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NEW TRENDS IN THE TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS (LITERATURE REVIEW)

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Abstract

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation that causes the destruction of cartilage and bone, ultimately leading to disability, disability, loss of function, reduced quality of life, and reduced life expectancy. Statistical data show that every fifth patient who seeks medical help from a doctor has a joint syndrome of various degrees of damage. Modern treatment options for patients with rheumatoid arthritis are mostly based on a compromise between the severity of the disease, prognostic factors, the proven effectiveness of the drug and the risk of developing side effects. At the moment, disease-modifying antirheumatic drugs (DMARDs), which can be combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids, are quite often used. DMARDs are divided into synthetic (methotrexate), targeted synthetic DMARDs (Janus kinase inhibitor) and biological DMARDs. Although a wide range of biologic DMARDs are available today, their comparative effectiveness remains uncertain.

Keywords: rheumatoid arthritis, disease-modifying antirheumatic drugs, immunobiological therapy, nonsteroidal anti-inflammatory drugs, glucocorticosteroids, Janus kinase inhibitors.

Ensuring adequate quality of life, increasing its duration and reducing disability and mortality in patients with rheumatoid arthritis (RA) remains an unsolved problem [5, 13]. Achieving this goal depends on timely diagnosis and rationally selected pharmacotherapy regimens [11, 14], primarily with the use of disease-modifying antirheumatic drugs (DMARDs), glucocorticosteroids (GCs), and nonsteroidal anti-inflammatory drugs (NSAIDs) [7, 19]. Pharmacotherapy does not always lead to remission, does not stop the progression of the disease, and at the same time has a number of side effects that cause the occurrence of concomitant diseases, burdening the clinical course and complicating the diagnosis of RA. Therefore, today there is a question regarding the optimization of RA treatment methods [18].

Over the past 20 years, a real revolution has taken place in the treatment of many rheumatological diseases, which was associated with the creation and introduction into clinical practice of new drugs with a unique targeted (targeted) mechanism of action - immunobiological therapy. Immunobiological drugs inhibit the activity of pro-inflammatory cytokines and pathological activation of T- and B-lymphocytes involved in the immunogenesis of rheumatic diseases. These drugs block certain biologically active substances or signaling pathways, thus interrupting pathological immunogenesis [20]. Currently, immunobiological agents used in rheumatology include a class of drugs called tumor necrosis factor (TNF) inhibitors, inhibitors of certain cytokines, in particular interleukin-1, interleukin-6, interleukin-17, T-lymphocyte activation blocker, B-cell depletion blockers and Janus kinase inhibitors. The use of biological therapy made it possible to significantly improve the prognosis of patients with rheumatic diseases and expand the understanding of the pathogenetic mechanisms underlying the progression of these diseases [15, 31].

This treatment allows you to stop the disease in the early stages, prevent progression, which is especially important for patients resistant to standard treatment. Such treatment allows not only to achieve stable remission, but also to significantly improve the prognosis.

The latest clinical guidelines of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed strict definitions of clinical remission of RA, namely: the number of painful joints ≤1; number of swollen joints ≤1; level of C-reactive protein (CRP) (mg/dL) ≤1; overall assessment of disease activity by the patient on the visual analog scale (VAS) (0–10) ≤1 or simplified disease activity index (SDAI) ≤3.3 [27].

Today, the following types of biological drugs are used in rheumatology [1, 4, 8, 25]:

I. Cytokine inhibitors:

1. TNF-α:

- adalimumab - 20-40 mg subcutaneously 2 times a week, for 12 weeks;

- golimumab - 50 mg subcutaneously once a month;

- infliximab - 3 times intravenous administration (3 mg/kg) at intervals of 2 and 4 weeks (weeks 0, 2, 6), then every 8 weeks (total of 9 infusions).

- etanercept - 25 mg subcutaneously 2 times a week, from several days to 16 weeks.

2. IL-1: anakinra - 75-100 mg subcutaneously daily for 12 weeks.

3. IL 6: tocilizumab - 8 mg/kg of body weight intravenously every 4 weeks.

II. Antilymphocyte:

1. T-lymphocyte blocker: abatacept - intravenous infusion for 30 minutes; body weight <60 kg — 500 mg, 60–100 kg — 750 mg, >100 kg — 1 g; subsequent doses 2 and 4 weeks after the first infusion, then every 4 weeks.

2. Anti-B-cell drug: rituximab - intravenously 1 g twice with an interval of 14 days; can be repeated after 6 months.

III. Inhibitors of interleukin signaling pathways (targeted synthetic HMPRPs):

1. JAK-STAT signal inhibitor:

- tofacitinib - 5 mg 2 times a day (5 mg 1 time a day in patients with liver failure class B according to Child-Pugh or creatinine clearance <30 ml/min);

- ruxolitinib;

- upadacitinib;

- baricitinib.

According to the recommendation of the European Antirheumatic League (EULAR) in 2019 and the American College of Rheumatology (ACR) in 2015, the appointment of biological drugs is necessary in case of ineffectiveness or intolerance of synthetic DMARDs [24].

According to the EULAR 2022 recommendation, a patient with RA needs [28]:

1. Start DMARDs therapy immediately after establishing the diagnosis of RA.

2. Treatment should be aimed at achieving stable remission or low disease activity in each patient.

3. Monitor disease activity every 1-3 months, and if improvement is not observed after 3 months of starting treatment or the goal is not reached within 6 months, therapy should be adjusted.

4. Methotrexate is the gold standard of basic therapy. Prescribe leflunomide or sulfasalazine when methotrexate is contraindicated.

5. At the beginning of treatment, GCs should be used in short courses, but they should be gradually reduced and discontinued as soon as clinically possible.

6. If the desired result is not achieved when using conventional synthetic- DMARDs (cs-DMARDs), the possibility of using other cs-DMARDs should be considered.

7. If the target treatment is not received, it is necessary to add biological DMARDs (b-DMARDs) or Janus kinase inhibitors to cs-DMARDs, taking into account all possible risk factors.

8. In patients who cannot use cs-DMARDs, IL-6 inhibitors and targeted synthetic DMARDs (ts-DMARDs) have advantages in use compared to other b-DMARDs

9. If there is no result from b-HMPRP or ts-DMARDs, another b-DMARDs or ts-DMARDs should be used.

10. In case of persistent remission and cancellation of GCs, the dose of DMARDs should be reduced.

However, certain rules must be followed when using immunobiological therapy [3, 17, 20, 21]:

1. Examine the patient for tuberculosis, hepatitis B virus, hepatitis C, human immunodeficiency virus (HIV) and infectious complications (fungal, herpes virus).

2. Patients should be vaccinated with killed (anti-influenza, pneumococcal, hepatitis B), live attenuated (against shingles), recombinant (against human papilloma virus) vaccines. Biological therapy should be started 2 weeks after shingles vaccination.

3. The effectiveness of the use of biological agents should be monitored at least once every 6 months with an assessment of disease activity DAS 28. If there is no response to treatment with these drugs, treatment should be stopped.

4. We can use TNF-α blockers (infliximab, adalimumab, etanercept) or IL-6 receptor blocker (tocilizumab) in patients with rheumatoid arthritis only if: DAS28 is higher than 5.1, confirmed at least twice, with an interval of 1 month and when two DMARDs, including methotrexate, were used.

5. TNF-α blockers should be used in combination with methotrexate (in case of intolerance - with another synthetic DMARDs).

6. Treatment with TNF-α blockers or tocilizumab can be extended for more than 6 months only if remission or minimal disease activity is achieved. In the absence of adequate effectiveness, the drug is canceled.

7. B-lymphocyte blocker (rituximab) is prescribed in combination with methotrexate only in severe active RA and in case of intolerance to other DMARDs, including treatment using TNF-α inhibitor or tocilizumab.

8. Treatment with rituximab should be continued only when there is an adequate response (improvement in DAS28 of 1.2 points or more). Repetition of the course of treatment no more often than every 6 months.

9. In the case of skin cancer in RA patients, immunobiological drugs are not the means of first choice [30].

Absolute contraindications for prescribing biological drugs are [20, 25]:

- active infection (in particular, tuberculosis, hepatitis B);

- recent (<5 years) history of malignancy;

- serious and/or recurrent infections;

- demyelinating disease or optic neuritis;

- primary/secondary immunodeficiency;

- heart failure of III/IV functional class;

- confirmed hypersensitivity to the components of the drug or active substance;

- simultaneous use of two or more biological agents.

For the last decade, scientists have been looking for a new approach to the treatment of autoimmune diseases, including rheumatoid arthritis. Significant pro-

gress has been made thanks to the development of modern biological agents. Janus kinase (JAK) inhibitors have become one of the most modern new-generation DMARDs [31].

Janus kinases (JAKs) are intracellular enzymes that transduce signals arising from cytokine or growth factor receptor interactions on the cell membrane to influence cellular hematopoietic processes and immune system cell function. They are named after the two-faced Janus because JAKs have two nearly identical phosphate-transferring domains. One of them is characterized by kinase activity, and the second negatively regulates the kinase activity of the first [6].

Currently, four representatives of the class of Janus kinase enzymes are known - JAK1, JAK2, JAK3, TYK2 (tyrosine kinase-2), which function together to transmit signals from the cell surface to the nucleus They are intracellular non-receptor tyrosine kinases that regulate signaling pathways. At the same time, each cytokine has its own JAK combination, which has biological significance for multiple pathophysiological targets (such as T-cell homeostasis, inflammation, granulocytopoiesis, antiviral properties, innate immunity, etc.) [16].

In general, JAK kinases are involved in a wide range of immune and cellular functions, such as cell proliferation and differentiation, their migration and apoptosis, anti-/pro-inflammatory effects, hematopoiesis, innate and acquired immunity. Many cytokines and growth factors intersect in the JAK signaling pathway, with only four kinases, which makes it possible for drugs with a selective effect on one or more kinases to cause the same clinical result [28].

Currently, a number of JAK inhibitors have been developed, some of which are already registered and used in clinical practice, and some are still in one or another phase of clinical trials, such as tofacitinib, upadacitinib, and baricitinib. In Ukraine, the first oral JAK inhibitor tofacitinib was approved for the treatment of RA [29].

JAK inhibitors, namely tofacitinib, are recommended by international rheumatological associations for the treatment of RA – the American College of Rheumatology (ACR, 2015) and the European Antirheumatic League (EULAR, 2019). Tofacitinib is a pan-JAK inhibitor (JAK1/3 inhibitor with little activity against JAK2 and TYK2). It is the first and most studied oral JAK inhibitor. The main advantage of JAK inhibitors is that they are easy to use (oral form), have a favorable tolerability and a quick onset of action already two weeks after the start of treatment [22].

Tofacitinib is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Tofacitinib is approved in more than 90 countries for the indication RA, it is used by 208,000 patients [32].

International studies have confirmed the clinical and radiographic efficacy of tofacitinib at a dose of 5 mg twice a day in people with RA [2]. It should not be used concurrently with biologic base antirheumatic drugs or strong immunosuppressants such as azathioprine and cyclosporine.

It should be noted that JAK inhibitors are not b-DMARDs, so they do not cause the production of antibodies to the drug. Monotherapy with JAK inhibitors is effective, but not as much as combined treatment. In patients who tolerate methotrexate well, the combined use of a JAK inhibitor and methotrexate is a better solution than switching to monotherapy. On the other hand, in patients who do not tolerate methotrexate, monotherapy with JAK inhibitors is appropriate [9].

It should be remembered that tofacitinib increases total cholesterol, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). Therefore, it is necessary to assess the level of lipids 4-8 weeks after the start of therapy with the drug. And also check the level of hemoglobin, neutrophils, and lymphocytes at the beginning of treatment, after 4-8 weeks and subsequently every 3 months against the background of tofacitinib therapy [26].

In a number of studies, it was established that the effectiveness of tofacitinib in achieving remission rates according to DAS28 and CDAI is the same as when using biological drugs during 16 months of observation. The proportion of patients who received monotherapy with tofacitinib was higher both at the initial stages of treatment and after 19-26 months, than when using b-DMARDs [10].

A rather interesting study was conducted with the participation of RA patients who used therapy with tofacitinib, TNF inhibitors (n=1862), b-DMARDs (n=1355) and JAK inhibitors (n=806). According to the obtained data, the risk of discontinuing treatment with TNF inhibitors due to ineffectiveness, side effects, etc. increased in the absence of concomitant therapy with traditional synthetic base drugs, in contrast to the use of other biological agents and tofacitinib [28].

In 2020, a study found tofacitinib alone or in combination with MT to be a less expensive treatment compared to b-DMARDs. Treatment with tofacitinib as a 2nd- or 3rd-line treatment after MT may be cheaper than using tofacitinib as a 4th-line treatment after failure of two TNF inhibitors [2].

Another new JAK inhibitor drug in the treatment of RA on the Ukrainian pharmaceutical market was upadacitinib. In 2020, it was registered in Ukraine and approved by FDA and EMA for the treatment of RA. Upadacitinib in RA is prescribed at a dose of 15 mg once a day [23].

In 2021, the FDA reported an increased risk of serious cardiovascular disease, cancer, thrombosis, and death with the use of Janus kinase inhibitors and required these warnings to be included in the package insert for the corresponding drugs. In 2022, the pharmacovigilance risk assessment committee of the European Medicines Agency initiated a safety review of the use of Janus kinase inhibitors for the treatment of chronic inflammatory diseases [12, 33].

Therefore, early pharmacotherapy is a necessary component of the optimal treatment of patients with rheumatoid arthritis to prevent further progression of the disease, restore the range of motion in the joints, and ensure a normal quality of life. According to the latest data, this disease cannot be considered benign. Although methotrexate is still considered the gold

standard for most cases of rheumatoid arthritis, biologic agents have made positive adjustments in the treatment of this disease. And according to all the recommendations of the American College of Rheumatology and the European Antirheumatic League, they should be used as soon as it becomes clear that the use of methotrexate in the patient is ineffective or poorly effective. Therefore, early intensive pharmacotherapy, appropriate employment and psychosocial support will improve the long-term quality of life in patients with rheumatoid arthritis.

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