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# Current Treatments for Rheumatoid Arthritis

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**Abstract:** Rheumatoid arthritis (RA) is an autoimmune disease in which the immune system attacks body tissues. It primarily affects the joints, but can also cause inflammation of organs such as the lungs, eyes, skin and heart. Patients may experience periods of increased symptoms, alternating with periods of reduced symptoms or no symptoms at all. It affects about 1% of the world's population, and it is estimated that about 75% of patients are women. There is no cure for rheumatoid arthritis, but medication can stop the progression of the disease and relieve symptoms.

**Keywords:** Rheumatoid arthritis, polyarticular synovial inflammation, articular cartilage, immune inflammation.

**Introduction.** Rheumatoid arthritis (RA) is a chronic, systemic immuno-inflammatory joint disease that affects approximately 1% of the population [1]. The disease affects people of all ages, but is most common between the ages of 40 and 60. The main clinical characteristic of the disease is polyarticular synovial inflammation with symptoms such as swelling, pain and stiffness in the joints, impairing joint function. Over time, synovitis leads to articular cartilage damage, bone erosions, subluxations, and even joint destruction, including bone ankylosis, leading to permanent disability. In addition, patients with RA have an increased mortality rate compared to the general population, which is primarily due to the increased risk of cardiovascular disease due to the rapid development of atherosclerosis due to immune inflammation [2]. The prevalence and severity of this pathology, the complexity of pathogenetic mechanisms, and the heterogeneity of the clinical forms and course of the disease make its therapy a major challenge. RA has a negative impact not only on patients and their families, but also on society as a whole due to disability, reduced patient productivity, and the need for resource-intensive medical care, which emphasises the importance of effective management [3,4]. Over the past two decades, the optimisation of the use of synthetic basic anti-inflammatory drugs (BARDs) and the advent of genetically engineered biologics (GEBPs) have made effective suppression of inflammation, inhibition of joint destruction and improved overall treatment outcomes possible. The goals of treatment have changed from controlling the symptoms of inflammation and achieving low levels of disease activity to achieving and maintaining clinical remission in a significant number of patients. In addition to suppressing inflammation, inhibition of the progression of joint destruction has also become an important and achievable goal. Finally, with the help of modern drug therapies, it is possible to preserve and restore functional capabilities, reduce the likelihood of developing RA-related pathology (atherosclerosis), restore patients' quality of life, and keep them socially active. An assessment of the outcomes of RA, based on an analysis of the long-term dynamics of activity and disease progression in long-term cohort studies and clinical observations, allows the following main conclusions to be drawn regarding the possibility of controlling the disease [6]:

- RA is a heterogeneous disease in terms of clinical and immunological characteristics, inflammatory activity and the rate of progression of destructive changes;

- the main factors determining the outcome of RA are the severity and persistence of inflammation;
- early treatment is most effective in the early stage of the disease;
- early prescribed pathogenetic therapy allows to some extent control the activity of RA, including the possibility of development of persistently low disease activity and clinical remission;
- different pathogenetic therapies may have different potential for inhibiting structural abnormalities.

One of the most important advances in the treatment of RA has been the introduction of DAAs. In the Russian Federation 8 drugs of this group are currently registered for the treatment of RA. While treatment with DAAs, primarily methotrexate, is the mainstay of drug therapy for RA, DAAs are the main means of overcoming drug resistance in patients with a severe, torpid course of the disease. The introduction of modern methods of aggressive therapy for RA has changed the idea of the goal of treatment - as mentioned above, it is to achieve clinical remission in most patients. Despite the importance of introducing new drugs, an optimal treatment strategy is now recognised as a major component of therapeutic success. The main principles of successful treatment of RA, based on data from a major meta-analysis, are:

- ✓ immediate initiation of active treatment once the diagnosis has been established;
- ✓ active management of the patient and careful monitoring of the patient's condition;
- ✓ selection of a new therapy if the previous one is not effective.

These principles are based on a large body of evidence. At the same time, the authors of the meta-analysis specifically point out that there is no reason to believe that any particular regimen has a significant advantage over others. Intensive treatment paradigm for early-stage RA. In patients with early RA, it has been clearly demonstrated that active DMARD therapy, especially methotrexate, started as soon as the diagnosis is made, is effective not only in suppressing symptoms (pain and stiffness), inflammatory activity, and functional impairment, but also in preventing disability (see below), including delaying the progression of destructive changes in the joints. Treatment with synthetic DMARDs (methotrexate, leflunomide or sulfasalazine) is not only clinically effective (8), but can also suppress radiological progression. GIBP has also been shown to be highly effective in relieving clinical symptoms of RA and slowing radiological progression [2, 3]. The paradigm for early intensive treatment is to administer aggressive RA therapy as soon as possible after verification of the diagnosis. A Finnish study of combination therapy with synthetic DAAs compared to DAA monotherapy (FIN-RACO) in the early RA group [2,4] showed that within 2 years, 71% of patients in the DAA combination therapy group achieved a 50% clinical response (ACR50) compared to 58% with monotherapy. Interestingly, both groups had similar rates of improvement in clinical activity parameters after 5 years, but the combination therapy group showed significantly less radiological progression [ 5 ]. A meta-analysis comparing early (disease duration less than 2 years) administration of DAAs versus delayed administration of synthetic DAAs at a later date demonstrated a significant reduction in the long-term rate of radiological progression in patients with RA who received DAAs early in the disease [ 6 ]. Targeted therapy and close monitoring in RA. Until now, many of the decisions physicians make to initiate and modify therapy for RA are based on subjective assessments of disease activity and functional impairment by the physician and the patient. At the same time, clinical tools for quantifying disease activity and functional status have been developed and validated and are recommended by the medical community and officially adopted in many countries [1,2]. In RA, the "tight control" paradigm borrowed from other fields of medicine, such as diabetology, has been actively used over the past decade. Several large studies (TICORA, BeST, CAMERA, the previously mentioned FIN-RACO) have provided important data showing that clinical outcomes in patients with RA can be improved without prescribing innovative drugs, but only using active case management with specific treatment goals and the use of quantitative methods to assess disease activity. In the TICORA study [2, 8], in the "strict control" group, or intensive care group, treatment with standard DAAs was intensified if disease activity at the time of the rheumatologist visit was

higher than the specific target values of the activity indices. In the conventional therapy group, changes in therapy at check-ups every 3 months were based on the physician's decision rather than on an assessment of disease activity, or were conducted with a specific target in mind. As a result, the intensive therapy group was characterised by lower disease activity and a higher rate of achieving clinical remission of the disease compared to the conventional therapy group.

In the CAMERA trial in early RA, patients in the intensive care group had their methotrexate dose revised monthly depending on the response to therapy by quantifying disease activity using a computerised decision-making programme. As a result, there was also a significant improvement in clinical response compared to the conventional management group. Thus, clinical studies have confirmed that targeted therapy of RA using quantitative assessments of disease activity leads to significant improvements in clinical outcomes. The Treat to Target strategy The current paradigm for the management of RA patients was introduced in 2010 in the Treat to Target (T2T) international programme [3]. T2T does not specify specific treatments, but outlines general principles and recommendations for the optimal management of patients. The consensus reached is based on evidence from a systematic review of the literature, which describes strategic therapeutic approaches that provide the best results. The latest guidelines were adopted in March 2009 and were developed with input from 60 experts from 25 countries in Europe, North America, Latin America, Japan and Australia, as well as patient representatives. The guidelines do not mention any specific drugs or classes of drugs; the emphasis here is on therapeutic strategies aimed at improving care for patients with RA. The general principles of T2T are formulated as follows: A. Treatment of RA should be based on the joint decision of the patient and the rheumatologist. B. The main goal in the treatment of the RA patient is to ensure the longest possible maintenance of a high health-related quality of life by controlling symptoms, preventing structural damage to joints, normalising function and increasing the patient's social opportunities.

C. Suppression of inflammation is the most important way to achieve this goal. D. Pre-targeting treatment by assessing disease activity and appropriately selecting therapy optimises outcomes in RA. Based on general principles, an international committee has developed 10 T2T recommendations for the treatment of RA prior to goal achievement, based on scientific evidence and expert opinion.

1. The primary goal of RA treatment is to achieve a state of clinical remission.
2. Clinical remission is defined as the absence of evidence of significant inflammatory activity.
3. Although remission remains the primary goal, current scientific evidence suggests that achieving mild, low-grade RA is an acceptable alternative treatment goal, especially in stable, long-term disease.
4. Review of drug therapy should be undertaken at least every 3 months until the treatment goal has been achieved.
5. The disease activity data should be assessed and documented regularly: in patients with moderate/high levels of activity, monthly; in patients with persistently low activity or in remission, less frequently (once every 3-6 months).
6. In everyday clinical practice, validated composite measures of disease activity, including joint assessments, should be used for treatment decisions.
7. In addition to the use of composite measures of disease activity, structural changes and functional impairment should be considered when making clinical decisions.
8. The desired treatment goal should be strived for throughout the course of the disease.
9. The choice of (composite) disease activity index and target parameters can be influenced by comorbidities, individual patient characteristics and risks associated with medication administration.
10. The patient should be sufficiently informed about the treatment goal and the planned strategy to achieve this goal under the supervision of a rheumatologist. For specific drugs and regimens,

recommendations are based on data from major meta-analyses. With regard to traditional (synthetic) DAAs such as methotrexate, leflunomide, etc., which are still the mainstay of pathogenetic therapy for RA, the following conclusions have been substantiated :

- methotrexate among all synthetic DAAs is the most effective against RA activity and structural damage;
- leflunomide is close to methotrexate in efficacy;
- sulfasalazine and gold salts (injectable) are effective against symptoms and structural damage;
- cyclosporine, hydroxychloroquine, minocycline, tacrolimus effective against joint syndrome;
- auranofin and D-penicillamine have no strictly proven superiority over placebo;
- cyclophosphamide and azathioprine increase the risk of tumours and infections. Thus, a systematic review has confirmed that methotrexate has a well-deserved position as the "gold standard" in pathogenetic therapy of RA and should be prescribed (in the absence of contraindications) as a first-line drug among DAAs.

Glucocorticoids (GCs) remain an important component of RA treatment. We know the following basic facts about their use in RA :

- ✓ GCs are effective as bridge therapy (i.e. when administered in low to medium doses for a relatively short period of time before the DAAs expire or when changing baseline drugs);
- ✓ In early RA, low doses of HA (≤7.5 mg/day of prednisolone) may reduce radiological progression;
- ✓ In advanced and late RA, HC doses ≤15 mg/day may reduce disease activity;
- ✓ The dose of HC can be slowly reduced when success is achieved.

At present, the most dynamically developing group of antirheumatic drugs, GIBP, is represented in Russia by 8 drugs with different mechanisms of action and directed against various target molecules. The most long-standing and widely used in rheumatology drugs among the SSRIs are tumor necrosis factor-α (TNF-α) inhibitors, which include monoclonal antibodies infliximab, adalimumab and golimumab, recombinant molecule containing soluble TNF-α receptor - etanercept, and the drug containing PEGylated Fab fragment of antibody to TNF-α certolizumab pegol. TNF-α inhibitors have traditionally been considered first-line biological therapies, as they (more specifically, infliximab and etanercept) were the world's first GIBPs and have the largest evidence base in RA. At the same time, evidence accumulated in recent years suggests that other DAAs, such as rituximab or tocilizumab, could also be used as first-line biological therapies. According to a major systematic review [14], the most evidence-based data on the use of GIBPs in RA is as follows

- Effective in initial administration in patients who have not previously received methotrexate: infliximab, adalimumab, etanercept, abatacept;
- effective in patients with insufficient response to methotrexate: infliximab, adalimumab, etanercept, rituximab, tocilizumab, abatacept;
- switching to rituximab, tocilizumab, abatacept is effective if the response to TNF inhibitors is insufficient;
- switching to another anti-PNF drug if the first drug in this group does not respond well is possible, but less well supported by evidence;
- TNF inhibitors increase the likelihood of infection. The European League Against Rheumatism (EULAR) established new clinical guidelines for the treatment of RA in 2010[3,16]. These, as well as the T2T programme, contain the basic principles and the guidelines themselves. The basic principles are formulated as follows:
- Rheumatologists are specialists who are primary caregivers for RA patients;

- The treatment of RA patients should aim at the best possible outcome and be based on the joint decision of the physician and the patient;
- RA is an expensive disease in terms of medical and performance-related costs; these circumstances should be considered by the treating rheumatologist. The EULAR guidelines for the treatment of RA are summarised below:

1. As soon as a patient is diagnosed with RA, treatment with synthetic DAAs should be prescribed immediately.
2. The aim of treatment is to achieve remission or low disease activity as quickly as possible in each patient. If this goal is not achieved, therapy must be selected by frequent monitoring (every 1-3 months).
3. methotrexate should be part of the first strategic regimen in patients with active RA.
4. If methotrexate is contraindicated (or intolerant), the following DAAs should be discussed as a (first) treatment strategy: sulfasalazine, leflunomide and gold salts (injections).
5. For patients who have not previously received a DAA, monotherapy rather than combination therapy with synthetic DAAs is recommended.
6. GCs can be useful as initial therapy (short-term) in combination with synthetic DAAs.
7. If the goal of therapy is not achieved after initial prescription of DAAs, then if there are adverse prognostic factors (positive rheumatoid factor and anti-citrulline antibody tests, early erosions, rapid progression, high disease activity), the addition of an SSRI should be discussed, and if there are no adverse prognostic factors, a switch to another synthetic DAA should be considered.
8. Patients inadequately responding to methotrexate and/or other synthetic DAAs should be prescribed DAAs. Current practice is to prescribe an TNF-α inhibitor to be combined with methotrexate.
9. If therapy with the first TNF inhibitor fails (ineffective or intolerant), the patient should be given a second TNF inhibitor, abatacept, rituximab or tocilizumab.
10. In refractory severe RA, or in the presence of contraindications to SSRIs or the synthetic DAAs mentioned above, the following drugs in monotherapy or in combination with the above agents may be discussed: azathioprine, cyclosporine A, cyclophosphamide.
11. Intensive treatment strategies should be applied in each patient, with priority given to patients with unfavourable prognostic factors.
12. If the patient is in persistent remission, the dose of HCV should be reduced, and a reduction in the dose of SSRIs may be discussed, especially if this therapy is combined with a synthetic DAA.
13. In long-term sustained remission, cautious titration of the dose of DAAs may be discussed as a shared decision between physician and patient.
14. In patients with poor prognosis factors and who have not previously received a DAA, methotrexate in combination with an SSRI (as first-line treatment) may be discussed.
15. In addition to disease activity, factors such as progression of radiological changes, comorbidities and safety considerations should be taken into account when selecting therapy. The EULAR clinical guidelines for the treatment of RA emphasise the earliest possible initiation of therapy with potent drugs, such as methotrexate and GIBP. However, for patients with a serious prognosis, the combination of methotrexate and GIBP as the first line of pathogenetic therapy is recognised. A specification of the T2T algorithm is needed for practice. Based on the EULAR guidelines, a conceptual framework can be presented. Treatment should start with methotrexate, optimally using its subcutaneous injectable form, which may be more effective and well tolerated compared to oral forms. If necessary, the patient should be switched to a combination of methotrexate and GIBP. If successful, the latter regimen is retained; if not successful, the therapy

is reviewed again quarterly. Medical and social implications of the modern RA treatment strategy.

In countries where rheumatological care is well established, there is now convincing evidence of significant improvements in reducing the burden of the disease on society. One of the most important consequences of a modern aggressive treatment strategy for RA has been a reduction in long-term disability. According to the Swedish National Social Insurance Register [3, 6], in the 1990s, RA was responsible for almost 2% of all permanent disability requiring a pension. This percentage had already fallen significantly (to 1.5 %) by the year 2000 and by 2009 it was halved (1 %). In Finland [7,15], a decrease in the disability among RA patients with disability during the first 2 years of the disease was observed, from 8.9% in 2000 to 4.8% in 2007. A report from the USA [8] has noted that a reduction in the risk of disability was already observed when comparing groups of RA patients taken under observation at the beginning and at the end of the 1990s. At the same time, in spite of good results in clinical practice in some cohorts of RA patients, for example, when using adalimumab, other cohort studies [4,11], as well as metaanalysis, show that prescription of GIBP does not by itself produce such a pronounced effect on the disability of patients. Thus, it is the new RA treatment strategy that has led to a significant reduction in long-term disability. Another important consequence of the change in treatment strategy for RA is the reduced need for major orthopaedic surgery, such as joint replacement. Reports from Scandinavian countries are a prime example. Thus, according to data from Swedish registries, between 1998 and 2006 the rate of total hip replacement in RA patients was also almost halved (from 12.6 to 6.6 per 1000 patients). To be fair, it should be noted that no such pattern has been found for total knee arthroplasty. Similar reports of decreased need for orthopaedic surgery in RA have been published by researchers in different countries with different levels of health care funding, such as the USA, Japan and Brazil. It is noteworthy that this trend emerged in the early 2000s, in the "prebiologic" era of RA (suggesting the importance of early aggressive therapy with methotrexate and other active DAAs), and has continued with the widespread introduction of DAAs[14,16]..

**Conclusions:** Thus, with the proliferation of drugs for the treatment of RA, physicians and patients are faced with difficult decisions regarding the initiation and discontinuation of different drug therapies. Numerous studies confirm the importance of choosing the right patient management strategy, which is currently most concentrated in T2T recommendations. There is a need to incorporate this strategy into routine clinical practice in order to optimise treatment outcomes and reduce the damage that RA causes to society.

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