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CONTEMPORARY UNDERSTANDING OF THE CLINICAL FEATURES OF RHEUMATOID ARTHRITIS AND METHODS OF ITS THERAPY

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Abstract: In recent years, rheumatoid arthritis has become a global problem, affecting 0.5-2% of the population over the age of 50 (up to 6% among women).The annual increase in new cases is 0.02%. The disease is also considered, a social issue, leading to disability among patients in young and middle-aged groups. The disease is based on joint structure disorders ankylosis, deformities, and contractures. The degree of their development is closely related to early initiation of treatment. This review article presents modern perspectives on the clinical features and treatment of rheumatoid arthritis.

Keywords: Rheumatoid arthritis, clinical features, immunopathogenesis, modern methods of therapy, medial unicondylar knee arthroplasty.

Rheumatoid arthritis (RA) is a significant health and social problem. The relevance of the disease is determined by its rapid progression, serious disorders of the musculoskeletal system and high prevalence among people of working age. In the early stages, there is a decrease in functional capabilities, loss of professional and social skills, as well as difficulties in physical and psychological adaptation to motor limitations. All these factors lead to significant disability and major economic losses. RA primarily affects people of working age, which contributes to a rapid deterioration in the quality of life and a reduction in its duration. (Nosonov E.L.)

The progression of rheumatoid arthritis is characterized by a significant variety of clinical manifestations - from mild forms accompanied by long-term remissions to severe articular-visceral ones. One of the characteristic features of chronic inflammation in RA is a long-term pain syndrome, which is not always proportional to the severity of polyarthritis or spondylitis, both according to clinical and laboratory data. Studies have shown that the first few years of the disease play a major role in its development and progression. At the early stage of RA, which is in the exudative phase, a higher recovery is possible, since autoimmune mechanisms are not yet fully formed, and there is no pannus - a structural basis for the destruction of joints for 17 seconds.

Rheumatoid arthritis exhibits significant clinical variability - from forms that allow a long-term remission state to severe variants involving joints and internal organs. Chronic inflammation is characterized by persistent pain syndrome, which does not always correspond to the degree of polyarthritis or spondylitis, assessed by clinical and laboratory methods. Research shows that it is the first years of the disease that determine the further development of the pathological process. In the early stages, when the disease is characterized by an exudative phase, the probability of reversibility is significantly higher, since autoimmune reactions have not yet fully formed, and pannus - the morphological basis of joint destruction - is absent.Diagnosing rheumatoid arthritis at the early stage of the disease is one of the most challenging and significant tasks for a physician.

During this period, there are many more opportunities to influence the pathogenic mechanisms of disease development with modern therapy, which are potential causes of irreversible changes both in the musculoskeletal system and in internal organs.

The clinic of rheumatoid arthritis (RA) is extremely diverse, characterized by a variety of forms and variants, which complicates the development of a classification algorithm for the disease [Folomeeva O.M., Amirjanova V.N., 2001]. Certain studies highlight the distinct patterns of rheumatoid arthritis (RA) progression across different climatic and geographical regions, as well as the impact of various environmental factors, as noted in research by Ahmedov K.S. (2017) and Pavlova A.B. (2006). The impact of unfavorable natural-climatic conditions, environmental factors, and temperature conditions in some works indicates rapid development of destructive processes (Akhmedov K.S.), while others highlight the formation of secondary immunodeficiencies, which serve as a trigger mechanism for the development of rheumatoid inflammation [Arzhakova G.S. et al., 1994; Satybaldiev A.M., 2001]. The initial stage of the disease is characterized by a variety of symptoms, and RA does not have any completely specific pathognomonic signs.

Only 10% of patients have a benign, monocyclic course of rheumatoid arthritis with rare relapses. About two thirds have a slow but stable progression of the disease with incomplete remissions and frequent exacerbations, while the remaining forms develop a "malignant" course, expressed by rapid and multiple joint damage with severe, potentially life-threatening dysfunction of internal organs. The only effective way to stop the gradual deterioration of the condition is timely diagnosis and early initiation of active therapy, which should be carried out over a long period with constant monitoring of the effectiveness and tolerability of the treatment. Therefore, the importance of early detection of RA is obvious. With a classic clinical picture, especially with typical hand lesions, an experienced rheumatologist can easily make a diagnosis. However, diagnosis is complicated by the following factors: - a typical clinical presentation is more commonly observed in patients with a long-standing disease. In the early stages, characteristic clinical signs (such as ulnar deviation of the fingers or rheumatoid nodules), immunological markers (like the presence of rheumatoid factor), and radiological findings (such as bone erosions) may be absent. The onset of rheumatoid arthritis (RA) is marked by significant symptomatic variability, and there are no truly pathognomonic symptoms unique to this condition. It is during the early stages of the disease that diagnostic challenges most frequently arise.

Modern Approaches to the Treatment of Rheumatoid Arthritis

Over the past decade, significant advancements have been made in the management of rheumatoid arthritis (RA), leading to improved treatment outcomes and enabling the establishment of a primary goal: achieving clinical remission, as outlined in the 2022 EULAR recommendations. This is not only due to the use of disease-modifying anti-rheumatic drugs (DMARDs) but also to specially developed innovative gene-engineered biologic drugs (GEBDs) that have made a breakthrough in rheumatology. However, the introduction of gene-engineered drugs alone is insufficient for achieving real positive dynamics in RA treatment; it is also necessary to improve the treatment strategy itself [Nosonov E.L]. This strategy is based on the early diagnosis and treatment of the disease, with the goal of achieving remission as quickly as possible. This concept is known as "Treat to Target" (T2T), which was first proposed by the European League Against Rheumatism (EULAR) in 2016, with the involvement of 60 scientists from 25 countries. The essence of this

concept is to achieve remission or low disease activity. It has become relevant not only for rheumatoid arthritis but also for other diseases such as ankylosing spondylitis, hypertension, etc.

Methotrexate is recognized as the "gold standard" medication for treating rheumatoid arthritis (RA). As a cytostatic agent, it works by blocking folic acid. At relatively low doses, the drug exhibits a potent immunosuppressive effect, which helps minimize its hematological toxicity. However, regular monitoring is essential to prevent potential side effects. Methotrexate can be used both as a standalone treatment (monotherapy) and in combination with other disease-modifying antirheumatic drugs (DMARDs) and biologic agents (GEBPs). Approximately 30-60% of patients taking methotrexate achieve disease remission. The mechanism of action of methotrexate (MT) is rooted in its anti-folate properties.Its anti-inflammatory effects are driven by metabolites that stimulate the production of adenosine, a potent endogenous anti-inflammatory mediator.The adenosine-dependent effects of MT include the reduction of pro-inflammatory cytokines such as IL-6, IL-8, IL-2 TNF-α inhibition; suppression of endothelial cell proliferation; reduced activity of synovial fibroblasts; and the slowing of leukocyte adhesion and their migration into inflamed areas through postcapillary venules—these mechanisms highlight MTX's role as an anti-inflammatory agent rather than an immunosuppressant. This distinction is supported by evidence from clinical practice, and not as an immunosuppressant, which is confirmed in clinical practice. The mechanism of MT involves activation of adenosine release in the area of inflammation, and an increase in the expression of cytokines, such as IL-4 and IL-10. In low doses, MT suppresses the production of T-cell-dependent proinflammatory cytokines, while increasing the level of anti-inflammatory ones.The mechanism of action of methotrexate is to block the proliferation of synovial fibroblasts and reduce the adhesion of leukocytes to the endothelium, as well as limit their migration through postcapillary venules to the inflamed area. These actions allow us to consider MT as an anti-inflammatory agent, and not as an immunosuppressant, which is supported by clinical data. The mechanism of methotrexate activation also includes the release of adenosine at the site of inflammation, as well as stimulation of the synthesis of anti-inflammatory cytokines such as IL-4 and IL-10.

Methotrexate (MTX) was initially developed in 1948, and its successful application in treating children with leukemia was reported shortly afterward. In 1988, the FDA (US Food and Drug Administration) formally approved its use for managing rheumatoid arthritis (RA). Today, MTX is regarded as the cornerstone of RA treatment. The guidelines for MTX usage are derived from a 1992 randomized, double-blind, placebo-controlled study. This study evaluated three groups of patients with treatment-resistant arthritis: one group received a low dose of MTX (10 mg/m² weekly), another received a very low dose (5 mg/m² weekly), and the third received a placebo. The findings prompted an increase in dosage for patients who showed an inadequate response to treatment. Further research has demonstrated that high-dose MTX (25–30 mg/m² or 0.8–1 mg/kg) is effective for RA patients who do not respond to standard doses (10–15 mg/m² or 0.3–0.5 mg/kg).

The lack of objective clinical studies comparing the toxicity and effectiveness of high initial doses versus standard doses of MT to support this practice. Therefore, scientists have not reached a consensus on the starting dose of MT therapy in RA patients . Several studies have shown that methotrexate (MT) slows the transformation of early (undifferentiated) arthritis into established rheumatoid arthritis (RA), especially in seropositive patients with anti-citrullinated protein antibodies (ACPA). For example, after 30 months, RA was identified in 30% of patients with persistent disease activity who received MT at a dose of 15 mg per week, which was later increased

to 30 mg per week, compared to 53% in the placebo group. Methotrexate (MT) has become the primary drug of choice for treating patients with rheumatoid arthritis (RA) . Its effectiveness in treating RA has been confirmed by numerous randomized studies . Most patients using MT experience remission, which in half of them stops after therapy is discontinued. Therefore, it is recommended to continue MT therapy for 12-24 months after the onset of remission. Silverman (2005) compared the efficacy of leflunomide and methotrexate (MTX). The study mainly included patients who had not previously received disease-modifying antirheumatic drugs (DMARDs). According to the results of the randomized trial, leflunomide showed its effectiveness in the treatment of rheumatoid arthritis (RA).

Leflunomide is considered an alternative first-line drug for disease-modifying therapy. It is recommended when methotrexate is ineffective or poorly tolerated , either as monotherapy or in combination with other DMARDs.

Hydroxychloroquine is recommended only as part of combination therapy with MT. Randomized, placebo-controlled studies indicate that leflunomide and sulfasalazine are similar to methotrexate (MT) in terms of both effectiveness and tolerability. However, in clinical practice, they are used less frequently for rheumatoid arthritis (RA) compared to MT.Hydroxychloroquine, while not inhibiting joint progression, is less effective than other DMARDs. Sulfasalazine and hydroxychloroquine therapy should be recommended in the presence of hepatitis B or C virus infection, human immunodeficiency virus (HIV), and during pregnancy [].Hydroxychloroquine, being less effective than methotrexate and leflunomide, can be used in undifferentiated arthritis, relatively mild course of the disease and low activity of the inflammatory process. In addition, its use is possible in combination with other disease-modifying antirheumatic drugs (DMARDs).

A double-blind, placebo-controlled study confirmed that sulfasalazine was superior to placebo in efficacy. The results were assessed based on improvement in laboratory parameters and reduction in synovitis.This drug is most often used to treat oligoarticular forms of rheumatoid arthritis, as well as spondyloarthropathies associated with HLA-B27. In addition, sulfasalazine is used for spondyloarthropathies accompanying chronic inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease. However, its use may be accompanied by side effects, including headaches, skin rashes, hypogammaglobulinemia, and increased transaminase levels.For this reason, liver function tests should be monitored weekly during the first 3 months, monthly during the next 3 months, and then every 3 months thereafter. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been a cornerstone in the treatment of adult arthritis for many years . NSAIDs inhibit cyclooxygenase, preventing the formation of pro-inflammatory prostaglandins. However, NSAIDs are not included in the basic therapy or the standard RA treatment guidelines in many European countries. They are recommended only for short courses due to the rapid development of tolerance to these medications, which can lead to irrational and uncontrolled use by patients, potentially resulting in serious side effects.

Glucocorticosteroids (GCS) have been used in the treatment of various forms of rheumatoid arthritis for over fifty years. The most common of these are prednisone and methylprednisolone, which provide a rapid anti-inflammatory effect. However, despite their effectiveness in reducing inflammation, these drugs do not prevent the destruction of bone tissue and the development of disability in the short term. According to EULAR recommendations, GCS can be used as bridging therapy, i.e., in combination with disease-modifying therapy. However, due to numerous side

effects, they are recommended in small doses and for short courses, not exceeding 6 months. Intra-articular corticosteroid injections are considered justified and yield excellent results, significantly suppressing inflammation in the joints.

Biologic disease-modifying antirheumatic drugs (bDMARDs) are an expanding class of drugs. These include inhibitors of tumor necrosis factor-alpha (TNF-α) such as etanercept, infliximab, adalimumab, and golimumab; interleukin-6 receptor inhibitors (e.g., tocilizumab); B-cell depleting agents (e.g., rituximab); T-cell activation blockers (e.g., abatacept); and the first targeted synthetic DMARD, tofacitinib.The development of synovitis in rheumatoid arthritis is supported by various cytokines, of which TNF-α plays a key role. Several drugs are TNF-α inhibitors. The first was etanercept, which is administered subcutaneously at a dose of 0.4 mg/kg twice weekly. Another member of this class is infliximab, a monoclonal antibody directed against TNF-α that is administered intravenously every eight weeks. Like etanercept, it reduces TNF-α levels, reducing inflammation. Infliximab is currently approved for the treatment of rheumatoid arthritis in adults, as well as Crohn's disease. The third drug in this category is adalimumab, a TNF-α antagonist that is administered subcutaneously once a week. The last in this series is golimumab (Simponi), a fully human recombinant antibody to TNF-α

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