Anti-Cytokine Therapy for Rheumatoid Arthritis

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ABSTRACT

Medical management of rheumatoid arthritis (RA) is aimed at controlling or reducing the inflammatory process in order to prevent or slow down damage to the joint and to maintain or improve the functional status. However, it is well established that inflammation indicators may be stable or improved, whereas radiographic evidence shows that joint damage progresses. A new class of agents termed "biological agents" have been approved for use in RA according to the data of the evidence-based medicine. Until more is known about the long-term safety and efficacy of these drugs, they should be reserved for patients with severe conditions who are progressing despite adequate doses of methotrexate or other DMARDs.

Keywords: rheumatoid arthritis, anticytokine therapy, biological agents.

Rheumatoid arthritis (RA) as a scientific and practical problem of modern rheumatology occupies a leading position. The significant prevalence of RA, its progressive nature, leading to early disability of patients, determine the relevance of the search for new effective methods of pathogenetic therapy for this disease.

As follows from numerous epidemiological studies, in different countries RA suffers from 0.3 to 1.5% of the working population, and there is no such population in which RA does not occur [3]. RA is a chronic progressive disease that mainly affects people of young working age. Quite quickly after the onset of the disease, persistent disability occurs: 38% of patients lose their ability to work in the first three years after diagnosis, after 5 years 50% of RA patients become disabled, and 30-40% of patients die after 20 years from the onset of the disease [4].

RA is an autoimmune disease characterized by chronic inflammation and progressive joint destruction. The pathogenesis of RA is closely related to the mechanisms of development of immune inflammation, which is most pronounced in the synovium of the joint. The inflamed synovial membrane undergoes hypertrophy - the so-called pannus is formed, which, penetrating into the articular cartilage, destroys the articular surface and the underlying bone. The reasons for this process have not yet been established, however, convincing evidence has been obtained that immunological tolerance to connective tissue components, immunoglobulins, in particular to immunoglobulin G, is impaired in RA. Autoantibodies to immunoglobulin G are a rheumatoid factor that can be detected in the blood of patients RA [13, 29].

In addition, with RA, serious disorders of cellular immunity occur, which are manifested by a change not only in the quantitative composition of lymphocytes and their subpopulations , but also in significant deviations in the functional state of immunocompetent cells. Due to a breakdown in the system of immunological regulation, the activity of T - suppressors decreases and T-helpers are activated, which stimulate the

activity of B-lymphocytes that produce antibodies [6, 15].

Cytokines are mediators of intercellular interaction. Studies of recent decades have found that in RA there is an imbalance between the production of cytokines with pro-inflammatory and anti-inflammatory activity [51]. Increased synthesis of pro- inflammatory cytokines predominantly of macrophage origin, such as tumor necrosis factor-a (TNF-a), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) [22 , 27].

I. The proven role of TNF-a in the development of RA as a pathogenetic rationale for anticytokine therapy.

In recent years, there has been growing interest in studying the role of TNF-α in the development of immune inflammation in various autoimmune processes, including RA [32, 38]. This interest is due to the proven biological activity of TNF-a against type 1 transmembrane receptors, which are expressed on leukocytes, endotheliocytes , fibroblasts, etc. By binding to these receptors, TNF-a is involved in the regulation of the synthesis of pro- inflammatory cytokines and other inflammatory mediators. It has been established that TNF-a stimulates the synthesis of prostaglandins, platelet activating factor, superoxide radicals, metalloproteinases , induces the synthesis of pro- inflammatory cytokines, stimulates the growth of new vessels (neoangiogenesis) and the proliferation of fibroblasts, which play an important role in the formation of rheumatoid pannus [39]. By activating transcription factors, TNF-a is able to induce programmed cell death (apoptosis) [9, 51].

In RA, an excessive amount of cytokines of macrophage origin (TNF-a, IL-1, IL-6, granulocyte -macrophage colony- stimulating factor - GMCSF) is produced in the tissues of the joints with minimal production of T-cell cytokines (IL-2, IL-3, IL-4, y-interferon) [26]. The results of numerous studies have shown that the main manifestations of the disease, such as chronic synovitis , destructive lesions of cartilage and bone, are caused precisely by the cytotoxic effects of pro- inflammatory cytokines, primarily TNF-a [6]. TNF-a is synthesized by monocyte-macrophage cells of the synovial membrane of the joint [13]. These cells are called "palisade" and are located in the zone of beginning destruction of cartilaginous and bone tissues between pannus and articular cartilage [16].

The variety of biological effects of TNF-a, mainly pro- inflammatory , allows us to consider this cytokine as a key one in the pathogenesis of RA (Table 1).

hyperproduction of this cytokine takes place [20]. Along with this, there is an increase in the expression of soluble TNF receptors [5, 46], which are not only an antagonist of TNF-a [41, 47], but also its kind of "depot" [5, 21].

It has been established that TNF-a activates the synthesis of other pro-inflammatory cytokines, primarily IL-6, which regulates the transformation of B-lymphocytes into plasma cells, stimulates the formation of rheumatoid factor and hypergammaglobulinemia [52].

As noted above, the biological effects of TNF-α and other cytokines contribute to the transformation of acute immune inflammation, characteristic of the early stage of rheumatoid arthritis, into chronic inflammation with the development of pannus and irreversible destruction of articular structures [29].

Summarizing the above information, it should be noted that the following mechanisms of the pathogenetic action of TNF-a have been proven [6, 22, 26, 27, 32, 38].

1. TNF-a is involved in the development of clinical signs of inflammation (pain, fever, loss of muscle and bone mass).

2. Induces the expression of adhesion molecules, which determines the transendothelial migration of leukocytes towards the joint cavity.

3. Stimulates the synthesis of pro-inflammatory mediators, such as: prostaglandins, platelet activating factor, superoxide radicals, metalloproteinases (collagenase , gelatinase , stromelysin , causing bone and cartilage damage).

4. Induces the synthesis of pro-inflammatory cytokines (IL-1, IL-6, GMCSF) and chemokines (IL-8, RANTES, monocytic chemoattractant protein-1 - MCP-1,

macrophage inflammatory protein-1a - MIP-1a).

5. Stimulates the growth of new vessels (neoangiogenesis) and the proliferation of fibroblasts, which play an important role in the formation of rheumatoid pannus.

The pathogenetic features of the development of rheumatoid inflammation served as the basis for the development and application in clinical practice of a new class of antirheumatic drugs related to biological agents [15, 27].

II. Clinical evidence of the effectiveness of anticytokine therapy in RA.

Anticytokine therapy (ACT) aims to inhibit the synthesis or inactivate pro-inflammatory cytokines to prevent the progression of the immunopathological process [1, 15, 16, 43].

The first drug recommended for the treatment of RA was Infliximab , which is a chimeric mouse monoclonal antibody to TNF-a. Numerous studies, including the " Attract " multicenter trial, confirm the high efficacy of this drug in the treatment of RA. It has been shown that the use of infliximab in the early stages of RA can quickly stop synovitis and prevent the development of erosive damage to the articular cartilage [12, 42].

The effectiveness of anticytokine therapy has been proven by the results of many large, placebo-controlled, blinded studies. To date, a large evidence base has been accumulated for the high efficacy of anticytokine drugs in the treatment of RA.

Already during the first open trial, it was shown that in the group of RA patients who received intravenous infusion infliximab (Remicade), there is a pronounced positive (more than 50%) dynamics of clinical and laboratory parameters reflecting the activity of the articular syndrome, such as the number of inflamed joints, pain count, erythrocyte sedimentation rate (ESR), C - reactive protein (CRP) [23].

Analysis of the results of these studies showed that the average duration of the clinical effect after a single injection of infliximab is 3 weeks . with the introduction of 1 mg / kg, 6 weeks . after administration of 3 mg/kg and 8 weeks . at a dose of 10 mg/kg of the patient's weight. Based on these data, and also on the assumption that the clinical effect of infliximab can be prolonged with the help of basic antirheumatic drugs, several placebo-controlled studies have been conducted to evaluate the possibilities of combination therapy of remicade with methotrexate (MT). It should be emphasized that MT is currently regarded as the most effective basic antirheumatic drug used for the treatment of RA (the "gold standard").

These trials included patients with persistent disease activity despite high doses of MTX (greater than 10 mg/kg/ week). The first 12-week comparative placebo-controlled study showed that the clinical effect according to the criteria of the American College of Rheumatology (ACR) was achieved significantly more often in patients treated with remicade (81%) than placebo (14%) [33].

In another study [24], it was shown that treatment with Remicade leads to a pronounced positive dynamics of the articular syndrome (the average number of inflamed joints decreased from 30 to 13) and a significant decrease in the concentration of CRP by the 12th week of treatment. It should be noted that all patients received Remicade

repeated (3 times with an 8-week interval). In 2/3 of the treatment remained remission for the next 40 weeks. It is noteworthy that, according to pharmacological studies, during treatment with MT, a higher level of the drug in the blood of patients remained, which was especially noticeable in patients receiving low doses of Remicade [37]. All this taken together indicates a synergism between the anti-inflammatory activity of Remicade and MT.

More recently, preliminary results of the use of infliximab in 428 patients with active RA refractory to high (more than 12.5 mg/kg/ week) doses of MT were presented [35]. Patients received injections of inflixim -ba (Remicade) at 3 and 10 mg/kg or placebo for 30 weeks. While in the placebo group, the clinical effect (20% improvement according to the DIA criteria) was achieved only in 20% of patients, during treatment with Remicade, positive

dynamics was noted in 52% of patients. Similar results were obtained when using more "rigid" criteria for evaluating effectiveness. Thus, a 50% improvement in DIA criteria was observed in 28% of patients treated with Remicade and only 5% in the placebo group, and a 70% improvement was in 12% of patients treated with Remicade and none in the placebo group. .

The therapeutic effect of infliximab is associated with its effect on the intracellular cytokine profile of T-lymphocytes and monocytes in patients with RA. The regulatory effect of this drug on the production of pro-inflammatory cytokines by monocytes, as well as stimulation of the secretion of anti-inflammatory cytokines by TI2-lymphocytes, has been proven [48].

of monotherapy comparable to MT infliximab [7], while the combination of infliximab and MT produced better results than MT alone [18]. Various variants of the combination of infliximab and basic agents have been proposed: sulfasalazine , leflunomide , cyclosporine A. These recommendations are based on clinical data demonstrating the possibility of increasing the effectiveness of treatment by adding infliximab to one or another basic agent. Three-component therapy for RA, including MT, cyclosporine A , and infliximab , is also not excluded [17, 30].

In recent years, there have been reports of the possibility of intra-articular administration of this drug to patients with resistant RA: after two injections of infliximab into the joint cavity, a long-term clinical remission was achieved [40]. Some authors suggest titrating the dose of the drug depending on the activity of RA, since this approach allows avoiding adverse events and increasing the effectiveness of treatment [12].

Analogue of infliximab (remicade) is the drug adalimumab (Adalimumab), which is also a monoclonal antibody to TNF-a, but, unlike inflixim -ba, is completely human. According to a number of European studies, monotherapy adalimumab in patients with severe, long-term course of RA, who were refractory to traditional basic therapy, made it possible to achieve a quick and lasting positive effect without serious adverse events [49]. In addition, combination therapy for RA with adalimumab and methotrexate has been demonstrated to be effective .

Drugs that block TNF-α activity include etanercept (enbrel), a soluble TNF-α receptor, which, along with infliximab , has found wide application in the treatment of RA. Under the influence of this drug, the activity of matrix metalloproteases decreases , and the ratio between metalloproteases and their tissue inhibitor changes. These effects are considered as an important mechanism for preventing articular destruction in RA [14]. Under the influence of etanercept therapy , a decrease in the activity of the process and a positive dynamics of the state of the synovial membrane were observed according to ultrasonography with spectral analysis [8]. Etanercept can be used in combination with MT in patients with severe RA with insufficient efficacy of MT. Conducted comparative trials of infliximab and etanercept demonstrated similar therapeutic efficacy of these drugs. Moreover, it is possible to replace one of these drugs with another.

Anticytokine therapy is aimed not only at blocking the effects of TNF-a, but also at regulating the biological effects of other inflammatory mediators. Five years ago, a new drug, anakinra , a recombinant interleukin-1 receptor antagonist, was introduced to clinicians. The efficacy and fairly good tolerability of monotherapy with this drug, as well as its combination with MT, have been shown in several clinical trials. It has been established that blocking the effect of the pro-inflammatory cytokine IL-1 is an effective protection of cartilage and underlying bone from destruction [31] . After a course of treatment with anakinra , healing of articular cartilage erosions was observed. Treatment of RA with anakinra leads to a decrease in the infiltration of the synovial membrane of the joint by mononuclear cells, which indicates a pronounced anti-inflammatory effect of this agent. The undoubted advantage of the drug is its good tolerability.

Thus, the therapeutic efficacy of anticytokine agents in RA has been convincingly proven. At the same time, there are quite serious obstacles to the use of these agents in wide clinical practice. The main problem is the risk of developing serious adverse events during long-term treatment with biological agents.

A group of leading rheumatologists who took part in an international symposium on the use of anti-TNF therapy in RA developed preliminary indications and contraindications for infliximab therapy in RA (Table) [28].

Table

Indications and contraindications for the use of monoclonal antibodies TNF-a (Remicade) in RA (preliminary provisions)

Indications	Contraindications
No effect on the background of MT treatment at the maximum effective and tolerated dose (approximately 15 mg/kg/ week) for 3 months	No treatment for MT
The need to reduce the dose of glucocorticoids	The use of mAbs for the relief of exacerbations of RA
Contraindications for MT treatment	The presence of severe infectious complications and malignant neoplasms

III. Modern recommendations for the use of anti-TNF therapy.

At a meeting of leading specialists of the WHO Collaborating Center in 2001, a consensus was developed on ACT RA [25]. This document includes answers to the main practical questions regarding indications and contraindications for ACT, evaluation of the effectiveness of treatment, patient monitoring.

1. First of all, which patients should be treated with anticytokine agents? Should ACT be given early in the disease or should it be used in severe cases only in patients after long-term treatment with other disease-modifying drugs?

The WHO Working Group believes that anti-TNF therapy is more effective in early RA. This opinion is based on large randomized trials indicating that ACT suppresses the activity of the rheumatoid process much faster than methotrexate at a dose of 20 mg / day . [8]. Along with this, the study compared the effectiveness of infliximab depending on the duration of RA. According to the results of this analysis, there was no significant difference between the positive effect of treatment in groups of patients with RA duration up to 3 years and more than 3 years.

Although it is generally accepted that anti-TNF therapy achieves a faster and more pronounced effect than MTX, at present there is not enough evidence to justify the use of ACT in early RA before treatment with MTX. The main condition for discussing the possibility of using ACT is a reliable, undoubted diagnosis of RA, which is not always possible in the early stages of the disease.

2. The next question concerns patients with a proven (reliable) diagnosis of RA. Which of the patients with a reliable diagnosis of RA should be treated with anticytokine agents ?

According to experts, ACT is indicated for those patients in whom the inflammatory process does not subside, despite adequate treatment with disease - modifying drugs (DMDs) . The concept of adequate therapy for BMP means course treatment of MT at a dose of 20 mg/kg/ week . for 3 months or at a lower dose if side effects are present. In the event that the patient has adverse events associated with MT therapy, treatment with other BMPs, in particular sulfasalazine , is indicated .

3. An important point for the appointment of ACT is the proven activity of RA.

The concept of disease activity activity score - DAS) used in clinical trials is not always used in clinical practice. The Expert Group suggests using the following indicators as criteria for RA activity : at least 5 swollen joints plus elevated acute phase indicators, in particular ESR > 28 mm/h and C-reactive protein > 20 mg/l. These indicators are almost

equivalent to a DAS index > 3.2 points. It should be reiterated that ACT is indicated for persistent RA activity (DAS > 3.2 points) despite treatment with other BMPs.

4. How to assess the effectiveness or failure of treatment with anti-TNF agents?

This aspect seems to be extremely important not only due to the need for effective blocking of TNF-α, but also due to the high cost of treatment. The criteria for evaluating the effectiveness or ineffectiveness of these drugs should be the same indicators that are used to determine the indications for ACT. Since signs of arthritis and the presence of an acute phase response are the basis for anti-TNF therapy , these indicators should be evaluated. Treatment is considered successful if it results in a 20% reduction in the severity of clinical and laboratory signs of inflammation and a decrease in DAS < 3.2 points. With more than 20% improvement, there is a decrease in the DAS score to 1.2 points. Therapy should be considered insufficient if the endpoints are not reached 12 weeks after treatment.

5. Contraindications to ACT are the following conditions:

- hypersensitivity to the drug;
- sepsis or risk of sepsis;
- the presence of any active infection.

6. Precautions are associated with a wide range of adverse events that can occur with the use of anti-TNF drugs.

Activation of chronic infectious processes or the development of an acute infection is possible, especially in the presence of diabetes mellitus or chronic heart failure. In this case, ACT should be discontinued. With extreme caution, anti-TNF drugs are used in patients with a history of tuberculosis, since frequent cases of reactivation of the tuberculosis process against the background of ACT have been described. In addition, it is necessary to take into account the possibility of developing such complications of treatment as optic neuritis, multiple sclerosis, and blood diseases.

7. Monitoring of patients.

There are no specific methods for monitoring patients. At the same time, a thorough general clinical examination is necessary throughout the entire period of ACT and after treatment. An important point is the fact that ACT should be carried out by a specialist with experience in RA immunotherapy.

Conclusion

Anticytokine therapy, in particular treatment with anti-TNF-a antibodies, represents a significant scientific and clinical advance in the pathogenetic treatment of RA. It provides rapid elimination of RA symptoms in case of ineffectiveness of MT or other BMP in patients with severe progressive course of RA. Anticytokine agents are at least as effective as MT in the early stages of the disease. If the ability to slow down the progression of the disease requires convincing instrumental evidence, then the fact of their unconditional influence on the clinical course of the disease is beyond doubt. These drugs are fairly well tolerated, although serious side effects are possible. In this regard, anticytokine therapy should be carried out by a specialist with experience in immunotherapy. Careful monitoring of the patient receiving drugs from the group of biological agents is necessary. ACT should be used in patients with failure of at least one BMP prescribed at a clinically effective dose. It should be continued in all cases except for the development of serious adverse events or treatment failure.

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