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WAY TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS WITH GENETIC ENGINEERED BIOLOGICAL DRUGS

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Abstract
The article describes the clinical and immunological features of juvenile idiopathic arthritis in children. Clinical features of the disease, laboratory analysis results are important when choosing an effective treatment method. An effective treatment method is characterized by a faster onset of remission, prolongation of its duration and reduction of side effects of drug treatment.

Keywords: juvenile idiopathic arthritis, prognosis, biological drugs

Introduction

For a long time, JIA was considered a steadily progressing disease, the course of which is extremely difficult to control. Since the mid-90s of the last century, significant changes have been observed in approaches to the treatment of JIA, which have led to a significant improvement in the prognosis of the disease. A real revolution in the treatment of JIA and other inflammatory rheumatic diseases, such as ankylosing spondylitis, psoriatic arthritis, etc., was made by the emergence of genetically engineered biological drugs (GEBD), which are specially created immunoglobulins that specifically affect the most important links in the immunopathogenesis of this disease [1 , 3,4,7,12,17,27]. The creation of GEBD is directly related to the idea of the key links in pathogenesis, on which they have a blocking or modulating effect. In rheumatology, GEBD occupy a place similar to molecular-targeted therapy in modern oncology [5,6,8,9].

GM-BPs have radically improved the treatment outcomes for previously incurable patients. It is well known that only 50-60% of patients respond satisfactorily to standard therapy with disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), leflunomide , sulfasalazine , in combination with glucocorticosteroids (GCS) (in early RA, when the disease duration does not exceed 1 year, the results may be better) [1,3,9]. Thus, about 50% of patients are resistant to DMARDs. About 10 innovative GM-BPs have been specially developed for the treatment of JIA over the past 20 years: monoclonal antibodies and recombinant

proteins that inhibit the activity of the most important proinflammatory cytokines and pathological activation of T- and B-lymphocytes involved in the immunopathogenesis of RA [4,6,11,13].

of infliximab (IFM) look impressive , according to the ASPIRE (Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset), which involved 1004 RA patients from 122 research centers. In JIA patients with a disease duration of up to 3 years, by the 54th week of observation, the remission rate was 21.2-31% depending on the drug dose (3 or 6 mg/kg, respectively). It was possible to achieve a significant slowdown in the progression of joint destruction compared with that with MT monotherapy [4,6,7,14,31,34] . Achieving clinical remission is a characteristic feature of biological therapy. The results of the randomized BeSt study (Behandel Strategienn) show that the frequency of achieving stable remission during treatment with MT in combination with each of the tumor necrosis factor-α blockers (IFM, adalimumab and etanercept) during observation for 2-3 years is comparable and amounted to about 50% [8 , 12, 16, 18, 24, 28].

The use of GIBP has significantly improved the prognosis in patients with JIA and expanded our understanding of the mechanisms underlying disease progression. However, it has now become obvious that a dramatic improvement in the prognosis for JIA depends not only on the use of innovative drugs, but also on the improvement of treatment tactics [6]. This tactic is based on early diagnosis, which determines the possibility of starting very early active, carefully controlled anti-inflammatory therapy aimed at achieving remission as quickly as possible (the concept of “treat to target” - treat to target) [9, 10]. This was reflected in the development of new classification criteria for JIA aimed at early diagnosis of the disease, and remission criteria [11, 12, 16 , 25, 28, 32].

Etanercept (ETC) was the first biological agent registered for the treatment of juvenile rheumatoid arthritis (USA – May 1999 r, EU – February 2000 r). How do biological agents differ from conventional antirheumatic agents? Chemically, they are proteins or other macromolecules that specifically affect certain stages of the inflammatory process. This mechanism of action involves blocking cytokines such as tumor necrosis factor After decades of stagnation, the use of so-called biological agents (BIs) in the late 1990s significantly changed the paradigm of pharmacotherapy for chronic arthritis in both adults and children. This mechanism of action involves blocking cytokines such as tumor necrosis factor α (TNF α) and interleukins (IL) 1, 6, suppression of T-cell activation and depletion of B cells. The term “ biologics ” or “ biologics” has become firmly established in English-language literature. agents " (biological agents), can be misinterpreted. It should not be taken to mean "naturally

existing molecules." Rather, the term encompasses a class of drugs that includes protein molecules created using technologies that "reproduce" natural processes, such as hybridoma technologies or using recombinant DNA [1, 2 , 5, 7, 32, 34].

In pediatric rheumatology, despite a number of specific problems, including " off label »-status of a number of GIBP for children, the importance of these new drugs is constantly increasing. First of all, we have received drugs that can effectively treat the systemic variant of juvenile idiopathic arthritis (JIA) - Still's disease and severe polyarticular JIA. This article provides a brief overview of GIBP currently used to treat JIA. GIBP - cytokine inhibitors The important role of cytokines in the pathogenesis of JIA [5] led to the idea of using cytokine blockers in the treatment of this disease. It seems that anti-cytokine therapy provides quite satisfactory results and is able to significantly improve the prognosis even in those severe forms of JIA, in which generally accepted therapeutic treatment strategies often did not give a positive result. TNFα inhibitors The role of TNFα in the development of inflammation TNFα is a cytokine involved in the formation of the systemic inflammatory process [6,7,9,12,23,25]. Primarily, it has a regulatory effect on the growth, survival, and function of immune system cells [8,10,14,16,27]. The biological functions of TNFα include the induction of proinflammatory cytokines such as IL 1 and 6, as well as TNFα itself, an increase in leukocyte mobility and their migration from the bloodstream to tissues by increasing the permeability of the endothelial layer of blood vessels in the microcirculatory bed and enhancing the expression of cell adhesion molecules. TNFα is able to induce cell death by apoptosis, trigger inflammatory processes, inhibit carcinogenesis, and viral replication. It plays a very important role in the pathogenesis of rheumatic inflammation, triggering a cascade of inflammatory and destructive processes involving osteoclasts, synovial fibroblasts and chondrocytes , which leads to the development of pain, swelling, the formation of bone erosions and narrowing of the joint space. By blocking the action of TNF α, we can count on the inactivation of the above processes. The following drugs belong to the family of TNF α inhibitors: etanercept, adalimumab , infliximab , certolizumab and golimumab . Infliximab (trade name Remicade) Infliximab (IF) is a chimeric monoclonal antibody that binds to human TNFα thus interfering with the action of endogenous TNFα. It neutralizes the biological action of TNFα by binding to soluble and transmembrane forms of TNFα with high affinity, inhibiting the binding of TNF α to its receptors. In addition, in In vitro, IF lyses cells expressing TNFα on their surface in the presence of complement . It is not able to neutralize TNFα (lymphotoxin α), a related cytokine that binds to the same receptors as TNFα. The half-life of IF is about 7-12 days. IF has no registered indications for use in children with JIA in the USA, Russia, or the European Union.

Infliximab : Dosage and Administration IF is administered by intravenous infusion. Premedication (antihistamines, glucocorticoids) is advisable to prevent infusion reactions. Dosage for JIA (unregistered indication): 3-4 mg/kg at 0, 2, 6 weeks, then every 8 weeks . Crohn's disease (in the USA and Russia, IF is registered for children aged 6 years and over for this disease, in Canada and the European Union - aged 9 years and over): 5 mg/kg of body weight in the following regimen: 0, 2, 6th weeks, then every 8 weeks . Clinical trials of infliximab A double-blind, placebo-controlled study of patients with JIA with persistent polyarthritis, despite previous treatment with MT, included and randomized 122 children who received IF or placebo for 14 weeks [34,35,37,38,39,40]. Subsequently, until the 52nd week, all patients received IF at a dose of 3 or 6 mg/kg. There were no statistically significant differences between the groups receiving IF at a dose of 3 mg/kg and placebo during the double-blind phase (the primary endpoint of treatment response was the achievement of improvement according to the ACRpedi 30 criterion), or between the groups receiving the drug at a dose of 3 and 6 mg/kg. The authors concluded: "... the use of IF in children requires further studies." The subsequent open-label extension phase up to week 204 demonstrated, first of all, "... a high percentage of patients who dropped out" [15]. Of the 122 patients initially included in the study, 78 patients reached the open-label extension phase, of which 42 interrupted IF treatment. The most common reasons for dropout were "agreed drug discontinuation," mainly due to achieving a persistent effect (11 patients), inefficacy (8 patients), or "patient/physician/sponsor's decision" (8 patients).

Conclusions. Despite the disappointing results of a double-blind, placebo-controlled trial of IF followed by an open-label extension phase in patients with JIA [23,26,27,34], experience using the drug in patients with JIA in real-life clinical practice demonstrates similar efficacy of IF and other TNFα inhibitors [15,17,25,28,29]. At the same time, the fact that IF is a chimeric molecule and is administered by intravenous infusions gives grounds to prefer it to ETC or ADA as the drugs of choice, especially since there is convincing evidence of their efficacy [13, 18].

IL-6 Inhibitors The Role of IL-6 in Inflammation IL-6 is a multifunctional interleukin secreted by T cells, macrophages, and other cell types. It causes many effects related to systemic rheumatic inflammation. In systemic JIA, serum IL-6 levels correlate with articular syndrome, fever, thrombocytosis, osteoporosis, and growth retardation [14, 15, 17, 27, 25, 33,41,42,43].

Tocilizumab (Tocilizumab; trade name Actemra or Ro-Actemra) Tocilizumab (TCZ) – humanized monoclonal antibodies to the human IL-6 receptor. It has been established that through simultaneous suppression of the membrane -bound and

soluble forms of IL-6R, specific inhibition of the action of IL-6 is ensured [21]. TCZ was approved in 2009 in the countries of the European Union and in the Russian Federation in combination with MT for the treatment of severe active RA, if treatment with two DMARDs and/or TNFα inhibitors was ineffective. Approval in the USA for the same indications was received only in January 2010. In Japan, TCZ was approved for the treatment of Castleman disease in 2005 and for the treatment of RA and JIA (systemic and polyarticular) in April 2008. Tocilizumab: dosage and administration In adult patients with RA: 8 mg/kg of body weight as an intravenous infusion at intervals of 4 weeks . Systemic JIA (off-label indication): 8 mg/kg body weight as an intravenous infusion at intervals of 4 (or 2) weeks .

The efficacy of TCZ in the treatment of systemic JIA has been demonstrated in open-label studies and in a randomized , placebo-controlled, double-blind study. In the initial open-label phase of this study, 56 Japanese patients with systemic JIA (age 2–19 years; duration 4.5±3.6 years) received TCZ 8 mg/kg body weight every 2 weeks . An improvement in ACR 30 and a serum CRP level of 5 mg/L were required for inclusion in the 12-week, double-blind , placebo-controlled phase of the study. Of the 56 patients, 13 were inadequate responders, while 43 patients met the response criteria. Of the 43 patients, 20 were randomized to receive TCZ and 23 received placebo. The primary endpoints were maintenance of improvement in ACR 30 and serum CRP levels of 5 mg/L. 4 (17%) of 23 patients in the placebo group and 16 (80%) of 20 patients receiving TCZ completed this phase of the study.

Rituximab (Rituximab ; trade name in the USA – Rituxan , in Europe – MabThera) Rituximab (RTM) is a chimeric (see Table 3) anti-CD20 antibody that has high affinity for CD20 [103]. CD20 is expressed on the surface of the membrane of pre- B lymphocytes and mature lymphocytes. Binding of RTM to the CD20 antigen prevents the activation and differentiation of B cells. Hematopoietic stem cells, pro- B lymphocytes (an earlier stage of differentiation than pre-B lymphocytes), and plasma cells do not express CD20. This allows for specific elimination of B cells without disrupting the reproduction of B lymphocytes from stem cells and pro-B lymphocytes and the production of immunoglobulins by plasma cells. Thus, short courses of RTM do not affect serum immunoglobulin levels. However, since plasma cells are continually derived from activated B cells, long-term treatment with anti-CD20 antibodies eventually reduces serum immunoglobulin levels. Following RTM infusion, rapid and sustained depletion of circulating and tissue B cells is observed. In patients with RA, the mean terminal half-life of RTM has been found to be 19 days. RTM can be detected in serum for 3-6 months after treatment. B-cell recovery begins 6 months after completion of the full course of treatment, and mean B-cell levels

return to normal values within 12 months after completion of therapy. RTM is approved for the treatment of moderate to severe active RA in combination with MTX (USA, European Union, Russia). It is an « off label » for the treatment of JIA. Rituximab : dosage and administration Adults with RA: intravenous infusion of 1000 mg rituximab on days 1 and 15; premedication with GC (methylprednisolone 100 mg intravenously) is recommended before each rituximab infusion . Clinical studies of rituximab There are a small number of studies or case reports of RTM treatment of systemic or polyarticular JIA with positive results. Similar observations have been reported in patients with systemic diseases of connective tissue. The drug was administered at a dose of 375 mg / m2 twice with an interval of 2 weeks or according to the so-called oncological scheme 4 times with an interval of 1 week . Randomized, placebo-controlled, double-blind studies of RTM in children have not been performed.

Conclusion

The introduction of biologic agents into clinical practice has greatly advanced the treatment of JIA and has brought about a paradigm shift. Although TNF inhibitors, ETC and ADA are mainly used for the treatment of refractory polyarticular JIA, IL-1 inhibitors, as well as IL-6 blockers, have proven successful in the treatment of systemic JIA. ABC serves as an alternative in the range of biologic agents, while the place of RTM in the treatment of JIA remains to be determined. The availability of these new therapeutic options will certainly lead to better results. In adult rheumatology, it is now increasingly stated that the main goal of treatment should be remission, and not just improvement [16]. With modern equipment, such a goal can certainly also be achieved in a higher percentage of JIA patients compared to the era before the advent of biologic agents. Our clinical experience, however, shows that remission in polyarticular and systemic JIA is still a minority, even when biologic agents are used. Furthermore, biologic agents remain a non-curative treatment and usually only work as long as they are used [11]. Since biologic agents can have serious adverse reactions, their use in the treatment of JIA requires careful monitoring to prevent such reactions or detect them as early as possible. If the pace of development of new genetically engineered therapies remains as rapid as in the past few years, we can expect further significant improvements in the near future. However, two disadvantages of biologic agents are likely to remain. The protein structure of these molecules is technologically difficult to reproduce. In addition, parenteral administration is required, a procedure that is very unpopular in children.

Thus, a desirable promising direction for antirheumatic therapy is “small molecules” (small molecules) that are at least as effective as GIBPs and can be administered orally. Given the excellent results of GIBPs in JIA and other inflammatory diseases, such desires may seem almost presumptuous. However, such agents are already appearing on the horizon and may be available in the not-too-distant future.

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