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PECULIARITIES OF DIAGNOSTICS AND TREATMENT OF RHEUMATOID ARTHRITIS AT EARLY STAGES OF ITS DEVELOPMENT

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Abstract:

The review summarises current advances in the study of early diagnosis and treatment of rheumatoid arthritis (RA). The evolution of RA includes several consecutive (or discrete) stages of development, culminating in the development of a complex of symptoms characteristic of RA. However, the nature of the interaction between environmental factors, genetic predisposition, and immune mechanisms that determine stage-to-stage transition and developmental variants is not entirely clear and is currently the subject of intensive research. The article lists modern classification criteria of RA (ACR/EULAR, 2010), created for early diagnosis of the disease. Emphasis is placed on the use of methotrexate (MT) as the "gold standard" of RA pharmacotherapy and a key component of the "Treat to Achieve" strategy. Early administration of MT (including in subcutaneous form) should be a mandatory component of RA treatment at all stages of the disease. When using MT as monotherapy or in combination with baseline anti-inflammatory drugs (BIDs), if remission is not achieved, then genetically engineered biological drugs (GEBPs) should be prescribed

Keywords: Rheumatoid arthritis, rheumatoid factor, antibodies to cyclic citrullinated peptides, methotrexate.

INTRODUCTION. Rheumatoid arthritis (RA) is the most common immunoinflammatory (autoimmune) rheumatic disease (IIRD) characterised by chronic erosive arthritis and systemic damage to internal organs [3].

According to WHO, the incidence of RA in the population reaches 0.6-1.3%, and in close relatives - 3-5%, which indicates the genetic determinism of the pathology. Women get the disease 2.5-3 times more often than men, mainly at the age of 35-50 years, the incidence of the disease increases in later age periods [1].

The social significance of RA is undeniable, as the disease quickly leads to disability and incapacity for work due to joint deformity and ankylosis, which significantly worsens the quality of life of patients. Most people suffering from the disease experience limitations in performing simple daily tasks, and in some cases may completely lose the ability to work. Therefore, an intensive search for the causes of RA and factors (exogenous and endogenous) contributing to its development, biological markers for early diagnosis, prognosis of clinical course and individual sensitivity to treatment continues worldwide[1,4].

It should be clearly understood that RA, like other chronic diseases, interacts with environmental factors and genetic predisposition, and undergoes several stages of evolution - preclinical and clinical, ending with the formation of a characteristic clinical and laboratory symptom complex for early and advanced RA [4,7].

In the world, the concept of early arthritis is perceived as the most important period of the disease (a collective concept including conditions that raise doubts about the development of chronic inflammatory rheumatic disease, primarily RA), and this largely determines the patient's further fate [10]. In 30% of patients, the disease at early stages manifests undifferentiated arthritis (UDA), which greatly complicates the diagnosis. According to some reports, only 19% of patients start pharmacological therapy within the first 3 months of disease onset. In Austria and Great Britain the delay in RA diagnosis is 16 weeks, in Greece - 38 weeks [2,9].

Foreign literature distinguishes very early RA ("very early RA") with a disease duration of less than 3 months and late early RA ("late early RA") - from 6 to 12 months of course. Early RA is characterised by the predominance of exudative changes in the affected joints, frequent atypical course and good response to treatment. If active treatment is administered at a very early stage of RA, remission is achieved after 6 months in 47% of patients, and after a year - in 58.1% of patients [6,12].

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The duration of the disease in foreign literature is indicated as very early RA ("very early RA") with a duration of less than 3 months and late early RA ("late early RA") is from 6 to 12 months of course. In the early stages of RA there is a predominance of exudative changes in the joints, frequent atypical course and good response to treatment. With active treatment at very early stages of RA, remission can be achieved in 47% of patients after 6 months and in 58.1% of patients after one year.

Patients with NDA require dynamic monitoring and careful differential diagnosis. The following clinical variants of NDA are frequently observed in practice [11]:

- oligoarthritis of large joints (knee, ankle, shoulder, hip)
- Asymmetrical arthritis of the hand joints
- RF seronegative oligoarthritis of the hand joints
- unstable polyarthritis.

In 2010. ACR together with EULAR experts introduced new criteria in RA classification - ACR/EULAR, 2010. [2]. They are based on the analysis and evaluation of the number of affected joints, serological parameters (RF and ADCP), duration of symptoms, acute-phase indicators of inflammation (erythrocyte sedimentation rate - ESR, C-reactive protein - CRP) and are aimed at early diagnosis of the disease [7].

In order to diagnose RA according to the new criteria, a physician must fulfil three conditions:

- find at least one swollen joint in the patient;

-exclude other diseases that may be accompanied by inflammatory changes in the joints (in differential diagnosis, in case of ambiguity with various diseases such as systemic lupus erythematosus, psoriatic arthritis, gout, it is recommended to consult a rheumatologist);

-score at least 6 points out of a possible 10 on 4 items describing the features of the disease picture in a given patient.

The authors' priority in developing these criteria was to identify patients in need of early prescription of PAP [9]. At the same time, the pathogenetic mechanisms of RA and the extreme heterogeneity of clinical and immunological manifestations somewhat complicate the problem of applying the ACR/EULAR 2010 classification criteria in clinical practice and require further research.

The essence of the pathological process in RA is systemic autoimmune inflammation, which affects the synovial membrane of the joints with maximum intensity. RA is a classic B-cell autoimmune disease, the most characteristic manifestation of which is the synthesis of a wide range of autoantibodies with different specificity, which are found in more than 90% of patients suffering from RA. In addition, B cells participate in the co-stimulation of T cells, cause activation of osteoclasts (OCS) and synthesize a wide range of "pro-inflammatory" cytokines - tumor necrosis factor alpha (TNF-α), lymphotoxin, interleukin (IL) 6, etc. The most characteristic autoantibodies for RA are rheumatoid factors (RF) IgG, IgM and IgA isotypes reacting with the Fc fragment of the IgG molecule, and autoantibodies reacting with antigenic epitopes, the universal characteristic of which is post-translational modification (citrullination, carbamylation, acetylation, peroxidation, etc.) [11].

RF is synthesized by a number of immunocompetent cells, which indicates a complex cellular interaction in the immunogenesis of the disease. It should be noted that RF occurs not only in RA, but also in SLE, SSD, nodular periarteritis, chronically active hepatitis, and can also occur in the elderly. In addition, patients with positive RF have a poor prognosis for the course of the disease. A correlation was noted between IgM RF and the activity of the articular process, and IgA and IgG RF with extra-articular manifestations. The relationship between the degree of disease activity and the RF level was noted [12].

It has long been noticed that in addition to the seropositive, there is also a seronegative variant of RA, in which RF is not detected. Currently, this option is considered as an independent version of RA, as evidenced by its inclusion in a separate ruble ICD 10. However, the clinical and immunological differences between these two variants have not been fully studied [21].

Consequently, the use of RF in the diagnosis of RA in most cases turns out to be impossible, because, firstly, in 15-20% of cases patients turn out to be seronegative for RF even at the stage of a detailed clinical picture, and on the other hand, its detection in a number of other rheumatological and non-rheumatological diseases significantly reduces its diagnostic value. Secondly, the phenomenon of seroconversion has long been known, namely its appearance and disappearance even in the natural course of the disease and with the use of certain immunosuppressants. In synovial fluid, the detection of RF acquires a slightly different meaning, being a criterion for the diagnosis of RA, since in other diseases (AS, SLE, reactive arthritis) it is never found in synovial fluid [13].

The introduction into clinical practice of the determination of antibodies to citrullinated peptides, in particular, antibodies to cyclic citrullinated peptide (ADCP), has become an important step in the early diagnosis of RA. The level of ADC in the blood serum is detected 10 years before the clinical manifestation of RA [12]. The detection of ADC is crucial from the point

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of view of the prognosis of the development of RA in patients with NDA.

In RA, inflammation of the synovial membrane leads to the formation of many antibodies to citrulline, due to which various connective tissue proteins (citrulline, vimentin and other peptides) are modified and citrulline residues are found in them, which become the target of antibodies. These include ADC, modified citrullinated vimentin (AMCV) and antikeratin antibodies (AKA). It should be noted that antibodies are detected at the preclinical (immunological) stage of RA [2]. ACP and AMCV are the main representatives of the ACB family, which are used in clinical laboratory practice.

According to the literature, in the diagnosis of the RF-negative variant, the differential diagnosis of RA with other rheumatological diseases and the prediction of severe erosive joint damage, it is important to determine the content of ADCs, which have high diagnostic sensitivity (DH) and specificity (DS). The detection of ADC in blood serum serves as a predictor of the development of RA in healthy people and patients with early NDA [7,8]. In RA, AMCV has a higher or similar DC, but a lower DC compared to ADCP. It is believed that an increase in the level of AMCV is better associated with clinical and laboratory indicators of inflammatory activity of RA and the development of severe destructive joint damage than ADCP [13].

According to the experiments accumulated in recent years, the only real way to slow down the progression of the disease is early diagnosis and active therapy in the early stages, while the treatment of the disease should be carried out for a long time and constantly, carefully monitoring the effectiveness and tolerability of the therapy.

Over the past decade, with the widespread introduction of new, effective GIBPS, significant changes have occurred in the RA treatment strategy: its basis has become the concept of "Treat to target" ("Treatment to achieve the goal"). It was noted that the main strategy is active early aggressive MT therapy. In case of insufficient effectiveness of MT monotherapy, then combination therapy of MT with standard basic anti-inflammatory drugs or MT with GIBP is used.

It has been proven that HDL, first of all, early administration of MT, more effectively inhibits the progression of RA than later administration of these drugs, forms the concept of the so-called "window of opportunity" [8]. New data obtained in the course of fundamental research to determine the mechanisms of action of MT and many randomized placebo-controlled trials (RCTs), materials from observational studies and national registries substantiate the significant place of MT in the treatment of RA, prevention of complications and concomitant comorbid diseases.

MT is considered a "first-line" drug and should be prescribed to all patients diagnosed with RA (degree of evidence A) and in patients with NDA with a high probability of developing RA (degree of evidence C) [13].

Timely and long-term administration of MT makes it possible to effectively control the symptoms and progression of joint destruction, and also has a satisfactory safety profile in patients with early and advanced RA ; treatment of MT slows down the transition of NDA to RA; in patients with RA, efficacy /safety / cost is indicated in favor of MT monotherapy compared with combination therapy of MT and other standard HDL and GIBP or GIBP monotherapy [1,9].

A number of studies are currently being conducted or are planned to be conducted, the purpose of which is to prevent the development of RA in patients with NDA or patients with "clinically questionable arthralgias". In this regard, the materials of the PROMT (Probable Rheumatoid Arthritis: Methotrexate versus Placebo Treatment) study are of great interest, dedicated to evaluating the effectiveness of MT treatment aimed at reducing the risk of developing RA among patients with NDA. The study included 110 patients with arthritis who did not meet the criteria of RA (ACR, 1987) [2, 5], who were divided into 2 groups: MT 15mg/week n/a or placebo [PL]. After 30 months and after 5 years [6.10], the incidence of RA was similar to that of the comparison groups. Nevertheless, in the group that received MT, there was a slowdown in the development of RA and a decrease in the rate of progression of joint destruction.

In addition, in ADC-positive patients treated with MT, the incidence of disease progression was significantly lower compared to the PL group (67% vs. 93%; $p<0.001$). A retrospective analysis of the materials of this study was also carried out [7] using the Leiden predictive rule, based on the stratification of patients depending on the risk of progression of early arthritis into reliable RA [61]. It turned out that in patients who received MT in the high-risk group ($n = 22$), the incidence of RA after 5 years was 55% (6 out of 11 patients), and in the PL group - in all patients (11 out of 11; $p = 0.011$). In addition, in the group receiving MT, there was a significant slowdown in the development of RA after an average of 22.5 months and in the PL group after 3 months ($p < 0.001$), as well as the frequency of "drug-free" remission (36% vs. 0%; $p = 0.027$). Similar data were obtained in the analysis of patients positive for ADC ($n = 18$). These materials show that early administration of MT will prevent the development of RA

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in a high-risk group of disease progression. As part of the treatment of MT, the transformation of NDA into RA may be associated not so much with the insufficient effectiveness of this drug, as with the use of short courses (1 year), the use of insufficiently effective doses and the tablet form of the drug, which is significantly inferior in effectiveness to the subcutaneous form of the drug. It should be noted that the effectiveness of MT in RA, including at an early stage of the disease, is theoretically very well substantiated [1] and confirmed by numerous research data on the model of experimental arthritis [3, 4].

Ученые Cribbs AP, Kennedy A, Penn H и соавт. получили данные, подтверждающие о влиянии МТ на эпигенетические дефекты функции Treg [12].

The results based on the use of xMAP multiplex technology [2] show that in patients with early RA who received subcutaneous MT (REMARK program), after 12 weeks of treatment, there was a significant decrease in the concentration of "proinflammatory" cytokines/chemokines such as IL6, IL17, TNFa, CXCL10 (C-X-C motif chemokine 10) and after 24 weeks - IL6, IL9, CXCL10, as well as an increase in the level of the "anti-inflammatory" cytokine-IL10, which correlates with a decrease in disease activity.

S. Agenova et al. [6] analyzed data on the course of the disease in patients with RA (n=1007) observed at the Early arthritis Clinic (Leiden) from 1993 to 2011. It was found that one of the most important factors in achieving stable drug-free remission is the early initiation of MT treatment: odds ratio (OR) = 113 (95% CI 0.48–2.64) in the period from 1996 to 1998, OR=2.39 (95% CI 1.07–5.32) in the period from 1999 to 2004 and OR=3.72 (95% CI 1.60–8.62) from 2005 to 2011, when patients received strictly controlled therapy with this the drug. At the same time, after reaching remission, normalization of the functional state of the joints was noted. These data show that early controlled use of MT is an important factor in the subsequent achievement of stable drug-free remission in RA.

According to the meta-analysis by N. Graudal et al. [4,10], which analyzed the results of studies concerning the comparative effectiveness of MT therapy in combination with GIBP and combination therapy of MT with HDL (including glucocorticoids - HA), indicate similar clinical efficacy of therapy in combination with GIBP and HDL and slow the progression of joint destruction in the early stages of RA. When MT is used together with other anti-inflammatory drugs, the most rational approaches to the treatment of RA, especially the place of GC [1,7], require further study.

Based on the position of "evidence-based medicine", MT is the only standard HDL that can be used for secondary prevention of RA in patients with NDA and for induction of remission in early RA.

CONCLUSIONS: Thus, RA is a heterogeneous disease, the results of which are largely determined by timely diagnosis of the disease and correctly chosen treatment tactics. The early stage of RA, especially the first 3 months from the onset of the disease, is considered the most favorable for effective basic therapy. The basis for the management of patients with early RA is careful monitoring of the adequacy of treatment (at least once every 3 months) with subsequent correction of therapy.

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