LECTURE

Difficult-to-treat rheumatoid arthritis. What is it?

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The widespread introduction into clinical practice of modern approaches to the treatment of rheumatoid arthritis (RA), the rational use of traditional and targeted antirheumatic drugs can effectively suppress inflammatory activity, restrain the progression of the disease and improve the quality of life of patients. At the same time, in some patients, even after the repeated change of targeted drugs, it is not possible to achieve the target level of RA activity. Serious difficulties arising in the management of such patients raised the question of identifying a special variant of the disease – difficult-to-treat (D2T) RA. The presence of various variants of D2T RA and the need to use a personalized approach to therapy justify the creation of special recommendations for the management of this category of patients. The first step in preparing these recommendations was the definition of D2T RA recently presented by the EULAR working group. It includes three criteria: 1) insufficient effectiveness of the therapy; 2) the presence of an active symptomatic disease; 3) clinical perception.

Key words: *difficult-to-treat rheumatoid arthritis; remission; low activity; refractoriness; pathogenesis.*

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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by gradually increasing destruction of joints and damage to internal organs. The prevalence of RA, according to various data, varies from 0.1% in rural areas of Africa to 5% among Indians belonging to the Pima, Chippewa and Blackfeet peoples [1]. In developed countries, it ranges from 0.5 to 1% [2]. The incidence of RA in Russia in 2015-2016 was 27.2 cases per 100 thousand population [3].

The widespread introduction of modern approaches to the treatment of RA into clinical practice, the rational use of traditional and targeted anti-rheumatic drugs can effectively suppress inflammatory activity, restrain the progression of the disease and improve the quality of life of patients. The current recommendations guide doctors to achieve remission or low RA activity and indicate the need for correction of drug therapy in cases where it is not possible to achieve the goal of therapy [4]. Unfortunately, in some patients, even a change of targeted drugs does not allow achieving the target level of activity.

Serious difficulties arising in the management of such patients make it necessary to allocate a special variant of the disease – difficult to treat (D2T) RA [5]. The term «refractory RA» is often used to refer to this form of the disease. However, refractoriness is usually understood as ineffectiveness of drugs that have good bioavailability when taking/administering the maximum possible dose that allows achieving the desired effect, while difficulties arising in the treatment of RA are by no means limited to this reason. In some cases, the choice of adequate therapy is hindered by its poor tolerability, as well as a high risk of developing adverse reactions associated with the presence of comorbid diseases. In addition, the result of treatment largely depends on the compliance of patients, their willingness to accurately follow medical recommendations. Refractoriness to treatment causes only a part of the unfavorable outcomes that one has to face in the management of RA patients. It can be noted in cases when a patient has received modern drugs aimed at suppressing the active inflammatory process for a sufficient period of time in adequate doses. The concept of «refractoriness» implies persistence of active inflammation against the background of the use of synthetic disease modifying anti-rheumatic drugs (DMARD) and genetically engineered biologics. At the same time, the need for constant use of moderate or high doses of glucocorticoids (GC) should also be regarded as a sign of refractoriness to treatment.

Currently, the effectiveness of drug therapy for RA is determined by its ability to provide remission or low activity according to composite indices [6]. The final values of these indices are not always accompanied by the presence of objective signs of inflammation, such as joint swelling, an increase in the level of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). The result of evaluating the RA activity indices is greatly influenced by the values of parameters assessed both by patients themselves and with their participation [7], which in some patients, even with sufficient suppression of inflammation, may reflect the presence of significant discomfort caused by the action of non-inflammatory mechanisms.

R. J. O. Ferreira et al. [8] analyzed the condition of 309 RA patients for the purpose of diagnosing remission using the ACR/EULAR criteria (American College of Rheumatology / European Alliance of Associations for Rheumatology): swollen joint count (SJC) ⩽1, tender joint count (TJC) ⩽1, the level of CRP ⩽1 mg/dl, the physician global assessment by (PhGA) ⩽1 cm, the patient global assessment (PGA) ⩽1 cm. They also identified a condition close to remission (CCR), in which all indicators corresponded to it, except for PGA. According to the study, only 9.4% of RA patients achieved remission, and 37.2% – CCR. The increased value of PGA was associated with fatigue, pain, anxiety and functional disorders. The authors concluded that an increase in the composite indices due to such causes cannot serve as a reason for correcting immunosuppressive therapy. In this regard, it was proposed to distinguish two independent components that determine the patient's status, which should be taken into account separately when deciding on the correction of therapy –

these are the inflammatory activity of RA and the discomfort associated with the disease.

According to P. Studenic et al. [9], in more than half of cases (52%), RA patients met 3 out of 4 remission criteria, while the value of PGA in 61% of patients did not fit the definition of remission. In 67% of patients with PGA >1 cm, PhGA did not exceed 1 cm, and 25% of them corresponded to remission according to the SDAI (Simplified Disease Activity Index). These data allow us to distinguish between two main variants of refractoriness to therapy: refractoriness associated with persistent inflammatory activity (IRF) and refractoriness due to non-inflammatory mechanisms (NIRF), which in some cases can overlap. However, from a practical point of view, it is important to distinguish between them, since IRF dictates the need for correction of anti-inflammatory therapy, and NIRF requires a different approach to treatment.

Generally accepted composite indices, which are widely used in clinical practice, provide a standard comprehensive characteristic of the activity level, but do not allow us to specify what exactly is associated with its increase in a particular case [10]. They cannot help to distinguish between the two above-mentioned forms of refractoriness either. Therefore, to characterize the patient's status, it is advisable to use not only the final values of the indices but also their baseline values. Y. C. Lee et al. [11], having examined 169 RA patients, identified three variants of pathological changes. In the first variant, low values of objective measures of inflammatory activity, pain, fatigue and psychoemotional distress were observed. In the second variant, low values of inflammatory activity measures were combined with a high level of pain, fatigue and psychoemotional distress, whereas in the third variant, all these parameters had high values.

The combination of low activity of the inflammatory process with high values of the parameters evaluated by the patient may be the reason for an unjustified change of medications. Thus, in some patients with clinical symptoms of arthritis, ultrasound examination of the joints showed no signs of inflammation, which confirms the absence of good reasons for strengthening anti-inflammatory therapy [12]. SJC, the concentration of CRP and the development of erosive changes in the joints are considered the main predictors of the progression of RA and its unfavorable outcome [13]. Apparently, these parameters can be used to distinguish between IRF and NIRF.

IRF may be due to the peculiarities of RA pathogenesis. It is known that biologics aimed at suppressing various cytokines involved in the development of the disease do not always have similar effects, even in the groups of patients with homogeneous clinical manifestations. This suggests that RA is not a single nosology, but a syndrome in which similar clinical manifestations may have different pathogenetic mechanisms [14]. The differences may be related to genetic characteristics, participation of various environmental factors in the development of the disease (for example, infection, smoking), localization of the key processes that induce chronic inflammation (for example, the oral cavity, lungs, gastrointestinal tract).

It is believed that the occurrence of a chronic inflammatory process characteristic of RA is due to hereditary predisposition, which can be realized when exposed to certain environmental factors that induce activation of the innate and acquired immunity, which, in turn, leads to the development of chronic autoimmune inflammation.

Genetic parameters determine not only predisposition to the disease, but also, to a large extent, the severity of the course of RA and the speed of its progression. The most significant alleles for RA belong to Class II of the main histocompatibility complex (HLA). A common epitope associated with the risk of developing RA was found in the third hypervariable region of the DRI chain. The main risk factors include DRB*0401, DRB*0404, DRB*0101 and DRB*1402. More than 90% of RA patients are carriers of at least one of these variants [15].

However, to date, there are no data confirming the presence of genetic factors predisposing to the development of IRF in RA patients. It is possible that genomic studies will allow to identify the genotypic trait responsible for the formation of this variant of the disease. At the same time, it should be taken into account that IRF can develop gradually.

The results obtained in the treatment of patients with early RA show that the good effect achieved at the beginning of therapy is often lost over time [16]. In some cases, this phenomenon is associated with the formation of antibodies to the drug. However, they occur only in some patients. Apparently, IRF can be mediated by epigenetic disorders that accumulate in chronic arthritis. Epigenetic factors such as DNA methylation, changes in microRNA and long non-coding RNA may occur before treatment or develop under the influence of aging processes and ongoing therapy, contributing to the formation of IRF [17].

It is possible that epigenetic changes in RA cause modification of the pathogenetic mechanisms. Thus, DNA methylation significantly differed in patients with early and late stages of RA, as well as in those who responded and did not respond to therapy [18]. These data not only demonstrate the role of methylation in RA, but also partially explain the heterogeneity of the course of the disease and the existing differences in the effectiveness of therapy. The features of DNA methylation, which are detected at different stages and with different subtypes of RA, allow us to speak about the participation of epigenetic changes in the formation of the disease variant that is resistant to treatment.

Changes in the expression of microRNA and long non-coding RNA, which serve as epigenetic regulators of gene expression and cell state, were also detected in RA [19]. Medications and environmental factors, including smoking, can contribute to the occurrence of epigenetic changes that cause resistance to therapy. It is believed that there is a two-way relationship between epigenetic changes and the inflammatory process. Thus, inflammation induces epigenetic changes, which, in turn, can modify the immune response, and vice versa [20].

Epigenetic disorders, apparently, are able to mediate the action of non-genetic risk factors and participate in maintaining the chronic course of the inflammatory process. It is likely that disturbance of DNA methylation partly explains the genetic risk associated with HLA, since it is one of the factors affecting gene expression [21]. Although epigenetic factors can support the chronic character of inflammation, their role in the formation of IRF is not yet clearly defined.

Somatic mutations affecting the components of the innate and acquired immune response involved in the pathogenesis of RA can also contribute to the occurrence of epigenetic changes in RA. In particular, somatic mutations of CD8+ T cells in early RA have been described [22]. Epigenetic and somatic mutations can affect the formation of IRF through smoking. In smokers, the level of DNA methylation can mediate the effect of smoking on

the rs6933349 genotype, leading to the formation of antibodies to citrullinated proteins [23].

It should also be taken into account that in patients with RA, smoking can induce refractoriness to treatment due to non-inflammatory mechanisms. This is indicated by the existence of an independent relationship between smoking and chronic pain [24]. The presence of clinical symptoms in RA patients that are not directly related to chronic inflammation may be due to a number of other factors. Thus, the development of NIRF can be facilitated by the peculiarities of pain perception, which differ in men and women [25]. In particular, refractory RA, which does not differ in the joint count, the level of CRP and the nature of radiological changes from the corresponding values in patients in remission, is more common in young women [26].

Persistent pain, which is noted in such patients, is not eliminated by powerful anti-inflammatory drugs, and may be associated with central sensitization, which develops with delayed administration of adequate therapy [27]. Therefore, such a delay can cause the development of NIRF. When performing multi-modal magnetic resonance imaging in RA patients, it was shown that pronounced inflammatory changes are associated with an increase in the number of connections between specific areas of the brain, and the presence of such connections is a predictor of the development of fatigue, pain and cognitive dysfunction [28].

In some cases, the target level of activity cannot be achieved in patients with concomitant diseases. Persistent arthralgia in such patients may be associated with concomitant osteoarthritis, and the presence of depression may negatively affect the outcome of RA treatment [29]. Cardiovascular pathology and osteoporosis are among the most significant comorbid diseases for patients with RA [30]. Concomitant pathology, on the one hand, can be an obstacle to the administration of adequate therapy, and on the other hand, it can significantly affect the result of determining the activity of RA [31]. The result of treatment largely depends on the psychological status of the patient. According to V. V. Rybakova et al. [32], one of the important factors determining insufficient effectiveness of therapy is the low level of resilience of patients, their inability to adequately adapt to a stressful situation.

The presence of various variants of D2T RA and the need to use a personalized approach to treatment emphasize the relevance of creating special recommendations for management of this category of patients. The first step towards the development of such recommendations was the definition of the concept of D2T RA, recently presented by the EULAR working group [33]. It provides for the patient's compliance with three criteria: insufficient effectiveness of the therapy; the presence of active symptomatic disease and clinical perception.

The first criterion includes ineffectiveness of at least two biologics or targeted synthetic DMARDs (tsDMARDs) with different mechanisms of action (if access to treatment is not limited by socio-economic factors) in a patient who previously received traditional DMARDs without sufficient effect. If traditional DMARDs are contraindicated, then ineffectiveness of at least two biologics or tsDMARDs with different mechanisms of action is a sufficient condition.

The second criterion provides for the presence of at least one of the following signs: a) at least moderate disease activity in accordance with one of the validated composite indices including joint score (for example, DAS28-ESR >3.2 or Clinical Disease Activity Index, CDAI >10); b) parameters (including acute phase reactants and data from instrumental imaging methods) and/or symptoms indicating disease activity (related or unrelated to joints); c) failure to reduce the dose of GC (<7.5 mg/day of prednisone equivalent); d) rapid radiological progression (a change in the score according to Sharp's method [van der Heijde modification] by at least 5 units per year) with or without signs of disease activity; e) a well-controlled disease in accordance with the above parameters, but persistence of RA symptoms that worsen the quality of life.

The third criterion suggests that the doctor and / or the patient should consider that correction of clinical and / or laboratory-instrumental manifestations of the disease is problematic. RA can be regarded as D2T if all three of these criteria are present.

Currently, the basis for the management of RA patients is a standardized algorithm set out in the international and national recommendations for treatment of this disease and provides for the early administration of anti-rheumatic drugs with subsequent regular correction of the therapy, depending on the results obtained. In most cases, such a scheme makes it possible to effectively control inflammatory activity and restrain the progression of destructive changes. However, in a number of patients, it fails to maintain remission or low RA activity.

Insufficient effectiveness of the therapy can be caused by various factors: individual features of the disease course causing the development of inflammatory process resistant to the therapy, epigenetic changes that can modify the course of chronic inflammation, the impact of adverse environmental factors, in particular smoking, as well as psychological characteristics of the patient. In general, in our opinion, such a situation may be associated with a number of «features»: errors in the treatment and monitoring of RA; individual properties of the organism; personal characteristics of the patient and rheumatoid inflammation itself.

Currently, among the possible subtypes of D2T RA we can distinguish true, pharmacokinetic and false-positive refractoriness. Each of these types has its own specific mechanisms of development [34].

Thus, the identification of a special form of D2T RA and the development of generally accepted criteria for identifying such patients are necessary conditions for further study of the problem of D2T RA and development of recommendations for management of such patients.

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