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DMOADs and DMARDs in the treatment of patients with joint and spine diseases

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SUMMARY

The data on the classification of drugs, which are prescribed for the treatment of patients with joint and spine diseases, such as osteoarthritis (OA) and rheumatoid arthritis (RA), are presented. The groups of drugs widely used in clinical practice are disease-modifying osteoarthritis drugs (DMOADs) and disease-modifying antirheumatic drugs (DMARDs). To help the practitioner, consolidated information is provided on the main differences between these groups according to the mechanism of action (immunomodulatory vs. immunosuppressive) and the main indications for use (autoinflammatory joint diseases (OA) vs. autoimmune joint diseases (RA, psoriatic arthritis, ankylosing spondyloarthritis)). The material of the article is focused on the clinicians to help them make a right choice of OA therapy, and to identify the problem of drug choice in RA. Information about the possibility of using nutritional support in patients with OA is presented.

KEYWORDS

Disease-modifying osteoarthritis drugs, DMOADs, disease-modifying antirheumatic drugs, DMARDs, chondroitin sulfate, glucosamine sulfate, undenatured type II collagen, ChondroguardTRIO.

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DMOADs и DMARDs в терапии пациентов с заболеваниями суставов и позвоночника

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РЕЗЮМЕ

Представлены данные по классификации лекарственных препаратов (ЛП), которые назначаются для лечения пациентов с такими заболеваниями суставов и позвоночника, как остеоартрит (ОА), ревматоидный артрит (РА). Рассмотрены группы ЛП, широко применяемых в клинической практике – болезнь-модифицирующие остеоартрит препараты (англ. disease-modifying osteoarthritis drugs, DMOADs) и болезнь-модифицирующие противоревматические препараты (англ. disease-modifying antirheumatic drugs, DMARDs). В помощь практикующему врачу приведена консолидированная информация об основных различиях данных групп ЛП по механизму действия (иммуномодулирующий или иммунодепрессивный) и основным показаниям к применению (аутовоспалительные заболевания суставов (ОА) или аутоиммунные заболевания суставов (РА, псориатический артрит, анкилозирующий спондилоартрит)). Материал статьи ориентирован на врача-клинициста, чтобы помочь сделать обоснованный выбор терапии пациентов с ОА, обозначить проблему выбора ЛП при РА. Дана информация о возможности использования нутритивной поддержки пациентов с ОА.

КЛЮЧЕВЫЕ СЛОВА

Болезнь-модифицирующие остеоартрит препараты, DMOADs, болезнь-модифицирующие противоревматические препараты, DMARDs, хондроитина сульфат, глюкозамина сульфат, неденатурированный коллаген II типа, ХондрогардТРИО.

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Highlights

What is already known about the subject?

- New pharmacological standards include disease-modifying osteoarthritis drugs (DMOADs), which should not only have a symptomatic effect, but also change the course of the disease and have a structural effect
- DMOADs and disease-modifying antirheumatic drugs (DMARDs) are used in clinical practice to treat patients with joint and spine diseases
- A significant proportion of patients with rheumatoid arthritis (RA), psoriatic arthritis (PA), and ankylosing spondyloarthritis (AS) may have poor tolerance to therapy with baseline anti-inflammatory drugs due to the development of adverse events associated with immunosuppressive drug activity

What are the new findings?

- Data on disease-modifying drugs were systematized and presented as consolidated information in a table on the main effects of the DMOADs and DMARDs groups
- The DMOADs and DMARDs drug groups were shown to have significant differences in their mechanism of action: immunomodulatory and immunosuppressive, respectively

How might it impact the clinical practice in the foreseeable future?

- The necessity of adhering to the choice of disease-modifying drugs specific for each nosological group in the therapy of OA or RA, PA, AS was substantiated
- The presented data will help the clinicians to make an informed choice of therapy for OA patients with potential DMOADs, and to outline the problem of choosing DMARDs in the treatment of RA, PA, and AS

Основные моменты

Что уже известно об этой теме?

- В новые фармакологические стандарты входят болезнь-модифицирующие остеоартрит (ОА) лекарственные препараты (англ. disease-modifying osteoarthritis drugs, DMOADs), которые должны не только оказывать симптоматическое действие, но и изменять течение заболевания, иметь структурный эффект
- Для лечения пациентов с заболеваниями суставов и позвоночника в клинической практике применяются DMOADs и болезнь-модифицирующие противоревматические препараты (англ. disease-modifying antirheumatic drugs DMARDs)
- У значительной части пациентов с ревматоидным артритом (РА), псориатическим артритом (ПА), анкилозирующим спондилоартритом (АС) может наблюдаться плохая переносимость терапии базисными противовоспалительными средствами из-за развития нежелательных явлений на фоне иммунодепрессивной активности препаратов

Что нового дает статья?

- Систематизированы данные о болезнь-модифицирующих препаратах, которые представлены в виде консолидированной информации в таблице об основных эффектах групп DMOADs и DMARDs
- Показано, что группы препаратов DMOADs и DMARDs имеют существенные различия в механизме действия: иммуномодулирующий и иммунодепрессивный соответственно

Как это может повлиять на клиническую практику в обозримом будущем?

- Обоснована необходимость придерживаться в терапии ОА или РА, ПА, АС выбора именно болезнь-модифицирующих препаратов, специфичных для каждой нозологической группы
- Представленные данные помогут врачу сделать обоснованный выбор терапии пациентов с ОА потенциальными DMOADs, а также обозначить проблему выбора DMARDs при лечении РА, ПА, АС

INTRODUCTION / ВВЕДЕНИЕ

Every year up to 700 thousand new cases of inflammatory or degenerative joint diseases and systemic connective tissue diseases are diagnosed in the Russian Federation. Osteoarthritis (OA) is one of the most common rheumatological diseases, affecting every 10th person in the world, and among people over 60 years of age the prevalence of clinically significant OA reaches 30%. As of 2017, more than 300 thousand patients with rheumatoid arthritis (RA) were registered in Russia.

Chronic inflammation is the main factor in the formation of many pathological conditions. Among the mechanisms of chronic inflammation, two fundamental pathological processes are considered – autoinflammation and autoimmunity. Tissue damage leading to irreversible dysfunction of internal organs is a consequence of autoinflammation and autoimmunity [1]. Autoinflammation is based on genetically determined/induced activation of innate immunity; autoimmunity is a pathological process related to impaired immunological tolerance to normal tissue proteins (autoantigens), associated with the predominance of acquired (adaptive) immunity activation and manifested by hyperproduction of autoantibodies [1].

DRUGS OF CHOICE IN THE TREATMENT OF OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS / ПРЕПАРАТЫ ВЫБОРА В ТЕРАПИИ ОСТЕОАРТРИТА И РЕВМАТОИДНОГО АРТРИТА

New pharmacological standards include disease-modifying drugs. Disease-modifying pharmacological therapy is prescribed to patients with Alzheimer's disease or neurodegenerative disorders, patients with cardiovascular disease, etc. Generally, disease-modifying drugs mean drugs that modify the course of the disease, preventing its progression, and acting directly on the underlying cause of the disease.

Disease-modifying osteoarthritis drugs (DMOADs) and disease-modifying antirheumatic drugs (DMARDs) are widely used in clinical

practice for the treatment of patients with joint and spine disorders. Drugs with proven disease-modifying effects should be the front-line treatment of patients with articular syndrome. DMOADs and DMARDs have significant differences, including its mechanism of action and clinical effects. Today, the group of DMARDs is well studied, while DMOADs are at the stage of accumulating data and forming criteria for including drugs in this group. Potential DMOADs include chondroitin sulfate (CS), glucosamine sulfate (GS), undenatured type II collagen (UC-II), vitamin D. These active ingredients have a proven disease-modifying effect on OA, and are included in medicinal drugs and pharmaconutraceuticals.

Consolidated information on the main differences between drugs in the DMOADs and DMARDs groups is provided to help practicing physicians (**Table 1**).

DMOAD THERAPY FOR OSTEOARTHRITIS / DMOAD-ТЕРАПИЯ ПРИ ОСТЕОАРТРИТЕ

The concept of early detection of OA is based on the assumption that early treatment of OA prevents progression of the disease before damage to the affected joints becomes irreversible. Early detection of OA is important for so-called regenerative medicine (RM), which aims to treat the disease by regenerating damaged tissue. In this regard, potential DMOADs can be considered as RM drugs [19]. Additional criteria for prescribing RM drugs may include data obtained as a result of phenotyping and endotyping of OA, monitoring and assessing the rate of disease progression.

Initially, the concept of early disease detection was formed in the context of such a systemic autoimmune rheumatic disease (SARD) as RA. Timely diagnosis (before the onset of clinical symptoms) and early treatment of RA has significantly reduced its incidence. More rapid progression is observed in RA than in OA, and therefore it is clear that early detection of RA and drug treatment will lead to expectedly better results (reduction of disability and associated social burden) [20].

The concept of early detection of knee OA was first reviewed in 2012 and was based on the following criteria [21]:

– knee pain,
– Kellgren–Lawrence radiographic stage 0, 1, 2, 3 (osteophytes only),
– structural changes according to arthroscopy or magnetic resonance imaging (condition of cartilage, meniscus, synovitis).

In 2014, these criteria were revised to include patient-reported outcomes (pain and function, clinical signs, and Kellgren–Lawrence stage 0 or 1) [22]. In 2017 [23], criteria for early diagnosis of knee OA were defined in the presence of at least one of the three factors:

– two mandatory symptoms (knee pain in the absence of any recent injury or bruise and very short-term stiffness of the joint, lasting less than 10 minutes, when starting to move even in the absence of risk factors);
– knee pain and one or two risk factors;
– three or more risk factors with at least one mandatory symptom present and symptoms lasting less than 6 months, even in the absence of risk factors.

In 2019, recommendations were published based on the analysis of accumulated data on the outcomes of OA according to patients (clinical features of the disease, state of physical functions and changes associated with lifestyle) [23]. According to some authors, early detection of knee OA [24] or facet syndrome is most common in people involved in professional sports [25].

When choosing tactics for managing a patient with OA, as a rule, physicians adhere to symptomatic therapy, including non-pharmacological (exercise, weight loss, physical means, including transcutaneous electrical nerve stimulation and pulsed electromagnetic stimulation) and pharmacological treatments (painkillers, non-steroidal anti-inflammatory drugs), intra-articular corticosteroids, intra-articular hyaluronic acid) to relieve pain and suppress inflammation. In later stages of OA, joint replacement is used to relieve pain and inflammation. Currently, increased attention is being paid to the development of DMOADs – drugs that should not only have a symptomatic effect, but also change the course of OA due to structural improvement of joint tissue [19].

It is the assessment of the effectiveness and safety of potential DMOADs, such as CS and GS, that allows us to recommend them in the treatment of OA [26]. In the clinical guidelines of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) the administration of CS and GS to patients with knee OA is the basic treatment [27].

THE POSSIBILITY OF NUTRITIONAL SUPPORT FOR PATIENTS WITH OSTEOARTHRITIS / ВОЗМОЖНОСТЬ НУТРИТИВНОЙ ПОДДЕРЖКИ ПАЦИЕНТОВ С ОСТЕОАРТРИТОМ

The new pharmaconutraceutical Chondroguard®TRIO (trademark owner: Sotex Pharm Firm CJSC, Russia) is an original combination of CS, GS and UC-II with a recommended dosage regimen of 1 powder sachet once every day, for at least 2 months. It can be used as nutritional support for patients with OA, either as a single remedy or as the second stage after previous therapy with any injectable symptomatic slow-acting drugs [28].

The mechanisms of action of CS and GS have long been studied, their effectiveness and safety have been proven in many studies. An additional component of the Chondroguard®TRIO composition is UC-II with an immunomodulatory effect [29]. The effect of UC-II in the composition of the pharmaconutraceutical is associated with a modulation of the mechanisms of innate and acquired immunity and a decrease in the activity of pro-inflammatory cytokines and prostaglandins [30]. UC-II extracts affect the autoimmune component of cartilage diseases and collagen discoidin receptors [30]. In addition, UC-II inhibits bone tissue aging by reducing inflammation and oxidative stress. Clinical studies have shown the prospectivity of using UC-II extracts in patients with OA on the background of diabetes mellitus [29].

PROBLEMS OF DMARD THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS / ПРОБЛЕМЫ DMARD-ТЕРАПИИ ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ

In recent years, there has been a lack of patient response to treatment with methotrexate (MTX) and other basic anti-inflammatory drugs (BAID), as well as genetically engineered biological drugs (GEBD) [8].

Currently, the proportion of patients with active RA who do not respond to treatment not only with standard BAIDs, but also with tumor necrosis factor alpha inhibitors and other GEBDs is increasing. In clinical practice, patients with active RA usually receive second-line treatment (targeted synthetic BAIDs or GEBDs) after unsuccessful attempts of therapy with not only MTX, but also other standard BAIDs, including their various combinations. GEBDs and Janus kinase inhibitors are recommended to be used in combination with MTX. Unfortunately, in clinical practice there is a significant proportion of patients with RA with poor tolerability to BAIDs and the development

Table 1 (beginning). Characteristics of disease-modifying osteoarthritis drugs (DMOADs) and disease-modifying antirheumatic drugs (DMARDs)

Таблица 1 (начало). Характеристика групп болезнь-модифицирующих остеоартрит препаратов (англ. disease-modifying osteoarthritis drugs, DMOADs) и болезнь-модифицирующих противоревматических препаратов (англ. disease-modifying antirheumatic drugs, DMARDs)

Parameter / Параметр	**Group / Группа**	
	Potential DMOADs* / Потенциальные DMOADs*	**DMARDs**
Group representatives / Представители группы	– Chondroitin sulfate [2-4] / Хондроитина сульфат [2–4] – Glucosamine sulfate [2-4] / Глюкозамина сульфат [2–4] – Undenatured type II collagen [2, 5, 6] / Неденатурированный коллаген II типа [2, 5, 6] – Vitamin D [5] / Витамин D [5] /	Synthetic [7–12]: methotrexate, leflunomide, sulfasalazine / Синтетические [7–12]: метотрексат, лефлуномид, сульфасалазин
		GEBD [1, 7–12] / ГИБП [1, 7–12]: – TNF-α inhibitors (adalimumab, infliximab, golimumab, certolizumab pegol, etanercept) / ингибиторы ФНО-α (адалимумаб, инфликсимаб, голимумаб, цертолизумаб пегол, этанерцепт) – IL-6 inhibitors (tocilizumab, sarilumab, olokizumab, levilimumab) / ингибиторы ИЛ-6 (тоцилизумаб, сарилумаб, олокизумаб, левилимаб) – T-cell co-stimulation blockers (abatacept) / блокаторы ко-стимуляции Т-клеток (абатацепт) – CD20 B-cell depletion (rituximab) / деплеция CD20 В-клеток (ритуксимаб)
		Targeted synthetic [8] / Таргетные синтетические [8]: – janus kinase inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib) / ингибиторы янус-киназ (тофацитиниб, барицитиниб, упадацитиниб, филготиниб) – glucocorticoids / глюкокортикоиды
Mechanism of action / Механизм действия	Inhibition of pro-inflammatory cytokines (IL-1β, -6, -8, NF-κB, TNF-α, MMP-1, -13) [2, 3, 13] / Ингибирование провоспалительных цитокинов (ИЛ-1β, -6, -8, NF-κB, ФНО-α, ММП-1, -13) [2, 3, 13]	
	– Stimulation of T- and B-lymphocyte secretion / Стимуляция секреции Т- и В-лимфоцитов – Stimulation of anti-inflammatory cytokines IL-4, -10, TNF-β production / Стимуляция выработки противовоспалительных цитокинов ИЛ-4, -10, ТФР-β	– Suppression of proliferation of B- and CD4+ T-lymphocytes / Подавление пролиферации В- и CD4+ Т-лимфоцитов – Inhibition of janus kinases / Ингибирование янус-киназ – Suppression of autoantibody production (IgG, IgM, IgA) / Подавление выработки аутоантител (IgG, IgM, IgA)
Main clinical effects / Основные клинические эффекты	Anti-inflammatory / Противовоспалительный	
	– Immunomodulatory / Иммуномодулирующий – Stimulation of bone and cartilage tissue repair / Стимуляция репарации костной и хрящевой ткани	– Immunosuppressive / Иммунодепрессивный – Antirheumatic / Противоревматический – Antiproliferative / Антипролиферативный
Pharmacological targets [14] / Фармакологические мишени [14]	– Cartilage / Хрящ – Subchondral bone / Субхондральная кость – Synovium / Синовия	
Indications for use, including / Показания к применению, в т.ч.	Autoinflammatory diseases affecting joints / Аутовоспалительные заболевания с поражением суставов	Autoimmune diseases affecting joints / Аутоиммунные заболевания с поражением суставов
	OA of various localizations in stages I–III according to Kellgren–Lawrence / ОА различной локализации в стадиях I–III по Kellgren–Lawrence: – gonarthrosis [15,16] / гонартроз [15,16] – coxarthrosis [15,17] / коксартроз [15,17] – OA of large and small joints of the extremities / ОА крупных и мелких суставов конечностей – degenerative diseases of the spine (facet syndrome) / дегенеративные заболевания позвоночника (фасеточный синдром)	Autoimmune joint diseases [1] / Аутоиммунные болезни суставов [1]: – rheumatoid arthritis / ревматоидный артрит – psoriatic arthritis / псориатический артрит – ankylosing spondyloarthritis / анкилозирующий спондилоартрит
Possibility of monotherapy / Возможность монотерапии	Yes / Да	No [4] / Нет [4]
First-line treatment / Является препаратом выбора первой линии	Yes / Да	Yes / Да

Table 1 (end). Characteristics of disease-modifying osteoarthritis drugs (DMOADs) and disease-modifying antirheumatic drugs (DMARDs)

Таблица 1 (окончание). Характеристика групп болезнь-модифицирующих остеоартрит препаратов (англ. disease-modifying osteoarthritis drugs, DMOADs) и болезнь-модифицирующих противоревматических препаратов (англ. disease-modifying antirheumatic drugs, DMARDs)

Parameter / Параметр	Group / Группа	
	Potential DMOADs* / Потенциальные DMOADs*	DMARDs
Second-line treatment / Является препаратом выбора второй линии	No / Нет	Yes / Да
LE, GR / УДД, УУР	1A, 2B [15–17]	1A, 2B [1, 4]
Duration of treatment course / Длительность курсового лечения	– Chondroitin sulfate and glucosamine sulfate are administered intramuscularly, course up to 6 months [2, 3] / Хондроитина сульфат и глюкозамина сульфат вводятся внутримышечно, курс до 6 мес [2, 3] – Undenatured type II collagen and vitamin D are administered orally / Неденатурированный коллаген II типа и витамин D назначают перорально	Each drug is administered according to its own scheme subcutaneously, intravenously or intra-articularly [4] / Каждый препарат вводится по своей схеме подкожно, внутривенно или внутрисуставно [4]
Course treatment is possible / Возможно курсовое назначение	Yes [2, 3] / Да [2, 3]	Yes [4] / Да [4]
Evaluation of therapy effectiveness / Оценка эффективности терапии	The effect is observed after 8–12 weeks / Эффект наблюдается через 8–12 нед	The effect is observed after 6 months / Эффект наблюдается через 6 мес
Side effects / Побочные явления	Не выявлены / Not identified	Intra-articular injection / При внутрисуставном введении: – osteonecrosis of the knee joint [12] / остеонекроз коленного сустава [12] – rapid progression of the disease [12] / быстрое прогрессирование заболевания [12]
		Systemic reactions / Системные реакции: – malignant neoplasms [18] / злокачественные новообразования [18] – toxic damage to organs and tissues (increased liver enzymes, retinopathy, changes in blood count, etc.) [4] / токсическое поражение органов и тканей (повышение печеночных ферментов, ретинопатия, изменение формулы крови и др.) [4]

Note. *GEBD – genetically engineered biological drugs; TNF-α – tumor necrosis factor alpha; IL – interleukin; NF-κB – transcription nuclear factor kappa B; MMP – matrix metalloproteinase; TGF-β – transforming growth factor beta; Ig – immunoglobulin; LE – level of evidence; GR – grade of recommendation. * Each substance has a proven symptom- and structure-modifying effect.*

Примечание. *ГИБП – генно-инженерные биологические препараты; ФНО-α – фактор некроза опухоли альфа; ИЛ – интерлейкин; NF-κB (англ. transcription nuclear factor kappa B) – ядерный фактор транскрипции каппа B; ММП – матриксная металлопротеиназа; ТФР-β – трансформирующий фактор роста бета; Ig (англ. immunoglobulin) – иммуноглобулин; УДД – уровень достоверности доказательств; УУР – уровень убедительности рекомендаций. * Каждая из субстанций обладает доказанным симптом- и структурно-модифицирующим действием.*

of adverse events against the background of the immunosuppressive activity of the drug, such as: development/addition of infections (nosocomial pneumonia), opportunistic infections, herpes zoster, malignant tumors (especially during long-term therapy), venous thromboembolic complications, increased cardiovascular risks, perforation of the intestinal wall, changes in laboratory parameters [8].

Due to the intolerance and lack of response to treatment with antirheumatic drugs in some patients, new drugs for the treatment of RA and other immune inflammatory rheumatic diseases (IIRD) are constantly being searched for and developed. Studying the mechanisms of action of new drugs for the treatment of RA allows us to expand our understanding of the main pathogenetic mechanisms of the disease, and the mechanisms that implement autoimmunity and autoinflammation. In 2022, Academician E.L. Nasonov developed a "theranostic" classification of IIRD, which is based on the disease diagnosis taking into account the immunophenotypes of IIRD and personalized treatment of the patient with improved efficiency and safety. Creation of new drugs and search for new targets are the main strategy for the treatment of SARDs within the framework of the "treat-to-target" concept aimed at achieving remission [1]. Control of

the “autoimmune” component of SARD pathogenesis is the primary goal of pharmacotherapy [1].

CONCLUSION / ЗАКЛЮЧЕНИЕ

The fundamental differences between the groups of DMOADs and DMARDs are not only in the mechanism of action (immunomodulatory or immunosuppressive, respectively), but also in indications and nosological groups, treatment regimens and the development of adverse events.

For patients with OA, the first-line drugs are molecules from the DMOADs group with high evidence and safety – CS, GS, UC-II, vitamin D, the disease-modifying effect of which is observed with long-term course use. Based on the existing evidence base for the effectiveness of using the components of Chondroguard®TRIO pharmaconutraceutic (CS, GS, UC-II) for prevention and adjunctive DMOAD therapy, its use may be justified both as an independent remedy and after previous therapy with any injectable symptomatic slow-acting drug.

For the treatment of other rheumatological diseases (RA, psoriatic arthritis, ankylosing spondylitis), drugs from the DMARDs group are used according to registered indications, always as part of complex therapy, under the control of liver function, kidney function, general and biochemical blood parameters, due to the high risk of developing systemic reactions.

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