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LITERATURE REVIEW OF MODERN TREATMENT OF RHEUMATOID ARTHRITIS

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Abstract
Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases of the joints (about 1% in the population), has a steadily progressive, relapsing course with exacerbations and periodically decreasing activity, is characterized by progressive synovitis , damage to the articular cartilage and bone marginal zones. The development and progression of the pathological process in the joints occurs in the first years of the disease, so the “window of therapeutic opportunities” is small, and the problems of early diagnosis and pharmacotherapy of this disease are relevant.

Keywords: rheumatoid arthritis, glucocorticosteroids , non-steroidal anti-inflammatory drugs, therapy, physiotherapy

Introduction

There are three main milestones in the treatment of RA. In 1948, corticosteroids were used for the first time, and patients and doctors had hope in the successful treatment of this pathology. In 1985, the first studies were completed demonstrating the high efficacy of low doses of methotrexate (once a week). The end of the twentieth century was marked by a breakthrough in the development of new anti-inflammatory drugs obtained using biotechnological methods (monoclonal antibodies).
For the treatment of RA, the following groups of therapeutic agents are used: basic anti-inflammatory drugs (DMARDs): synthetic, biological; non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCS).
Severe progressive course, early disability of patients determine the modern strategy for the treatment of RA and provide for the earliest possible administration of basic anti-inflammatory drugs (DMARDs) in the most effective and tolerable doses.

Main Part

The main goal of DMARD treatment is remission, or at least very low disease activity. Previously, the position was cultivated that treatment with antirheumatic drugs was “good enough,” and remission was considered as much as desirable, as little achievable . Today it is believed that basic therapy can slow down the progression of

the disease and cause a stable remission, especially if it is started with a duration of symptoms <12 weeks, so treatment with "basic" drugs should be started no later than 3 months later. If their appointment is delayed, then not all basic preparations may “have time” to show their effect. The longer the duration of the disease (long-term RA sufferers) before the appointment of "basic" drugs, the worse the response to "basic" drugs (category 1a) compared with patients who received this therapy at an early stage of the disease. It is better if they are prescribed immediately after the diagnosis is established.

The indications for immediate consultation with a rheumatologist and the decision on the subsequent appointment of basic therapy are the presence of criteria for early rheumatoid arthritis [2]:

- 3 swollen joints;
- involvement of the metatarsus / metacarpophalangeal joints (positive compression test);

Morning stiffness > 30 minutes.

Early start and duration of basic therapy are considered to be signs of a favorable prognosis in RA [3, 4]. The appointment of DMARDs in the first months after the onset of the disease can improve long-term functional and even life prognosis.

The means of basic therapy include the following groups of drugs: cytostatics - methotrexate , leflunomide , cyclosporine , aminoquinol derivatives - plaquenil , chloroquine , sulfasalazine , gold preparations, o-penicillamine. In recent years, the so-called biological agents (infliximab , rituximab , adalimumab) have also been referred to as basic drugs for the treatment of RA.

Among DMARDs, the drug of choice is methotrexate , the gold standard of therapy. Compared to other DMARDs, it has the best efficacy/toxicity ratio [4, 5]. It belongs to the group of antimetabolites, is a folic acid antagonist (inhibits dihydrofolate reductase), which is associated with its antiproliferative effect, and also has an anti-inflammatory effect. Methotrexate is prescribed once a week, using a fractional dose with a 12-hour interval, in the morning and evening hours [5].

It is believed that the minimum dose that can provide an immunosuppressive effect is 12.5 mg/week. Maximum doses of methotrexate up to 20-25 mg/week. We adhere to the following algorithm for prescribing methotrexate : an initial dose of 7.5-10 mg/week, after 4 weeks its efficacy and tolerability are assessed.

If the tolerability is good (there are no side effects according to clinical and laboratory parameters - first of all, liver enzymes (ALT and AST), a general blood test are evaluated), but the effectiveness of the drug is not manifested, then we increase the dose to 12.5-15 mg per week (4 -8th week).

Subsequently (9-10 weeks of admission), the dose of methotrexate , if necessary, can be increased even more (up to 20 mg / week). Reception at a dose of more than 25-30 mg/week is inappropriate (the increase in the effect has not been proven) [5].

When prescribing methotrexate , it is necessary to take folic acid to reduce the risk of developing side effects (gastroenterological and hepatic and, probably, cytopenia). Folic acid at a dose of 5-10 mg per week is prescribed 24 hours after taking methotrexate . The dose of folic acid should not exceed a weekly dose of methotrexate. To reduce the severity of side effects, it is also recommended: use short-acting NSAIDs, avoid prescribing acetylsalicylic acid (and if possible diclofenac), on the day of taking methotrexate , replace NSAIDs with glucocorticoids in low doses, reduce the dose of NSAIDs before and / or after taking methotrexate , exclude alcohol (increases the toxicity of methotrexate) and substances or foods containing caffeine (reduces the effectiveness of methotrexate) [5]. It is known that no more than half of patients can continue taking methotrexate for more than 5 years.

In recent years, data have appeared on the high efficacy of leflunomide in the early stages of RA. Leflunomide inhibits the proliferation of activated cells (T-lymphocytes, monocytes, macrophages), affects the production of antibodies and a number of cytokines (interferon-a and TNF-a), cell adhesion processes, which prevents them from activating the rheumatoid process [4].

Leflunomide is distinguished by the rapid development of the effect (after 2-4 weeks from the start of treatment). According to our data, in patients older than 50 years, the expected effect develops only by the 3rd month of treatment. Therapy with leflunomide is long-term and has been going on for years. Initial dose of 100 mg for 3 days (saturating), then 20 mg daily (maintenance).

The appointment of leflunomide in undifferentiated arthritis leads to the development of clinical and laboratory remission; it is possible to expand the indications for its use with the appointment at the first manifestations of arthritis in patients with moderate and high clinical and laboratory activity. This assessment allows us to consider leflunomide as a first-line drug in RA.

Leflunomide therapy is well tolerated by most researchers, side effects occur mainly in the first months of therapy, for the most part these symptoms are not severe and do not serve as a reason for discontinuing the drug [4, 5].

Sulfasalazine is prescribed only for non-severe forms of RA. The onset of the clinical effect of sulfasalazine is determined on average after 1.5-2 months. The effective dose of the drug is 2 g per day, which is achieved by gradually increasing it from 0.5 g per day. May be used in patients for whom methotrexate treatment is contraindicated. An

important component of combination therapy (primarily methotrexate , leflunomide, sulfasalazine) [2].

Today, D - penicillamine (cuprenil), in particular, and to a certain extent, aminoquinoline derivatives, gold salts are losing their importance as basic drugs in the treatment of RA. Cyclosporine is a drug with a reversible anticytokine effect, but not the drug of choice in patients with RA.

Regular monitoring of disease activity and side effects should lead to decisions on the choice and change of basic therapy.

Criteria for evaluating the effectiveness of treatment

Monitoring of disease activity according to the criteria of the American College of Rheumatology (ACR) includes:

- account of painful and swollen joints;
- determination of the level of pain assessed by the patient on a visual analogue scale;
- general assessment of the condition by the doctor and the patient on a visual analogue scale;
- duration of morning stiffness;
- ESR and C-reactive protein (CRP).

The effectiveness of basic therapy is assessed according to the positive dynamics of the above indicators: an improvement of more than 50% from the original indicates about the good effect and the possibility of continuing treatment; change by 20-50% - about a satisfactory effect and resolving the issue of combining basic funds; an improvement of less than 20% characterizes the absence of a therapeutic effect of monotherapy - a transition to another basic drug is necessary. At the same time, other reasons for the ineffectiveness of therapy (accession of concomitant pathology, etc.) should be excluded [2].

Disease activity should be assessed at least

1 time in 3 months until remission is achieved. It is also possible to evaluate remission according to the ASN criteria:

1. Absence of malaise.
2. Absence of joint pains.
3. Morning stiffness less than 15 minutes.
4. Painful joints.
5. Swollen joints.
6. ESR = normal, with five criteria must be present for more than 2 months.

The above methods for assessing activity should be supplemented with an assessment of the functional state of patients. (Health Questionnaire - HAQ). Structural joint

damage should be assessed using X-ray examination of the joints of the hands and feet. every 6–12 months during the first few years of illness [2].

During X-ray examination, the following rules must be observed:

- during the initial examination, perform radiography not only of the hands, but also of the feet (erosion in 23-36% of patients in the first 2-3 years is found only on the feet, and without any clinical manifestations);
- X-ray examination should be bilateral (erosion can be unilateral);
- X-ray should be performed annually during the first three years of the disease, which allows monitoring the course of the disease and the effectiveness of basic therapy.

Portability control. Let us immediately note that for all groups of drugs used in the treatment of RA, in contrast to drugs used in other areas of internal medicine, common side effects are pronounced side effects that can lead to serious complications, sometimes life-threatening for the patient.

When prescribing them, the issue of patient awareness is especially acute. The doctor is obliged to warn the patient about possible undesirable effects (most of which are predictable), the time of their occurrence, duration, the need for clinical and laboratory monitoring. At the beginning of treatment, side effects are monitored after 2 weeks for 24 weeks, then this period is extended to 2-4 months. Before starting therapy and during treatment, monitoring is carried out: a detailed blood test, a biochemical blood test (liver enzymes, urea, electrolytes) and blood pressure measurement are performed [2].

Currently, there is a serious problem of " under- treatment " of RA with basic drugs, even if they are timely prescribed: they treat with the wrong drug (rarely), insufficient doses of drugs, insufficient duration of therapy, they rely on monotherapy and, as a result, their combined prescription is delayed, late prescription of basic therapy .

Articular erosions can occur during the first 6 months after the onset of the disease and develop faster during the first year compared to later periods. The contribution of structural damage to the indicator of "disability" is very significant: they determine the functional activity of patients in the long term.

Recommended provisions can help the doctor navigate the optimal therapy with basic drugs:

1. The choice of the drug depending on the level of activity: low - aminoquinoline , sulfosalazine , high - methotrexate or leflunomide (if there are contraindications - cryotherapy or alkylating cytostatics). Treatment should begin immediately with the most effective drugs.
2. An individual selection of the dose of basic preparations is necessary, taking into account the degree of activity, the nature of the disease, the patient's gender and age,

body weight, and concomitant diseases. The dose should not only be individually selected, but also sufficient.

3. When conducting treatment, it must be borne in mind that, as a rule, the clinical effect of basic drugs is delayed. The main feature of all basic drugs is the slow manifestation of the clinical effect - on the 1-2-3rd month from the start of their administration. Knowing this is important not only for the doctor, but also for the patient, who should not expect the immediate action of the drug. If the patient is not aware of the delayed effectiveness of the drug, he can independently stop taking it at the initial stages of therapy. In other words, basic remedies refer to drugs that involve long-term (multi-year) treatment.

4. Inform the patient about the interaction of prescribed drugs with drugs used to treat comorbidities (arterial hypertension, infectious diseases, etc.); find out pregnancy planning.

Basic therapy can be started by local therapists, family doctors. Consultation with a rheumatologist is indicated in cases of its ineffectiveness or the appearance of side effects. At the same time, the most common basic means can slow down the process of destruction of the joints, but they are not always able to stop the progression of the disease according to radiography.

The emergence of biological preparations of monoclonal antibodies to tumor necrosis factor a (TNF-a) and to the surface receptors of B-lymphocytes - CD-20 (rituximab) radically changed the approach to RA therapy. Treatment of RA with TNF-a inhibitors (infliximab , adalimumab) reduces the clinical manifestations of the disease and improves the quality of life [6]. A distinctive feature of TNF-a inhibitors is a slowdown in the rate of development of radiological signs of destructive changes in the joints for a period of time previously considered unattainable. Official indications for their use are a reliable diagnosis of RA, a high activity of the process, and the lack of effect or poor tolerance of adequate therapy with at least two basic drugs, one of which should be methotrexate [2, 6].

Monoclonal antibodies to tumor necrosis factor have a selective effect and minimally disrupt the physiological mechanisms of the functioning of the immune system. This reduces the risk of generalized immunosuppression , which is characteristic of corticosteroids and cytostatics .

It is known that the use of TNF-blockers is accompanied by a number of events that are important for the safety of treatment, such as respiratory viral infections, opportunistic infections (including tuberculosis), malignancies, demyelinating diseases, lupus-like reactions and congestive heart failure. It is recommended to conduct a screening examination for tuberculosis (Mantoux test, chest X-ray) before

prescribing TNF-a antagonists as an effective measure to identify patients at risk and reduce the number of cases of reactivation of tuberculosis infection [6].

Rituximab significantly reduces disease activity (significant improvement in all ACR criteria, significant reduction in inflammatory markers). The official indication for its use in RA is active RA that is resistant to previous biological therapies. An indicator of the effectiveness of the drug is the disappearance of B-lymphocytes. It is important to note that the drug does not affect stem cells and proB - lymphocytes, thus, the possibility of an adequate immune response remains, which makes it possible to successfully fight infection if it occurs [2].

To date, treatment with biological preparations of monoclonal antibodies should be carried out only under the supervision of a rheumatologist with experience in diagnosing and treating RA.

Glucocorticosteroids in the treatment of RA. In the treatment of RA patients in everyday practice, it is difficult to do without glucorticoids (GCS). Purpose of system glucocorticoids quickly provides a state of clinical well-being. Subsequently, the known side effects and complications of corticosteroids led to the development of steroid phobia in both doctors and patients. Steroid phobia leads to inadequate GCS therapy (insufficient dose, duration of administration, rapid withdrawal, etc.). Often GCS is prescribed only in those cases and only when nothing else helps. GCS are still the most effective anti-inflammatory drugs and potentially have the ability to suppress most of the mechanisms underlying rheumatoid inflammation.

Indications for the appointment of glucocorticoids are formulated as follows:

• Transitional (bridge) therapy until the development of the effect of basic drugs or reactivation of the disease (lasting 1-2 months).

• Consolidation of the effect of basic drugs (as a component of basic anti-inflammatory therapy for RA). The rheumatology clinical practice guidelines for the use of HA in RA state the following: HA at doses equal to or less than 10 mg are more effective than NSAIDs, and in some cases slow the progression of joint destruction (only in combination with DMARDs). Some side effects develop less frequently than with the use of NSAIDs and basic drugs. Side effects are more likely to develop with prolonged use of high doses. It should be recalled that according to modern nomenclature, "low" means a dose of HA < 7.5 mg / day . (in terms of prednisolone), under the "average" 7.5 mg / day . - 30 mg / day . and under "high doses" -> 30 mg / day .

Ineffectiveness and contraindications to the appointment of NSAIDs (for example, in elderly people with an "ulcerative" history and / or impaired renal function).

Treatment of systemic manifestations of RA (eg, active visceritis - pericarditis or pleurisy, interstitial lung disease (rheumatoid lung), systemic rheumatoid vasculitis) requires the mandatory appointment of systemic glucocorticoids .

To reduce local manifestations of inflammation, intraarticular administration of glucocorticoids is advisable . It is used to suppress arthritis at the onset of the disease or exacerbations of synovitis in one or more joints, improve joint function. Intra-articular administration of corticosteroids is not used in the absence of inflammation in the joint (synovitis), if it is impossible to exclude a concomitant infection. Repeated injections into the same joint are possible no more than 3 times a year [5].

The use of HA allows to achieve the following main positive effects: reduce pain in the joints, improve functional activity, slow down the radiographic progression of articular destruction that persists after stopping the use of HA, reduce the need for NSAIDs.

Upon reaching the initial therapeutic effect (improvement of well-being, complaints, normalization of temperature, reduction of morning stiffness and pain, etc.), a gradual decrease in the starting dose is carried out, ensuring a stable condition of the patient and the course of the disease. The reduction is carried out strictly individually. The control of the time and rate of decline is carried out, first of all, by the patients themselves according to the doctor's recommendations - "GCS is easier to prescribe than to cancel."

Rules for reducing the dose of GCS:

1. Decrease to begin when clinical and laboratory remission of the disease is achieved.
2. The longer the patient received steroids, the more gradually and slowly they should be canceled.
3. The smaller the dose, the slower they should be reduced.
4. Particular attention should be paid to the dose corresponding to the physiological need, which is 5-7 mg per day.
5. In case of exacerbation, it is necessary to increase the dose until the clinical and laboratory parameters normalize.

Premature reduction in the dose of corticosteroids, or too fast its rate can and provoke an exacerbation of the pathological process. The most appropriate "wavy" scheme for reducing the dose and rate of corticosteroids. At the slightest deterioration in the condition - return to the previous dose for a few days, then again switch to the previous dose. There should be no notorious stepwise reduction scheme up to the abolition of GCS. The reduction of the daily dose is carried out by 1/4-1/2 tablets in 5-10 days until the daily equivalent dose for each patient is reached (on average, up to 10-12.5 mg). The problem of GCS cancellation can be put only after reaching a stable remission. Of

course, corticosteroids are not a routine type of therapy. Today it is strongly suggested that the treatment of corticosteroids can only be prescribed by rheumatologists. But it's not. A qualified doctor should not be "dependent" on rheumatologists and can carry out this therapy subject to the above principles. It should be noted that modern therapy with biological agents makes GCS therapy less and less relevant, and the attitude towards GCS therapy is becoming more restrained.

Non-steroidal anti-inflammatory drugs. The mechanism of their action (analgesic and anti-inflammatory) is realized through the blockade of cyclooxygenase (COX-1 and COX-2). The problem of " undertreatment " of RA is associated with the use of NSAIDs: the achievement of clinical well-being (easing the course of the articular syndrome) leads to a delay in the appointment of basic therapy by a doctor and, in part, the patient's unwillingness to take them. Synovial inflammation, in principle, can be controlled by NSAIDs, but they do not control the destructive process. At the same time, in the treatment of patients with RA, it is almost impossible to do without the use of NSAIDs due to chronic pain syndrome. They must necessarily be combined with basic therapy. The main purpose of prescribing NSAIDs is to reduce pain, swelling in the joints, and morning stiffness.

It is necessary to prescribe NSAIDs taking into account risk factors for gastrointestinal, cardiovascular and renal side effects [7]. It is advisable to prescribe non-selective NSAIDs to patients who do not have NSAID risk factors - gastropathy (age over 65 years old, comorbidities of the gastrointestinal tract, taking low doses of acetylsalicylic acid, anticoagulants and glucocorticoids) and clinically significant pathology of the cardiovascular system (including uncontrolled hypertension, heart failure, severe coronary artery disease). The "gold" standard among NSAIDs is diclofenac , which combines high efficiency and safety [7].

If there are risk factors for the development of side effects of NSAIDs, preference should be given to selective COX-2 inhibitors (nimesulide , meloxicam , coxibs). Their use is advisable in RA patients with arterial hypertension, heart failure - no effect on water-salt metabolism through prostaglandin mechanisms. Patients with a history of severe gastrointestinal damage, or taking low doses of acetylsalicylic acid, warfarin and glucocorticoids , the use of selective NSAIDs is permissible only in combination with proton pump inhibitors [7].

In acute pain, drugs with maximum analgesic activity should be prescribed: diclofenac , ketoprofen , lornoxicam , celecocosib , nimesulide .

The presence of an injectable form of NSAIDs (in particular, diclofenac sodium, lornoxicam , and a number of others) makes it possible to use the principle of stepwise therapy of pain syndromes: in the acute period, intramuscular administration of

NSAIDs (no more than 2-3 days) is indicated, followed by a transition to oral therapy with this drug in that period. same dose. Unfortunately, in clinical practice, there is an "abuse" of NSAID injection therapy, which is indicated only in cases of very severe pain to quickly alleviate the patient's condition. With their prolonged use, serious local complications are often encountered.

The appointment of NSAIDs in the form of retard forms, enteric tablets, rectal suppositories, as well as taking after meals does not reduce the risk of developing serious complications from the gastrointestinal tract [7]. Thus, it is possible to take NSAIDs on an empty stomach early in the morning to relieve morning stiffness, provided that it is well tolerated by the individual. While taking NSAIDs, dyspepsia may occur - a range of various unpleasant sensations from the upper gastrointestinal tract (pain, a feeling of heaviness, nausea). The risk of dyspepsia is reduced when using NSAIDs in the form of rectal suppositories.

The effectiveness of the prescribed dose of the drug should be assessed within 7-10 days [7]. If there is no effect, it is necessary to raise the question of changing it, since the effectiveness of NSAIDs for each patient is individual. The ineffectiveness of NSAIDs in relation to pain suggests a discussion of another, non-inflammatory cause of pain.

Even with a good effect according to the ACL criteria, the patient may have 3-5 painful or swollen joints. Early therapy for RA means not only the appointment of classic DMARDs in the first months from the onset of the disease, but also the choice of the most active drugs for rapidly proliferating synovitis . Therefore , in the treatment of RA, local methods of therapy are important , aimed at and contributing to the preservation of the function of each affected joint.

Among the most widely used methods of local therapy, the application of drugs (NSAIDs, local irritants, drugs that affect microcirculation and peripheral circulation) is distinguished [8].

It is recommended to prescribe topical NSAIDs, which are based on the most effective analgesic substances - diclofenac , ibuprofen, ketoprofen , piroxicam , the form of NSAIDs in the form of a gel also has some advantages.

In RA, therapy with ointment preparations is preferable in cases where the process is limited (monoarthritis , oligoarthritis), as well as when it is necessary to stop pain or inflammation in the soft periarticular tissues (myofascial syndrome, bursitis, etc.), also in the elderly. The use of this group of drugs in the form of ointments, creams and gels makes it possible to virtually eliminate the effect on the upper gastrointestinal tract, while maintaining or possibly enhancing the clinical effects of oral administration of NSAIDs [8]. The effectiveness of application therapy depends on

the correct prescription of the drug. To achieve the effect, it is necessary to apply a local agent 3-4 times, and with active inflammation - up to 5-6 times a day. The amount of the drug applied depends on the size of the joint. The approach to the choice of topical NSAIDs for each individual patient should be individual, since there is no universally effective remedy. Evaluation of the effectiveness of local therapy drugs in the treatment of diseases of the musculoskeletal system is carried out after 5-7 days of use (visual analog scale, range of motion in the joint in centimeters) [8].

Local therapy with dimethyl sulfoxide (dimexide , DMSO) can be used to ensure faster and deeper conduction of the active substance to the site of inflammation (NSAID ointments, novocaine, heparin, hydrocortisone, kenalog , etc.). To enhance the anti-inflammatory effect on the skin, it is advisable to apply gels, ointments containing NSAIDs, glucocorticoids before applying a compress . As shown by the results of various studies, such therapy has a high anti-inflammatory activity, analgesic and resolving effect [8]. Non-pharmacological methods such as exercise therapy, physiotherapy can be used in addition to drug therapy.

Conclusions

The appointment of physiotherapy in RA is determined by the activity of the process, the severity of the articular syndrome and the patient's condition. In the acute phase of inflammation in the presence of joint synovitis , UHF therapy (non-thermal doses), UV radiation, magnetotherapy , laser radiation, and local hypothermia are indicated. With a decrease in the activity of the disease, a decrease and relief of synovitis , for the purpose of analgesia, microwave therapy, SMT therapy, ultraphonophoresis of NSAIDs, DDT therapy (DDT- phoresis of anesthetics), drug electrophoresis, magnetotherapy , EHF therapy, massage, exercise therapy are used. With low RA activity and in remission, it is also possible to carry out paraffin -ozocerite applications, hydrotherapy, mud therapy, spa treatment, however, these methods can exacerbate local inflammation [8]. Systematic physiotherapy exercises, as well as a change in the stereotype of physical activity, improve the functional status of the joints. Methods of conservative and operative orthopedics are of great importance . The main indications for joint replacement are pain and/or loss of function refractory to medical therapy. Pain relief is the most achievable outcome of surgery. Recovery of movement and function is less predictable.

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