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Modern Approaches to the Treatment of Rheumatoid Arthritis: Issues of Low Efficacy of Pharmacotherapy from the Point of View of Treatment Adherence

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Abstract: The psychological and social aspects of rheumatoid arthritis have been the subject of research for many years, but there are still many contRFversial, insufficiently studied issues, and the interpretation of some of them is very contradictory. Among them is the relationship between the clinical, psychological and social characteristics of patients with RA; work on a comprehensive assessment of quality of life as an integral indicator of health is rare; factors influencing quality of life have been little studied. The World Health Organization (WHO) recommends defining quality of life as the relationship between human health indicators and socio-economic factors, which is assessed as a set of physical, emotional, mental and intellectual characteristics of a person that determine his ability to function in society. However, the medical concept of quality of life includes primarily indicators related to human health.

Keywords: rheumatoid arthritis, pharmacotherapy, gene engineering biological drugs, compliance.

Joints the most wide spread out inflammatory chronic from diseases one is this rheumatoid Arthritis (RA) is considered h . This is the reason unknown has been chronic autoimmune disease of the joints synovial of the veil proliferation with late , ya qq ol manifestation has been eRFsive arthritis and internal of members systematic inflammatory damage with It is described with the world of the population by about 1% near suffering smokes [1]. In the first 5 years of the disease, more than 40% of RA patients become disabled due to severe joint destruction. The course of the main disease in patients with RA is characterized by a high risk of developing comorbid pathologies such as cardiovascular diseases, amyloidosis, osteoporosis (OP). It has now been shown that in RA, not only local joint periosteum, but also diffuse OP develops, leading to vertebral and peripheral bone fractures. RA belongs to the group of diseases characterized by the polarization of the immune response of the Th1 type, which is manifested by the high production of inflammatory cytokines, primarily TNF, and at the same time is a classic B-cell autoimmune disease, which has the characteristic of causing damage to the joint tissue in its most prominent manifestations. includes the synthesis of a wide range of autoantibodies, such as antibodies to citrulline proteins (ACCP), rheumatoid factor (RF) [2,3]. According to KA Kuhn and co-authors [4], these autobodies are formed long before the appearance of clinical symptoms of the disease and are later associated with the development of severe RA. In addition, B-cells stimulate the activation of T-cells and increase the production of high-spectrum pro-inflammatory cytokines, such as TNF, lymphotoxin, interleukin-6, etc., which are of fundamental importance in the development and exacerbation of RA [5].

Today, this disease has a high prevalence, severe consequences such as fractures, significant mortality, significant mortality (for example, up to 35.1% in the first year after a fracture of the tibia), reduced

quality of life, the need for external care, prevention, rehabilitation and due to the high costs of treatment it is a social disease [6].

Despite significant advances in the treatment of RA, the life expectancy of this category of patients remains low compared to the general population. In clinical trials (CT), the main therapy prescribed in the early stage of RA preserves or even improves the quality of life of patients with RA, increases its duration and reduces the overall cost of medical care [7]. The basis of RA treatment is drug-based anti-inflammatory therapy, which includes the use of a wide variety of drugs that differ significantly in terms of composition, pharmacological properties, and mechanisms of action. In recent years, there have been significant changes in the treatment of RA. This is due to several factors: firstly, with the expansion of early diagnosis of RA, it allows to start an active, carefully controlled treatment with the main anti-inflammatory drugs (MAID), primarily methotrexate (MT) at the initial stage of the disease [8,9,10]; secondly, the development of a new class of anti-inflammatory drugs called genetically engineered biological drugs (GIBP) that selectively block important links of immunopathogenesis [11,12,13]. According to different authors, OP is 2-3 times more common in patients with RA than in the general population [14,15,16]. Fear of fractures by patients with musculoskeletal injuries leads to further limitation of physical activity and exacerbation of OP. Often, the treatment of RA patients is accompanied by the use of drugs that affect bone metabolism, in particular, glucocorticoids (GC) and cytostatic therapy. M. B. Nasonova in her work[17] showed that patients with RA who received treatment with GK≥7.5 mg/day for more than 12 months had a decrease in bone mineral density (BMD) regardless of RA activity and functional deficit in the patient. In RA patients treated with GC, the risk of developing OP is almost 3-fold higher in the spine and proximal thigh [18], where the total dose of GC is an independent risk factor for the development of OP [19]. The use of GIBP not only significantly improved treatment outcomes, but also allowed to expand the understanding of the mechanisms of RA development and exacerbation. However, a dramatic change in the prognosis depends not only on the implementation of innovative drugs, but also on improving the strategy of RA pharmacotherapy with the rational use of standard anti-inflammatory drugs (MAID), primarily methotrexate (MT) and possibly glucocorticoids [20]. The strategy for treatment of patients with RA was formed within the concept of "Treat to Target" (T2T) [21] and RA [22,23] and early arthritis [24] and All-Russian public organization "Russian Association of Rheumatologists" It is clearly stated in the recommendations prepared by the EULAR expert group [25]. The main principles of the "Treatment until the goal" strategy in RA include the following basic rules:

- Treatment of RA should be based on a close interaction between the doctor and the patient.
- Treatment with ACE inhibitors should be started as early as possible, during the so-called "window of opportunity" - within the first 3 months from the time the first symptoms of RA appear.

The main goal of treatment is to achieve (and maintain) remission (in early RA) and/or low inflammatory activity (in advanced RA), allowing to preserve work capacity, quality of life and reduce the risk of early death. Compared to patients with moderate or high disease activity, patients in remission (or low disease activity) have better functional status, work capacity, and disease prognosis (reduced risk of early death). ACE inhibitors should be used in all patients with RA and should be prescribed as early as possible, no later than 3-6 months after the onset of symptoms of joint damage. It is a "first-line" drug that should be prescribed to all patients diagnosed with MT-RA and to patients with undifferentiated arthritis (UDA) who are at high risk of developing RA [26,27,28]. MT should be prescribed individually. If there is no risk of unexpected reactions (old age, impaired renal, hepatic function, liver, hematological disorders, etc.), MT treatment should be started at a dose of 10-15 mg per week, depending on effectiveness and intolerance, every 2-4 weeks 2.5- Rapidly increase from 5 mg to 25-30 mg per week. In patients with active RA who are resistant to MT monotherapy (including the subcutaneous form of the drug) at the maximum effective dose for at least 3 months with risk factors for poor outcomes, it is recommended to prescribe MT and other standard NSAIDs (sulfasalazine and hydroxychloroquine) in combination with GK or combined therapy with GK. In most cases, it is not less effective than the combined therapy of MT and GIBP. One of the most striking achievements of RA pharmacotherapy is related to the development of a completely new

group of drugs called " biologic " agents, whose mechanism of action is related to the suppression of the synthesis of TNF-α and IL-1- " inflammatory " cytokines. . It plays a key role in the immunopathogenesis of RA, as mentioned above.

It is recommended when GIBP therapy is insufficiently effective (maintains moderate/high activity) or when MT (including the subcutaneous form of the drug) or combination therapy with MT and standard ACE inhibitors are poorly tolerated. If there is an indication against MT (including the subcutaneous form of the drug) and other ACE inhibitors and they tolerate them poorly, GIBP monotherapy can be performed.

Currently, 3 groups of drugs are used in the treatment of RA, 2 of them - monoclonal antibodies (mAT) to TNF - α - infliximab (Remicade) and IgG (Etanercept) combined with Fc fragment α receptor - recombinant soluble TNF - functional activity of IL-1 inhibits the synthesis and biological effects of suppressor α -TNF and recombinant soluble antagonist IL-1 (Anakinra). There is evidence that the use of biological inhibitors of α-TNF and IL-1 can reduce the activity of the immunopathological process and achieve a clinical effect, improve the quality of life and slow down the radiographic development of joint damage even in patients resistant to previous therapy with standard "main" drugs. All drugs are effective in combination with methotrexate in patients with active RA unresponsive to methotrexate monotherapy. Infliximab is allowed to be used together with methotrexate, and Etanercept and Anakinra - as monotherapy or in combination with other "primary" drugs, except for "biological" inhibitors of α-TNF.

The use of GIBP has made it possible to achieve significant progress in the treatment of RA, which could not be achieved with standard chemical ACE inhibitors and glucocorticoids (GC). In recent years, a number of randomized placebo-controlled studies (RPNT) and open-phase studies have been conducted, which not only confirmed the high efficacy and safety of rituximab in RA patients resistant to therapy with standard ACE inhibitors and α-TNF inhibitors, but also created the necessary conditions for optimizing the use of the drug in this disease. [29,30,31,32]. The choice of rituximab as the first GIBP should take into account its high efficacy in rheumatoid and cryoglobulinemic vasculitis associated with carriage of the hepatitis C virus, in the RF/ABTs-positive variant of RA. Other possible reasons for choosing rituximab include the presence of contraindications to the use of α-TNF inhibitors (autoimmune disorders, malignant tumors in the previous 10 years, risk of reactivation of latent tuberculosis infection, demyelinating diseases of the central nervous system, in particular multiple sclerosis). Rituximab is a very effective and relatively safe drug for the treatment of RA, which can be considered as a prototype of a new direction in the treatment of autoimmune diseases based on the modulation of B-cell immunity.

About 40% of patients do not respond well to treatment with α-TNF inhibitors [33], have contraindications or serious side effects [34]. The most characteristic unexpected reactions associated with GIBP treatment are infusion reactions and severe infections, including reactivation of latent tuberculosis infection, as well as post-injection reactions with subcutaneous administration of GIBP [35,36]. The risk of reactivation of latent TB infection during treatment with GIBP is high with infliximab, adalimumab, golimumab, and certolizumab, moderate with etanercept, abatacept, and tocilizumab, and low with rituximab. Risk factors for infectious complications include comorbid diseases (chronic kidney and lung diseases), older age, and treatment with GC. Against the backgRFund of treatment with all GIBPs, the development of psoriasis (often α-TNF inhibitors), increased activity of liver enzymes (tocilizumab, less often other GIBPs), cytopenia (leukopenia, thrombocytopenia), neutropenia, including "late" (rituximab) neutropenia can be observed.

As can be seen from the presented review, many drugs have been developed and used in practice for the treatment of RA, which differ in the mechanism and the point of application of drug action. These drugs, affecting different directions in the pathogenesis of this complex disease, significantly "change" the clinical-biochemical and clinical-pathophysiological shifts in the body, stabilize the destructive processes in the joints, and improve the course of the disease. However, the use of these drugs does not always and not in all patients lead to the expected result, often leads to the development of side effects.

Perhaps this is due to the empirical approach to the selection of these drugs, the lack of selection of drugs based on the "molecular picture" of the patient. These are based on the use of new methods of molecular analysis such as genomics, genomics, transcriptomics, proteomics, metabolomics, etc. [37]. Thanks to this approach, the doctor will be able to choose the most effective and safe drug and its dosage, which will undoubtedly help to increase the effectiveness of therapy, as well as reduce the frequency of side effects, as well as affect the costs of drugs, including expensive drugs, which in empirical selection may be ineffective [38].

It is known that the effectiveness of pharmacotherapy in a particular patient depends not only on the correct selection of a particular drug, but also on the patient's correct compliance with the doctor's instructions, taking into account the recommendations for their intake, that is, ensuring the correct intake of the selected drug. At the same time, if the question of choosing the right medicine is closely related to the professional skills and knowledge of the doctor, then the correct acceptance of the drugs prescribed by the doctor is related to the patient's self-discipline. At the same time, these two aspects of the treatment process are the basis for effective and safe pharmacotherapy.

Despite the intRFduction of new drugs with proven effectiveness into medical practice, the results of treatment are not good. Low adherence of patients to the treatment also plays a huge role in this.

There is a concept related to the fulfillment of the doctor's recommendations - " compliance " (English compliance - to agree, to say okay), which means " the patient's willingness to follow the recommendations " or " the patient's voluntary agreement to follow the recommendations " . Some authors use broader concepts: "therapeutic partnership" and "therapeutic alliance" [39]. What are the similarities and differences between these concepts? This concept describes the completeness of the patient's compliance with the doctor's instructions. Is compliance different from another commonly used term adherence ? The Oxford English Dictionary explains the meaning of the word "compliance" as " acting according to instructions " . JA Kramer and his co-authors in the review [40], from the point of view of developing a single understanding of this term, defined « compliance » (syn. « adherence ») as « the degree or extent to which a patient acts in accordance with the prescribed treatment recommendations » (degree or extent to which a patient acts in accordance with the prescribed recommendations about treatment). Therefore, when translating the word " compliance " in a medical text, it is most correct to use the Russian transcription " komplaens " , that is, according to the meaning of this term, the completeness of the patient's compliance with the treatment recommendations set by the doctor. According to some researchers, if the concept of "adherence" means active cooperation between the doctor and the patient during treatment, then the concept of " compliance " is the patient's unsatisfactory attitude to the doctor's instructions and the patient's simple compliance with medical instructions. At the same time, both concepts help to increase the patient's sense of responsibility for his health and timely compliance with the doctor's recommendations [41,42,43]. Danilov D. S. according to [44], the listed terms are not absolutely equivalent, but in daily clinical practice, these concepts are often used interchangeably and are mainly used to describe patients' correct adherence to medical instructions. [45].

Monitoring the patient's compliance with the doctor's instructions is a complex process. At the same time, it is very important to monitor the use of "necessary" drugs, the patient's lifestyle and diet. In this regard, in recent years, adherence to therapy has attracted the attention of doctors of all specialties. Therefore, the problem of low adherence to treatment is a global problem of practical medicine.

Adherence to treatment is considered unsatisfactory when a patient takes ≤80% or ≥120% of prescribed medication doses for a long period of time [46]. Taking the wrong dose of the recommended medication or taking it at the wrong time, sometimes not taking the medication, represent different forms of non-adherence. This includes the possibility of taking more drugs than recommended by the patient.

According to the WHO, one of the most pressing problems of modern medicine is the problem of insufficient adherence of patients to treatment, in particular, low adherence to recommendations, which in turn leads to the development of complications [47,48]. Osterberg. and co-authors [49], showed that

poor adherence to outpatient treatment resulted in a 33-65% increase in hospital readmissions. In the United States, hospitalization costs account for 11.7% of health care costs due to the low proportion of patients with chronic diseases [50]. According to expert research, long-term adherence to any treatment, regardless of disease, does not exceed 50% [51] Adherence rates in chronic disease adherence studies range from 43 to 78% [52,53,54,55]. Despite the fact that high adherence to treatment has a significant positive effect on the survival of patients with chronic diseases, only 50% of them adhere to treatment recommendations [56].

The duration of treatment required to significantly reduce the risk of cardiovascular complications is a subject of debate, but studies show that long-term therapy of 5 years or more produces the greatest effect [57,58]. However, in actual clinical practice, at least half of patients with arterial hypertension (AG) stop taking antihypertensive drugs six months after they are prescribed. [59]. Antihypertensive drugs have been found to reduce the risk of stroke and coronary heart disease by 34% and 21%, respectively [60 , 61]. In addition, high adherence to antihypertensive treatment was associated with a 38% lower risk of cardiovascular complications than low adherence. [62]. High adherence to treatment (90%) results in a 45% risk reduction compared to low adherence in patients with and without IUD [63].

According to the literature, approximately 54% of patients who recently started taking statins to correct hypercholesterolemia have periods of nonadherence of more than 90 days [64,65]. Studies from Western EuRFpe and the USA show that 18-50% of patients with SYuE show poor adherence to therapy (PRQ) [66,67]. Only 45% of patients with osteoporosis continue to take drugs after the first year [68]. Depression and cardiovascular disease (CVD) often coexist: the prevalence of depression in various CVD is aRFund 15% to 20% [69,70]. According to the WHO, by 2020 depression will be the second leading cause of disability in developed countries after heart disease [71]. Several studies have shown that patients with less than 80% of ideal antipsychotic medication adherence are 50% more likely to be hospitalized than those with high adherence [72].

In patients with diabetes, poor adherence to prescribed hypoglycemic, antihypertensive, and lipid-lowering medications was associated with a significantly higher risk of all-cause hospitalization (23.2% vs. 19.2%, r<.001) and all-cause mortality (5.9% vs. 4.0%). , correlated with r<.001) compared to highly adherent patients [73].

It is known that the main therapy prescribed in the initial stage of rheumatoid arthritis preserves or even improves the quality of life of patients suffering from this pathology and naturally reduces the overall cost of medical care [74]. However, this can be achieved if patients follow their doctor's recommendations for treatment regimen and duration [75,76,77]. Studies by several authors show that in clinical practice, 35 to 55% of patients with rheumatoid arthritis have problems with adherence to treatment [78,79]. L. F. In the research conducted by Ryabtseva and his co-authors [80], it was shown that only 22.5% of patients with rheumatoid arthritis received pathogenetic treatment more than 80% of the time. However, 5% of patients never received the prescribed treatment at all. Also, O.V. Research by Kremleva and co-authors[81] confirms that patients with rheumatoid arthritis have low adherence to pharmacotherapy. In doing so, the researchers found that disease outcomes were the same in patients who received irregular treatment as in patients who did not start treatment. The main reasons for drug discontinuation were side effects related to their administration and unauthorized drug discontinuation [82].

Thus, in recent years, a problem affecting the effectiveness of treatment of patients according to the most modern medical standards has been clearly identified. There is considerable evidence on the impact of high adherence on endpoints during long-term treatment and follow-up of patients with chronic diseases and in primary prevention settings. Currently, the problem of adherence to treatment (both drug and non-drug) is arguably a greater problem than the disease itself and the problems directly related to the drugs.

It should be noted that early determination of the level of adherence to treatment in a particular patient helps the doctor to orientate himself and determine the directions of working with the patient, in

addition to prescribing drug therapy. Assessment and control of patient adherence during long-term follow-up and treatment reduces the frequency of disease exacerbations, improves the patient's quality of life, and reduces the progression of the disease due to adequate therapy and monitoring of its acceptance.

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