MODERN VIEW ON THE MANAGMENT OF THE *RHEUMATOID ARTHRITIS IN EARLY STAGES*

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Abstract: The importance of timely and correct diagnosis of RA, its differentiation from reactive arthritis and other joint diseases can hardly be overestimated, since the correct tactics at the onset of the disease determine the nature of the course of arthritis, the progression of joint destruction and functional joint failure. The problem of accurate early diagnosis of RA, which is inextricably linked with the study of the immediate and long-term outcomes of the disease, is currently especially relevant, due to the possibility of slowing down the development of the disease with the help of modern methods of treatment, if the therapy is started early. At the same time early development of adequate basal combined pharmacotherapy early rheumatoid arthritis reduces the severity of the clinical manifestations of RA, improves functional activity and retards radiographic progression of joint damage, reducing the risk of disability and significantly improves the economic efficiency of the treatment of rheumatoid arthritis.

Keywords: rheumatoid arthritis, diagnostics, treatment, basic anti-inflammatory drugs, combined therapy.

Rheumatoid arthritis (RA) is associated with the early disability of persons of working age and increased cardiovascular lethality as a result of chronic inflammation. At the same time during the first 3 years of the disease 37,5% of the patients lose the ability to work, and in 5 years more than 50% of the patients of RA are no longer able to continue working. These facts testify to the fact that during the first few years from the beginning of the disease, the course of RA is particularly aggressive. The life expectancy of the RA patients is lower than in the general population: by 3 years - in women and by 7 years - in men. In recent years, it has been demonstrated that only timely diagnosis and early active treatment of RA patients can improve the prognosis and outcome of the disease [1].

Articular syndrome in RA is associated with lesions of a synovial shell of joints, its hyperplasia and rapid increase in the volume of synovial tissue, accompanied by progressive destruction of cartilage and bone tissue. But at the same time, there is also tendon lesions and muscle changes, which play a leading role in the formation of persistent deformities. Consequently, this lesion leads to stiffness up to ankylosis in the joints, which significantly reduces the quality of life of the patients [2]. In the very early period of RA, when the process is in the primary, exudative phase, the reversibility of the disease is significantly higher, due to the incompletely developed autoimmune mechanisms and the absence of pannus, the morphological basis of joint destruction. Therefore, one of the key points in the treatment of RA patients is intervention already at its early stage.

Early RA is a conventionally isolated clinical and pathogenetic stage of the disease with the duration of active synovitis up to a year. Foreign literature also singles out very early RA ("very early RA") with the disease duration of less than 3 months and late early RA - from 6 to 12 months of the current. Early RA is characterized by the prevalence of exudative changes in affected joints, frequent atypical flow and good response to treatment. If active treatment is administered at a very early stage of RA, remission can be achieved in 6 months among 47% of patients, and a year later among 58.1% of patients [3,7]. Thus, the early stage of RA is strategically important for treatment and at the same time, the most difficult for diagnosis.

Until today, the criteria of the American College of Rheumatologists (ACR) revision of 1987 were actively used to diagnose the RA. They were characterized by quite high sensitivity (91-94%) and specificity (89%) at the developed stage of the disease. However, in the early RA, they were not sufficiently informative. Thus, according to the results of the conducted studies, the sensitivity of ACR criteria at the duration of the disease up to 3 months is 44.8%, up to 6 - 57.03%, and up to 12 months - 65.1% [6]. The EULAR recommendation (2007) for the management of patients with early arthritis includes the following symptoms: morning stiffness for more than 30 minutes, more than 3 inflamed joints, lesions of the metacarpal and/or plus phalangeal joints (positive test "compression").

Early RA may debut as "undifferentiated arthritis" (UDA), i.e. arthritis that does not meet the classification criteria of RA and other rheumatic diseases. Patients with UDA require dynamic observation and a thorough differential diagnosis. The early RA immunological marker is the detection of antibody to cyclic citrullin-containing peptide (ACCP) in serum, especially in a negative rheumatoid factor (RF) test. ACCP is a heterogeneous group of IgG autoantibodies that recognize the antigenic determinants of phyllagrine and other proteins containing the atypical citrulline amino acid. It has been found that ACCP are more specific to RA and at least as sensitive as traditional RF: the sensitivity of anti- ACCP in RA diagnosis is 70-80%, specificity - 98-99%. The seropositivity of ACCP is also a risk factor for erosive changes in joints and indicates a possible adverse course of RA [19].

The new markers are necessary for early diagnosis of rheumatoid arthritis, as seronegativity in both early and established RA remains the main limitation of both ACCP and RF. Protein 14-3-3 may represent a new biomarker for the detection of RA. There are seven forms of the 14-3-3 family of intracellular proteins. They have approximately 50% similarity of amino acids to each other and interact with a large number of intracellular proteins, thus controlling many biological processes including protein synthesis, cell metabolism, protein transport, and cytoskeleton transport [2]. The total number of isomers, only 14-3-3η was present in synovial fluid with high level (at least 5 times higher than its level in co-responding serums), that indicates the joint as a probable source 14-3-3η [3,4]. In the extracellular medium, soluble 14-3-3η has ligand activity, mainly activating cells of the innate immune system [12]. Soluble 14-3-3η acts through signal cascades as an extracellular kinase and P38 pathway, which leads to

increased regulation of some proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), matrix metallopeptidase 9 (MMR-9) and nuclear factor ligand receptor activator -κB (RANKL) [13]. Serum levels 14-3-3η contribute to elevation in patients with RA, but not in other diseases such as osteoarthritis, osteoporosis, gout, psoriasis, Crohn's disease, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, Schegren's primary syndrome, scleroderma and multiple sclerosis [15].

The X-ray of joints is the most accessible method of investigation, but it has low diagnostic value in the early stages of the disease. In the first weeks of the disease it is not expedient to perform joint X-ray. In addition to swelling of soft tissues and some expansion of joint slots due to perspiration, initial signs of periarticular osteoporosis can be detected in the pictures of hands and feet. Periarticular osteoporosis (a non-specific sign) takes at least a few weeks to develop, and bone erosion - the classic and most important symptom of RA - is a late sign and can only be detected many months later. Some patients do not have radiological findings until the stage of joint ankylosis. Although clinically foot lesions are usually somewhat delayed compared to hand lesions, first erosions are more likely to be detected in the pluphalangeal joints: first on the lateral surface of the head V of the pluphal bone, then on the medial surfaces of the heads II-IV of the pluphal bones. Even after 3 years from the onset of the disease, erosions in the metacarpalangeal joints are detected 1.5 times more frequently than in the metacarpal phalangeal joints. In brushes, the first erosions should be found on the styloid process of the elbow bone, in the joint of the pea-shaped bone, later - in II-V proximal interphalangeal and metacarpal phalangeal joints. In patients with polyarthritis it is not expedient to perform X-ray of large joints to diagnose RA, as in them erosion may not be detected throughout the disease. This research is usually performed to solve tactical treatment problems [6].

In the case of subclinical synovitis and in the absence of changes in X-rays, an additional ultrasound Doppler scan (Ultrasound) of the joints or Magnetic Resonance Imaging (MRI) may be used. Such methods have a higher sensitivity than X-rays in detecting signs of synovitis and bone erosion. The disadvantage of ultrasound is the diagnostic difficulties in the study of small joints of the hands and feet, as well as the quantitative assessment of erosions. The most accurate assessment of not only erosive, but also pre-ererosive (bone marrow edema, rheumatoid osteitis) changes in bone tissue allows MRI joints. This method allows detecting changes in soft tissue, including pannus, synovitis, thinning cartilage, tendovaginitis, as well as focal bone oedema (as a harbinger of erosions) or erosion, including in joints that are difficult to visualize by X-ray (e.g., wrist joints) [14]. Among patients with early RA, according to MRI data, hand synovitis was found in metacarpal phalangeal and/or wrist joints in 93% of patients, bone erosion in the same joints - 66%, while according to X-ray data erosive arthritis was found only in 17% of patients. MRI provides an opportunity to make an effective diagnosis of RA, to predict the development and outcome of the disease. It has been established that about 70% of erosive and destructive changes in joints develop during

the first 3-6 months from the disease debut, which determines an unfavorable prognosis of its course [2].

Poor prognosis in RA means X-ray progression of joint destruction, the formation of irreversible decrease in the function of the musculoskeletal apparatus, increase in the risk of the need to perform surgical operations on joints and decrease in the life expectancy of patients.

The issue of accurate early diagnosis of RA, which is inextricably linked with the study of the nearest and distant outcomes of the disease, is now particularly relevant, due to the possibility of using modern methods of treatment to slow down the development of the disease in the case of early therapy. The monitored treatment of RA is aimed at improving the outcomes of RA and preserving the quality of life of patients. An objective assessment of parameters reflecting the activity and progression of the disease is a necessary component of more successful treatment of a patient with RA [22].

During the recent year's considerable success has been achieved in the treatment of the RA. A significant reduction in the activity of the disease (70% of the "response" according to the criteria of the American College of Rheumatology - ACR) and an overall improvement in the prognosis of the disease have been achieved with the help of co-temporal basic antirheumatic drugs (methotrexate, leflunomide, etc.) and especially "biological" agents (for example, monoclonal antibodies to the tumor necrosis factor - Remicaid) in many patients. Nevertheless, pharmacotherapy of this disease remains one of the most difficult problems of medicine, and the possibility of complete "cure" of patients seems doubtful. There are many reasons for this: unknown etiology, poorly studied pathogenesis, heterogeneity of the disease, difficulty of early diagnosis, difficulty in assessing the risk of adverse prognosis, lack of universal anti-inflammatory drugs [7].

The early stage of RA, especially the first 3 months from the onset of the disease, is most favorable for effective basic therapy. The principle of management of patients with early RA is careful monitoring of the adequacy of treatment (at least once in 3 months) with subsequent correction of therapy if necessary [8].

The modern requirements for the treatment of RA include:

1. Prescription of basic anti-inflammatory drugs (BAID) immediately at diagnosis, ideally within the first 3 months after the debut of clinical symptoms;

2. The purpose of treatment: as soon as possible to achieve remission or low activity of the disease in each patient, if this goal is not achieved, the selection of therapy by frequent and direct monitoring (every 1-3 months);

3. Thorough monitoring of the dynamics of RA activity indicators and timely correction of therapy.

The most recent ACR(2008) [20] recommendations on the treatment of patients with RA BAID and Genetically engineered biological drugs (GEBD) include the definition of the main parameters to be taken into account when prescribing drugs. These include:

1. RA duration, which is subdivided into early RA (disease duration < 6 months), intermediate RA (disease duration 6-24 months) and established RA (long-term symptoms are present for more than 24 months);

2) The activity of the disease, which is subdivided by different indices (DAS, etc.);

3. Presence of prognostically unfavorable signs: active disease (large number of painful and swollen joints), presence of erosions at early stage, increase of RF and/or ACCP, increase of ESR and/or ESR [15]. Early therapy of BAID reduces the rate of radiological progression, increases the frequency of long-term remissions (up to 65% of patients), allows to avoid severe functional failure and reduces the mortality of patients.

BAID is required to be administered no later than 3 months from the beginning of RA with rapid dose escalation to achieve the optimal effect (DAS < 2,4) with subsequent drug replacement within 2-4 months if the drug is ineffective [10]. BAID substitution should be continued even when the disease activity is reduced and remission is achieved. Against the background of the use of BAID assess the dynamics of disease activity by DAS index, which helps to individualize the selection of baseline therapy and significantly improve its effectiveness. It is important that long-term RA patients are significantly less likely to "respond" to "basic" antirheumatic medications than patients who have received this therapy from an early stage of the disease.

The first-line methotrexate (MT), leflunomide and sulfasalazine (SL) have been identified as BAID because they have been proven to be effective in preventing destructive joint changes (evidence level A). The "second line" preparations - hydroxychloroquine, gold preparations, etc. have been proved to be effective in preventing destructive joint changes (level A). - are used when first-line drugs are ineffective or in combination with them. They are rarely used due to high toxicity and lack of reliable data on the impact on disease progression.

MT is the "gold standard" for active RA therapy. In comparing to other BAID has the best ratio of "efficiency/toxicity". If it is necessary to apply MT in a dose of more than 7.5 mg/need, it is recommended to use parenteral route of administration (intramuscular or subcutaneous). In order to minimize side effects, it is recommended to use folic acid 1-5 mg/day, excluding days of MT administration. Since the monotherapy of BAID does not always allow to effectively control the destruction of joints and achieve the development of remission of the disease, in certain cases, it is justified to use combined therapy.

There are two of its schemes:

1. "step-up"-strategy - additional prescription of one or more BAID in case of ineffective monotherapy;

2. "step-down"-strategy - a transition from combined therapy after achieving clinical and laboratory remission to monotherapy of one or another BAID [12].

A number of researches have shown that combinations of synthetic BAIDs are more effective than monotherapy of BAIDs, especially in early RA. The most widespread is the so-called "triple therapy" (a combination of MT + SL + hydroxychloroquine). In the study, "triple therapy" was significantly more effective in patients than "double therapy"

(a combination of 2 drugs) or monotherapy. The efficiency of the combination of synthetic BAID can be compared with the efficiency of the combination of MT and GEBD [14]. The majority of authors believe that combination therapy should start with leflunomide and only after making sure that it is tolerable, HIPI should be connected. And a combination of leflunomide and MT is more effective than monotherapy of MT and is convenient for patients because of a single daily dose of leflunomide and even rarer intake of MT (once per week) [9].

SL is slightly inferior than MT and leflunomide in efficacy, but its important advantage is the possibility of its use in women of childbearing age, including during pregnancy. In some patients, parenteral forms of gold preparations have good results, but their use in clinical practice has sharply decreased in recent years due to the high frequency of serious side effects. A considerably less effective, but comparatively safe remedy - cryptvenil - is widely used. At the high activity of RA, cryptoglobulin is prescribed as a part of combined basic therapy. The listed four basic medications can be combined in pairs in any combination. As for the combination of the three drugs, only the com-bination of MT + SWD + cryptoglobulin is studied in controlled randomized trials [7].

The application of leflunomide at the early stage of RA seems to be rational and theoretical, taking into account the original mechanism of leflunomide action - inhibition of de novo synthesis of pyrimidine ribonucleotides. In activated lymphocytes in RA, an 8-fold increase in the level of uridinmonophosphate (UMP) and other pyrimidine ribonucleotides has been observed during a certain phase of the cell cycle (G1-S); a pathological pathway has been developed leading to the proliferation of lymphocytes, monocytes/macrophages, and other cells and an increase in the synthesis of many pro-inflammatory factors. However, at an early stage of RA, the rate of accumulation of the active metabolite leflunomide may probably be of special importance for obtaining the desired result and improving the prognosis of the disease as a whole [11].

Other medicines, non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GC), are primarily prescribed for symptomatic purposes - to relieve pain, swelling, stiffness and other manifestations of inflammation. Several studies have demonstrated the properties of GC modifying the course of the disease (basic), in particular, the ability of prednisolone in a daily dose of 7.5 mg (against the background of traditional basic therapy) to slow down the rate of X-ray progression by more than 2 times compared to placebo in early RA [9].

At a high degree of inflammatory process activity, GCS is used, and in cases of systemic manifestations of RA - in the form of pulse therapy (only GCS or in combination with cytostatic - cyclophosphamide), without systemic manifestations - in the form of course therapy. GCS is also used as a supportive anti-inflammatory therapy when other drugs are ineffective.

In a number of cases, GCS is also used as local therapy. Indications for their use are mainly mono- or oligoarthritis of large joints, a prolonged exudative process in the joint, the prevalence of "local status" over systemic, the presence of contraindications for

systemic use of GCS. In the case of intraarticular injection, corticosteroid depots also have a systemic effect. The drug of choice is Diprospan, which has a prolonged effect [5].

Previously, it was believed that treatment of RA should start with "monotherapy" of NSAID, and the prescription of "basic" antirheumatic drugs should be reserved for patients who are "not responsible" for these drugs. This provision was based primarily on the notion that RA is a "benign" disease, and that NSAID treatment is safer than "basic" antirheumatic drugs, whose toxicity exceeds the "benefit" of their prescription. In addition, NSAIDs have only a symptomatic effect, without affecting the progression of the disease. No differences between NSAIDs and "basic" antiretroviral drugs have been observed in the frequency and severity of side effects [9].

In recent decades, there have been significant changes in rheumatology, primarily due to the active introduction into clinical practice of the so-called GIBDs, which are specially created immunoglobulins or other protein molecules. The creation of GEBD is directly related to the idea of key pathogenesis mechanisms, on which they have a blocking or modulating effect. In rheumatology, GIBDs have a place similar to that of targeting therapy in modern oncology. After the implementation of GIBDin clinical practice, in addition to controlling the symptoms of the disease, such tasks as inhibition of erosive process in joints, normalization of functional status and quality of life of a patient, potential increase of life expectancy to the population level are now being set [10].

The GIBDs have radically improved treatment results for early non-smoking patients. It is well known that only 50-60% satisfactorily meet the standard therapy of BAID, such as MT, SL, leflunomide, including when combined with GC. The frequency of clinical remission on the background of combined therapy even in severe patients in randomized clinical (RCR) and observational studies reaches 30-40 % and more [1].

Achieving remission is extremely important from the standpoint of preventing structural destruction of joints, maintaining physical activity and preventing disability. With existing biological agents and traditional BAIDs, achieving remission is a realistic goal. The advent of biological therapy has ensured that 50% of patients in 1 year of the disease have achieved this goal. In other 50%, the inability to achieve remission is associated with inadequate response to therapy, contraindications for aggressive treatment, drug resistance, and serious adverse reactions [23].

The most effective inhibitors of FNO-α (infliximab, etc.) are biological drugs that can delay the progression of RA. FNO-α inhibitors are mainly considered as second-line drugs, which are recommended to be administered in case of inefficiency of methotrexate and other BAID. Treatment with FNO-α inhibitors in combination with methotrexate, can be administered to patients with early RA who did not receive BAID if there is high activity of the disease or adverse prognostic factors. Biological preparations are not recommended for the low or medium activity of early RA [14].

Early prescription of basic therapy in RA reduces the severity of clinical manifestations in "early" RA, improves functional activity and slows down the

radiological progression of joint lesions (as compared to monotherapy of BAID), improves quality of life and reduces the risk of disability, reduces mortality in RA to the population level.

The essential role is played by the data concerning the influence of basic therapy on life prognosis of RA patients. It has turned out that those patients who have received adequate "basic" therapy during the whole period of the disease have a significantly higher life expectancy (almost no difference from the population) than patients who for various reasons did not take basic drugs or took them occasionally. It is remarkable that effective treatment with MT (but not with other basic medications) allows to significantly reduce cardiovascular mortality in RA patients, which is one of the main causes of life expectancy reduction [22].

It is well known that only early diagnostics and correctly chosen treatment can preserve the motor function of joints for a sufficiently long time. However, the complexity of treatment approaches based on basic therapy is not the least important in solving this problem. Application of rehabilitation measures at the early stage of RA in combination with other therapy of conservative nature significantly accelerates the recovery period, as well as contributes to disease prevention. Therapeutic physical training aimed at maintaining maximum joint mobility and preserving muscle mass is of great importance in treatment. Physiotherapeutic procedures (electrophoresis of non-steroidal anti-inflammatory agents, phonophoresis of hydrocortisone, applications of dimexide) and spa treatment are of secondary importance and are used only in case of small arthritis. The main point in the treatment of RA is the prevention of osteoporosis - the restoration of the disturbed calcium balance in the direction of increasing its absorption in the intestine and reducing excretion from the body. A diet with increased calcium content is a necessary component in the complex of antiosteoporotic measures. The source of calcium are dairy products (especially hard cheese containing 600 to 1000 mg of calcium per 100 g of the product, as well as processed cheese; to a lesser extent cottage cheese, milk, sour cream), almonds, hazelnuts, walnuts, etc., and calcium preparations in combination with vitamin D or its active metabolites [5].

Consequently, active RA therapy initiated early enough may lead to a significant improvement in the course of the disease and may potentially cause prolonged clinical remission. In this connection, the early prescription of adequate treatment of RA is a critical point, to a large extent determining the further fate of the patient.

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