trials in which more than 5,000 people took part, we can distinguish a number of its clinical effects:

- analgesic effect and the possibility of reducing the dosages of NSAIDs or completely canceling them [6, 7, 8, 24, 82, 90, 93, 94, 95, 96, 97, 98] in the treatment of gonarthrosis, coxarthrosis, and shoulder joint periarthrosis [1], dorsopathies [7, 95, 99], including in the presence of a neuropathic component of the pain syndrome [5];
- secondary muscle relaxant effect [47];
- anti-inflammatory effect [6, 7, 8, 24, 82, 98];
- structurally-modifying effect [2, 8, 47], confirmed by radiographic [2, 87, 100], ultrasound [8, 82] and MRI [47, 82, 100, 101] studies regarding the progression of the narrowing of the interarticular gap and osteophytosis [8].

The clinical effects proven lead to an increase in the range of motion [3, 10], an increase in the thickness of the cartilage, lining of the articular surfaces [24, 47], and to improvement in the quality of life of OA patients [47].

It seems necessary to separately focus on the effectiveness of *Alflutop* in the OA treatment in athletes. Thus, the use of chondroprotective therapy in athletes with OA helps reduce the severity of pain, improves the functional activity of the affected limb, increases sports activity and quality of life, increases the strength of the muscles of the affected limb. The clinical efficacy of chondroprotective therapy for OA in athletes was confirmed by ultrasonographic signs of restoration of the structure of hyaline cartilage of the knee joint [20].

Pathogenetic treatment of osteoarthritis in athletes from the perspective of evidence-based medicine

The main component of the drug *Alflutop* is chondroitin sulfate, a high molecular weight polysaccharide (MM 10000-40000 MM) having a high chondroprotective effect (level of evidence 1A based on 13 clinical trials) [8].

Pathogenetic treatment of osteoarthrosis in athletes from the standpoint of therapy safety

In a number of studies, a high safety profile of the drug *Alflutop* was proven [82]. In the course of its use, no patient had deviations from the normal values of the total (hemoglobin, leukocytes, platelets) and biochemical (glucose, bilirubin, creatinine, transaminase) blood counts [96]. When evaluating the hepatotoxic effects, there was no negative effect on the structural and functional parameters of the liver during the therapy with *Alflutop* for three months, including its use in patients with steatosis [35].

In combined use of *Alflutop* and NSAIDs, it was shown that *Alflutop* reduces the healing time of erosive and ulcerative defects of the gastric mucosa caused by NSAIDs, which is probably associated with the restoration of normal prostaglandin synthesis, disrupted by NSAIDs [37, 47, 82].

In patients with chronic obstructive respiratory diseases in whom a number of NSAIDs are contraindicated, the use of *Alflutop* did not aggravate the concomitant symptoms but achieved a proper therapeutic effect of treating the underlying disease [96].

The safety and sustainability of the clinical effects of *Alflutop* during repeated courses of therapy was confirmed by a five-year study [97].

Pathogenetic treatment of osteoarthritis in athletes from a doping control perspective

Chondroitin sulfate [20], like other components of the *Alflutop* preparation, is not included in the current WADA list, which makes it possible to use the drug for the treatment of OA in athletes, regardless of their level of sports skills and upcoming competitive events.

Scheme of pathogenetic treatment of osteoarthrosis in athletes

The administration of *Alflutop* in OA is based on a number of principles. First of all, it is advisable to prescribe it as early as possible [20, 82] for 3 weeks at least twice a year [20]. A greater positive therapeutic effect is observed with combined use (intramuscularly and intraarticularly) than exclusively with intramuscular or intraarticular administration of the drug [82]. However, with intra-articular administration (with its practical feasibility), the risk of developing septic complications is not excluded [14], which to a greater extent limits this route of administration. Positive dynamics of subjective symptoms was observed six months after the first course of therapy with *Alflutop* [3].

For OA, *Alflutop* is administered intramuscularly deeply by 1 ml per day for 20 days. If large joints are affected, the intraarticular route of administration may be used. It is indicated in the dose of 1-2 ml intraarticularly with an interval of 3–4 days 5–6 times in each joint.

Alflutop cannot be used to treat persons under 18 years of age.

Non-medication correction of functional disorders of large joints in sports medicine

The largest role among the methods of non-medication therapy for correcting disorders, especially the biomechanical function of the joint, is played by timely informing the patients about the course and measures to prevent the development and progression of OA. Patient participation in educational programs and "OA schools" significantly increases patient compliance, improves quality of life, helps reduce the need for NSAIDs, and potentiates the effects of analgesic therapy [93]. An important part of educational programs is played by recommendations on physical therapy exercises, body weight correction, selection and use of rehabilitation technical means (canes, crutches, etc.) [7].

Thus, the use of *Alflutop*, along with non-pharmacological agents, for treatment and rehabilitation of athletes with arthralgic pain in the shoulder, knee and ankle joints shows its high clinical effectiveness. The drug can be successfully used in the clinical practice of sports medicine doctors, therapists, orthopedic traumatologists, specialists in the field of medical rehabilitation and restorative medicine.

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