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CLINICAL STUDY

Experience of using genetically engineered biological drugs in children with a systemic form of JIA in the Karaganda region

Tattigul KENZHETAEVA[1], Zamira KENZHETAYEVA[2], Ainur MELDEBEKOVA[2], Lazat BATYRBEKOVA[2], Abi ABLASANO[3], Gaukhar ZHUMANOVA[2]

Department of Pediatrics and Neonatology, Karaganda Medical University, Karaganda, Republic of Kazakhstan. **kenzhetaeva_ta@ir-url.gb.net**

ABSTRACT

Despite all the achievements of science and medicine, juvenile idiopathic arthritis today remains one of the main childhood diseases that lead to severe irreversible consequences. This, in turn, makes it urgent to search for effective drugs for the treatment of juvenile idiopathic arthritis, of which interleukin 1 (anakinra) and interleukin 6 (tocilizumab) inhibitors are becoming increasingly popular.

AIM: to analyse the efficacy of genetically engineered biological drugs, namely anakinra and tocilizumab in children with systemic juvenile idiopathic arthritis among patients of the Karaganda region. The study involved 176 patients aged 4–17 years with a diagnosis of systemic juvenile idiopathic arthritis and with resistance to methotrexate for 3 months. Among all patients, 64 children received injections of anakinra, and 63 received tocilizumab in standard doses. The control group consisted of 50 patients of the same age category. Assessment of the efficacy of treatment was conducted at 2, 4, 8, 16, 24, and 48 weeks using ACR Pediatric criteria. The clinical effect of both drugs was detected as early as the second week after the start of therapy. At week 12 of the study in the tocilizumab group, the efficacy of treatment for ACR Pediatric 30, 50, and 70 reached 82 %, 71 %, and 69 %, and in the anakinra group – 89 %, 81 %, and 80 % respectively, while in the control group ACR Pediatric 30 after 12 weeks of treatment was achieved in 21 % of patients, ACR Pediatric 50 – in 12 %, and ACR Pediatric 70 – in 9 % ($p < 0.001$). By the end of the extended open phase, after 48 weeks of the study among patients treated with tocilizumab, the number of patients who reached ACR Pediatric 70 was 85 %. Those who reached ACR Pediatric 90 were 55 %, whereas, in the anakinra group, 89 % reached ACR Pediatric 70 and 61 % – ACR Pediatric 90. Moreover, the clinical effect was accompanied by an improvement in blood parameters, for example, haemoglobin and pro-inflammatory markers (C-reactive protein, procalcitonin), which indicates the role of interleukin 1 and interleukin 6 in the aetiology of anaemia in juvenile idiopathic arthritis. The use of tocilizumab and anakinra as treatment for systemic juvenile idiopathic arthritis resistant to methotrexate leads to a stable improvement in the general condition of patients *(Ref. 36)*.

Text in PDF *www.elis.sk*

KEY WORDS**:** systemic arthritis, polyarthritis, tocilizumab, anakinra, genetically engineered biological drugs.

Introduction

Juvenile idiopathic arthritis (JIA) is arthritis of unknown aetiology that affects children under the age of 16 and persists for at least 6 weeks, provided that no other reasons have been identified to explain the clinical symptoms (1). According to the classification of the International League of Associations for Rheumatology (ILAR), JIA is divided into 7 main forms, depending on the features of etiopathogenesis and laboratory and clinical signs prevailing in the first 6 months of the disease: oligoarthritis, polyarthritis rheumatoid factor positive (RF+)/negative (RF–), systemic JIA, juvenile psoriatic polyarthritis, arthritis associated with enteritis, and undifferentiated form (2). Because of the multifactorial nature of JIA, the prevalence of the disease varies from the studied region and country, which is associated with both the interaction of exo- and endogenous factors, and with the health care system. Epidemiological data in the world indicate an average incidence of 1–22 cases per 100000 population and a prevalence of 7–150 cases per 100000 population (3–5).

According to Palman et al (6), the average incidence of JIA in Europe in 2018 averaged 8.3 cases per 100000 population (7). Therewith, according to epidemiological data for 2021, the average incidence of JIA in the world is 1.6–23 cases per 100000 population, and the prevalence is 3.8–400 cases per 100000 population (8). The heterogeneity of the etiopathogenesis of JIA complicates the process of creating a specific highly effective treatment (9). However, one of the most acceptable theories of the development of the disease is the immunogenic theory, according to which JIA arises due to atypical immune reactions as a result of infectious diseases, genetic predisposition (10–12).

[1]Department of Pediatrics and Neonatology, Karaganda Medical University, Karaganda, Republic of Kazakhstan, [2]Department of Family Medicine, Karaganda Medical University, Karaganda, Republic of Kazakhstan, and [3]Department of Pediatrics, Khoja Akhmet Yassawi International Kazakh-Turkish University, Turkestan, Republic of Kazakhstan

Address for correspondence: Tattigul KENZHETAEVA, Department of Pediatrics and Neonatology, Karaganda Medical University, 100008, 40 Gogol Str., Karaganda, Republic of Kazakhstan.

Induced immunocompetent cells produce proinflammatory cytokines (interleukins-1, interleukins-6 (IL-1, IL-6), tumour necrosis factor (TNF)-α), and markers of the acute phase of inflammation (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), causing a typical JIA. Moreover, it was found that the number of T-lymphocytes in the synovial fluid may differ depending on the JIA subtype, which explains the difference in the clinical efficacy of treatment of varying forms of the disease (13–15). Thus, the purpose of treatment of patients with JIA is to control the inflammatory process in the joints, the standard of treatment for such patients are nonsteroidal anti-inflammatory drugs and glucocorticosteroids (GCS). For highly active JIA, basic therapy (methotrexate, sulfasalazine) is used, however, recent studies indicate a high chance of side effects and the efficacy of the use of drugs at 40–60 %, which, despite serious complications of JIA (impaired physical development, growth retardation, osteoporosis, macrophage activation syndrome, iridocyclitis, visual impairment) and the side effects of drugs make it urgent to search for more effective and safe methods of treating the disease (16–18).

The growing knowledge about the physiopathological mechanisms of the disease led to the development of genetically engineered biological drugs (GEBDs), the main purpose of which is specific cytokines or cellular interactions that interfere with the activation and regulation of the immune system, which over 15 years of their use have led to a noticeable improvement in the treatment of JIA (3). One of the most effective and studied GEBDs today is anti-TNF drugs, which include etanercept, adalimumab, infliximab, certolizumab-pegol, and golimumab (19). Their clinical efficacy has repeatedly been investigated, as a result of which they were recognised as the most effective drugs for the treatment of JIA (20–24). However, more modern drugs are interleukin 1 blockers (anakinra) and interleukin 6 (tocilizumab), the efficacy of which still needs to be investigated, considering the complex pathophysiology of various forms of JIA.

Aim: to assess the efficacy of anakinra and tocilizumab GEBDs in the complex treatment of patients with systemic JIA in the Karaganda region.

Materials and methods

A study to assess the efficacy of the use of fixed doses of tocilizumab and anakinra was conducted based on the cardio-rheumatology department of the Children's Hospital of Karaganda from December 1, 2018, to February 1, 2022 inclusive. The study involved 176 patients aged 4–17 years with a diagnosis of systemic, resistant to basic therapy JIA. The study consisted of 2 phases: a randomised, double-blind, placebo-controlled 12-week phase and an open extended (up to 48 weeks) phase. The diagnosis was made based on ILAR criteria (2001) after a clinical, laboratory, and instrumental examination (25). The control group consisted of 50 patients of the same age category who received standard treatment without GEBD.

Patients who failed to achieve the efficacy of treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids (GCS), and/or methotrexate in standard doses during the last 3 months of treatment were admitted to the study. After 2–4 weeks of screening, 64 patients were prescribed injections of anakinra at a dose of 1–2 mg/kg/day at a weight of < 50 kg and 100 mg/day at a weight of > 50 kg. Injections of tocilizumab were administered to 63 patients at a dose of 10 mg/kg with a weight of < 30 kg and 8 mg/ kg if the child's weight exceeded 30 kg. Patients were stratified depending on body weight, duration of the disease (< 4 years versus ≥ 4 years), a concomitant dose of oral glucocorticoid (< 0.3 mg per kilogram per day of prednisone equivalent versus ≥ 0.3 mg per kilogram per day), and methotrexate therapy (yes or no). All patients were offered open treatment with tocilizumab or anakinra in advance if they met the criteria for no response to treatment: fever (> 38 °C for ≥ 3 consecutive days); symptomatic serositis; macrophage activation syndrome.

At week 12, all placebo-treated patients switched to open therapy with tocilizumab or anakinra. It was allowed to reduce the dose of glucocorticoids (starting from the 6th week) in accordance with pre-determined rules. For safety reasons, in all patients taking methotrexate, the drug had to be discontinued at least 14 days before the start of the study. Basic therapy, other than methotrexate, had to be discontinued at least 28 days before the start of the study. NSAIDs or low doses of corticosteroids (< 0.2 mg/kg of prednisone per day, up to a maximum of 10 mg/day, including subcutaneous or intramuscular injections) were allowed in stable doses. Painkillers could not be taken for 12 hours before the joint assessment during the research visit. The use of immunosuppressants, alkylating agents, and analgesic alkaloids of opium/synthetic drugs was also prohibited. The efficacy of treatment was assessed at 2, 4, 8, 16, 24, and 48 weeks using the ACR Pediatric (ACR Pedi) criteria (16). The following main criteria of the JIA were used to calculate the ACR Pedi scores of 30, 50, 70, and 90:

1. Physician's Global Assessment of disease activity (PhGA).
2. Patient Global Assessment of well-being (PaGA).
3. Active Joint Count in 73 joints (AJC73).
4. Limitation of Motion in 69 joints (LOM69).
5. Childhood Health Assessment Questionnaire (CHAQ) to assess physical function and concentration of C-reactive protein (CRP).

The study was funded by the Karaganda Children's Hospital in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (26). All patients took part in the study voluntarily. After the consent of the parents or legal guardians, they signed an informed consent form to take part in any procedures related to the study. For statistical analysis, descriptive statistical methods were used in the Statistica 10 programme (StatSoft, Inc., United States of America).

Results

Sample characteristics

Of the 176 patients under study, 63 were included in the tocilizumab group and 64 in the anakinra group. The remaining 50 patients were assigned to the placebo (control) group. 50 were randomised to the placebo group and 63 to the tocilizumab group. The initial demographic criteria (age, gender, weight) and clinical

criteria of the disease (duration of the disease, previous methods of treatment of JIA, taking GCS) were maximally balanced between the groups. At this stage, it was discovered that at the beginning of the study, the average duration of the disease in all groups was more than 5 years, while 67 % of patients from the tocilizumab group and 72 % from the anakinra group had earlier experience using GEBDS in the form of one or another anti-TNF drug, which appeared to be ineffective. In addition, all patients showed signs of polyarthritis with the presence of more than 3 active joints, 73 % of patients in the tocilizumab group, 77 % and 73 % of patients in the anakinra and placebo groups, respectively, had systemic signs (fever, rash, etc.), which allowed diagnosing systemic JIA.

During the study, a total of 17 patients from the placebo group, 1 patient from the tocilizumab group, and 2 patients from the anakinra group met the criteria for lack of response to treatment, which is why they did not complete the double-blind phase of the study and switched to open therapy with tocilizumab or anakinra. Notably, during the entire study period, there was no case of withdrawal of patients, all patients underwent a full course of therapy, which averaged 60.2 weeks for the tocilizumab group and 62.1 weeks for the anakinra group.

Efficacy of therapy during the double-blind phase of the study

A positive clinical effect was detected when assessing the status of patients in the second week of the study in both the tocilizumab group and the anakinra group. For example, among those taking tocilizumab at week 2 of the study, ACR Pedi 30 was observed in 64 % of patients, and ACR Pedi 50 – in 52 %. However, only 32 % of patients managed to achieve ACR Pedi 70, which may be explained by the delayed action of the drug in this form of the disease. Regarding the anakinra group, 69 %, 43 %, and 37 % reached ACR Pedi 30, 50, and 70, respectively at week 2 of the study, which may be explained by both the individual characteristics of patients and the pharmacokinetics and pharmacodynamics of the drug, which requires additional investigation. In addition, starting from the second week of the study, there was a statistically remarkable difference in the responses of patients for ACR Pedi in the tocilizumab and anakinra groups, compared with the placebo group, in which ACR Pedi 30, 50, and 70 was reached only by 15 %, 8 %, and 5 %, respectively ($p < 0.001$).

By week 6 of the study, in the tocilizumab group, ACR Pedi 30, 50, and 70 were observed in 68 %, 56 %, and 36 % of patients, and in the anakinra group, these indicators were 72 %, 48 %, and 49 %, which supposedly indicates greater efficacy of anakinra. Notably, in both groups, the results significantly prevailed over those in the control group, where at week 6 the efficacy of treatment for ACR Pedi 30, 50, and 70 was only 16 %, 8 %, and 7 %, respectively ($p < 0.001$). Moreover, both in the tocilizumab group and in the anakinra group, a remarkable decreases in indicators of CRP (from "+++" to "++" or "+") and other pro-inflammatory markers were found, whereas among the control group they did not change or increased throughout the study. By the last assessment, during the double-blind phase of the study at week 12 in the tocilizumab group, the efficacy of treatment for ACR Pedi 30, 50, and 70 reached 82 %, 71 %, and 69 %, and in the anakinra group – 89 %, 81 %, and 80 %, respectively, which shows high efficacy of both drugs. Therewith, in the control group, ACR Pedi 30 was achieved in 21 % of patients after 12 weeks of treatment, ACR Pedi 50 – in 12 %, and ACR Pedi 70 – in 9 % ($p < 0.001$).

When examining the pharmacokinetic effects of drugs during the double-blind phase of the study, no difference in the concentration of tocilizumab or anakinra was found in patients, depending on their body weight. In the group of tocilizumab for patients with a body weight of less than 30 kg, the minimum concentration of the drug in the blood was 61.3 mcg/ml, and the maximum concentration was 263.3 mcg/ml. Furthermore, for persons with a body weight of 30 kg or more at week 12 of the study, the minimum concentration of tocilizumab was 54.5 mcg/ml, and the maximum concentration was 225.7 mcg/ml, which indicates that there is no statistically-valid difference in the concentration of the drug in the blood, depending on body weight. The same results were found in the anakinra group, in which, with a weight of less than 50 kg, the minimum concentration of the drug in the blood of patients was 55.3 mcg/ml, and the maximum was 245.5 mcg/ml. Therewith, for patients weighing more than 50 kg, the minimum concentration of anakinra was 62.1 mcg/ml, and the maximum was 251.7 mcg/ml. In addition, during the double-blind phase of the study, no association was found between the concentration of drugs in the blood and the response rate of ACR Pedi 30, 50, and 70, which requires additional investigation.

Efficacy of therapy during the extended open phase of the study

In the open extended phase, which included 63 patients randomly assigned to receive tocilizumab, 63 patients who continued taking anakinra because of a good response in the double-blind phase, and 50 patients randomly assigned to receive placebo, there was a progressive improvement in the symptoms of systemic JIA and laboratory parameters. By the last assessment during the double-blind phase of the study at week 12 in the tocilizumab group, the efficacy of treatment for ACR Pedi 30, 50, and 70 reached 82 %, 71 %, and 69 %, and in the anakinra group – 89 %, 81 %, and 80 %.

In the tocilizumab group at week 24 of the study, 73 % of patients managed to achieve ACR Pedi 70 responses, and in the anakinra group, these indicators increased to 82 %. Moreover, at the 48th week of the study, 85 % of patients treated with tocilizumab managed to achieve ACR Pedi 70, and 55 % achieved ACR Pedi 90. Moreover, in the anakinra group, 89 % of patients reached the ACR Pedi 70, and 61 % – ACR Pedi 90, which indicates extremely high efficacy of therapy with both tocilizumab and anakinra. Notably, the positive dynamics in the clinical condition of patients were accompanied by normalisation of laboratory parameters, in particular, a decrease in CRP and procalcitonin, and an increase in haemoglobin concentration. Nevertheless, the results of 2 patients from the tocilizumab group and 4 patients from the anakinra group who reached ACR Pedi 70 and 1 patient from the tocilizumab group with an ACR Pedi 90 response were not counted and were not allowed for subsequent statistical analysis due to the presence of fever, despite therapy. Furthermore, 12 patients from the anakinra group had a decrease in temperature below 36.2 °C, which may primarily be conditioned upon inhibition of IL-1, which

is involved in the development of fever. However, the presence of anakinra-resistant fever in 4 patients with systemic JIA requires follow-up studies to accurately detect its etiopathogenesis. In addition, it was found that in the tocilizumab group, the average (± SD) number of active joints decreased to 3.5 ± 2.4 at week 24, to 2.1 ± 2.3 at week 48, and among the anakinra group, these indicators were 3.71 ± 3.1 and 2.8 ± 2.45, respectively. Moreover, by the end of the study, 46 % of patients from the tocilizumab group and 52 % of patients from the anakinra group had no active joints, which also indicates the efficacy of both drugs.

To summarise, a total of 43 % of patients in the tocilizumab group met the criteria of clinically inactive JIA, and in the anakinra group, this indicator was 45 %. Joint functionality also improved in a large number of patients: at the 48th week of the study, only 29 % of patients taking tocilizumab and 27 % of patients receiving anakinra had moderate functional disorders, while 17 % and 20 %, respectively, had severe disorders, whereas by the beginning of the study this indicator was 83 % and 85 % in the groups of tocilizumab and anakinra, respectively. It is also worth noting the reduced need for taking GCS: 4 8% of patients taking tocilizumab stopped taking glucocorticoids after completing a full course of therapy, and the average dose equivalent to prednisone decreased to 0.04 ± 0.06 mg per kilogram per day. In addition, in the anakinra group, 45 % of patients stopped taking GCS, and among those who continued taking corticoids, the average dose of prednisone decreased to 0.06 ± 0.09 mg/kg/day. Thus, the results of both the double-blind phase of the study and the extended open phase indicate the high efficacy of tocilizumab and anakinra in patients with systemic JIA resistant to basic therapy, which allows both drugs to be used in patients with this form of arthritis.

Safety of anakinra and tocilizumab

This subsection describes the undesirable consequences that occurred during the double-blind or open extended phases of the study in connection with taking anakinra or tocilizumab. In the double-blind phase of the study, a greater number of side effects were detected in the tocilizumab group (23 cases) than in the anakinra (19 cases) or placebo (12 cases) groups, however, most of the reported side effects were mild or moderate severity, which allowed not to cancel the treatment in patients. Therewith, during the open extended phase, more side effects were detected in the anakinra group (31 cases) than in the tocilizumab (27 cases) and placebo (18 cases) groups, which may be related to the specific features of the drug's action and requires subsequent investigation.

In the tocilizumab group, the infection rate during the double-blind phase of the study averaged 4.1 patients/year, and during the extended open – 3.7 patients per year. In the anakinra group, these indicators were 3.6 and 4.32 patients per year, respectively, and in the placebo group – 2.1 in the double-blind phase of the study. Serious adverse effects in the double-blind phase were detected in 4 patients in the tocilizumab group, compared with 3 in the anakinra group and 1 in the placebo group. In total, during the entire study period, 12 serious adverse effects were registered in the tocilizumab group, among which 8 were infections. In the anakinra group, 9 serious adverse effects were detected, of which 5 were infectious diseases of different genesis. However, it is worth noting that all the consequences, regardless of their severity, were successfully treated. In addition, no cases of activation of opportunistic infections and/or tuberculosis were detected during the entire study period. The main infectious diseases were viral respiratory infections (57 %) and intestinal infections, in particular, enteritis (41 %). Because of adverse events, drugs were discontinued in 5 patients from the tocilizumab group and in 2 patients from the anakinra group. There were also 2 episodes of macrophage activation syndrome among patients taking tocilizumab and 1 episode among those taking anakinra, however, all of them were successfully stopped and cured.

In addition, during the study, the development of neutropenia of varying severity was observed in patients of both groups. For example, in the tocilizumab group, 12 patients developed grade 3 neutropenia ($0.5 \times 10^9 – 1.0 \times 10^9$ neutrophils/litre), whereas grade 4 neutropenia ($< 0.5 \times 10^9$ neutrophils/litre) occurred in only 1 patient. Therewith, only 7 cases of grade 3 neutropenia were registered in the anakinra group, which may be associated with better tolerability of the drug and requires subsequent investigation. An increase in the level of alanine aminotransferase by more than 2.5 times from the upper limit of the norm occurred in 25 patients taking tocilizumab and in 21 patients in the anakinra group. In 35 % of patients in the tocilizumab group, an increase in cholesterol and/or low-density lipoproteins was observed during the study, whereas in the anakinra group, similar changes in lipid metabolism were detected in 27 % of patients. In addition, when the patients were initially tested for antibodies to tocilizumab and anakinra, the test was negative in all patients, however, antibodies to tocilizumab were formed in 3 patients, which is why the drug was discontinued and replaced with anakinra, antibodies to which were not formed in any of the study participants. Antibodies to tocilizumab were formed in two patients; both refused to take part because of adverse effects (see Appendix). During the entire study, no deaths were reported from taking tocilizumab or anakinra, which, together with the above data on undesirable side effects from taking them, indicates a high safety of both anakinra and tocilizumab and allows them to be used for the treatment of JIA.

Discussion

Systemic JIA resistant to basic therapy is a serious therapeutic problem that often leads to irreversible consequences. Conventional methods of treatment, including GEBD – tumour necrosis factor inhibitors, often have a limited clinical effect, and long-term use of GCS or basic therapy exposes patients to danger because of an unfavourable safety profile. However, numerous data indicate excessive activity of proinflammatory cytokines IL-1 and IL-6 in systemic JIA, which possibly indicates the role of these factors in the development of the disease. For example, Mellins et al (27) demonstrated that IL-1 is able to stimulate the destruction of cartilage and bone tissue, affecting the regulation of follistatin-related protein 1, which is also considered one of the markers of systemic JIA activity. de Benedetti et al (28) suggested that the potential role of IL-6 in the development of the disease is its ability to create foci of bone resorption, and contribute to thrombocytosis and

growth retardation, which can also explain the normalisation of the number of platelets in patients in this study using an IL-6 inhibitor (tocilizumab). Moreover, Stock et al (29) discovered that patients with polymorphisms in the genes encoding IL-1 and IL-6 proteins have a much greater chance of developing JIA compared to controls, which also indicates the role of these pro-inflammatory cytokines in the development of the disease. Therewith, the use of drugs capable of inhibiting IL-1 and IL-6 in most cases contributed to a notable improvement in the general condition of patients, which was also achieved in this study. Indeed, over the past 10 years, the treatment of systemic JIA with the advent of inhibitors IL-1 (anakinra) and IL-6 (tocilizumab) has radically changed. Due to the use of these drugs, it is possible to influence inflammatory processes in the body better, thereby controlling the course of the disease more effectively and improving the patient's prognosis in the future. As mentioned earlier, the efficacy of these drugs is primarily explained by the mechanism of their action.

Tocilizumab is a recombinant humanised monoclonal antibody. The mechanism of action of the drug consists in binding and blockade of IL-6 receptors (3). It is usually used alone or in combination with methotrexate in patients older than two years with systemic JIA. In this study, the response rates of ACR Pedi 30, 50, and 70 showed that tocilizumab is highly effective against systemic juvenile idiopathic arthritis among patients of the Karaganda region. For example, during the double-blind phase of the study, as early as week 2, 64 % of the responses reached ACR Pedi 30, 52 % had ACR Pedi 50, and 32 % had ACR Pedi 70, which considerably differed from the indicators in the control group ($p < 0.001$). The tendency to improve the clinical condition of patients and their laboratory parameters was stable until the end of the entire study, and therefore, at week 48, ACR Pedi 70 in the tocilizumab group managed to reach 85 % of patients, and ACR Pedi 90 – 55 % of patients, which indicates good efficacy of the drug. Similar results were achieved by Yokota et al (30) in the Japanese population. Their study involved 56 children aged (2–19 years) with systemic JIA, refractory to conventional treatment, who were prescribed tocilizumab at a dose of 8 mg/kg every 2 weeks. As a result of the first open phase of the study, ACR Pedi 30, 50, and 70 was reached by 91 %, 86 %, and 68 % of patients, whereas, by the end of the second phase of the study for 48 weeks, these indicators increased to 98 %, 94 %, and 90 %, respectively. However, during the experiment, researchers registered cases of serious complications, in particular, anaphylactoid reactions and gastrointestinal bleeding, which were not observed in this study and may be related both to the individual characteristics of patients and to the effect of the drug in a certain population, which requires further investigation.

Therewith, Opoka-Winiarska et al (31) demonstrated the efficacy of the drug among the Russian and European populations. In their observational study among 41 patients, the researchers demonstrated that during the period of taking tocilizumab in standard doses, all patients from the study group managed to achieve an ACR Pedi of 70. The effect of the drug was also characterised by high resistance since most patients had no cases of active JIA 2.5 years after the last injection of tocilizumab. In addition, researchers confirmed a high safety profile of the drug. As in the conducted study, in the experiment of Opoka-Winiarska et al (31) most of the adverse reactions were viral respiratory infections of mild or moderate severity, whereas only one case of severe neutropenia was detected during the entire study period, which was successfully compensated without non-reversible consequences for the patient. Thus, despite the increase in the frequency of serious side effects when analysing the results of other studies among European and Asian populations, it can be assumed that there are ethnic characteristics in susceptibility to tocilizumab, however, this theory requires future studies with a larger sample.

Moreover, by the end of the open extended phase of the study, 43 % of patients had clinically inactive disease, and 48 % of patients were able to refuse subsequent administration of glucocorticoids, which can notably improve their prognosis in the future. The stability of the positive therapeutic effect of tocilizumab was also confirmed by de Benedetti et al (32), in whose study, during 52 weeks of taking tocilizumab, control over clinical symptoms (fever, rash, joint pain, and their functional activity) and laboratory parameters (CRP, procalcitonin, leukocyte formula, erythrocyte levels, platelets, and haemoglobin concentration) was maintained. Moreover, as in the study by de Benedetti et al (32) this study did not detect a statistical pattern between the concentration of drugs in the blood and the frequency of responses ACR Pedi 30, 70, 90, however, the body weight-based dosing regimen of both tocilizumab and anakinra ensured uniform exposure to the drug and the appearance of the desired therapeutic effect.

Another drug, the efficacy of which was examined in the study is anakinra. It is a recombinant antagonist of the human IL-1 receptor, which blocks the activity of IL-1 α and IL-1 beta using competitive antagonism and binding with type 1 receptor to this cytokine (3). In this study, as in the case of tocilizumab, high efficacy of the drug was found according to the responses of ACR Pedi 30, 50, and 70. As already demonstrated, by week 12 of the double-blind phase of the study, 89 %, 81 %, and 80 % of patients achieved ACR Pedi 30, 50, and 70, respectively, and by the end of the open phase at week 48, ACR Pedi 70 was achieved in 89 % of patients, and ACR Pedi 90 in 61 %, which indicates high clinical efficacy of anakinra. Other sources also indicate an extremely high clinical effect of treatment with anakinra. For example, Davies et al (33) demonstrated that among the European population, within 4 weeks after the start of therapy, 80 % of patients achieved ACR Pedi 90 responses. In addition, the researchers found strong stability of the positive clinical effect, which lasted for more than 12 months. Similar results were achieved by Kearsley-Fleet et al (34), among 77 patients, 22 of whom were prescribed anakinra, and 54 – tocilizumab in standard dosages. Researchers established that despite the reliable high efficacy of both drugs ($p < 0.05$), anakinra had greater efficacy compared to tocilizumab (42 % achieved ACR Pedi 90 during the study period) and a more stable effect, however, when treated with anakinra, patients more often experienced adverse effects in the form of macrophage activation syndrome (38 % with anakinra versus 8 % with tocilizumab, $p < 0.004$). Moreover, Phadke et al (35) demonstrated that anakinra is the drug of choice in patients with JIA and macrophage activation syndrome, because of its high safety profile.

Thus, the results of the study and other sources allow the use of anakinra for the treatment of systemic JIA resistant to basic therapy, and the risk of serious side effects such as macrophage activation syndrome requires further investigation. Moreover, analysing the dynamics of changes in blood tests, it can be concluded that, like a number of other biological drugs (adalimumab, etanercept), tocilizumab and anakinra reduced the number of pro-inflammatory markers during treatment, but the treatment process was accompanied by an increase in the concentration of haemoglobin in the blood, which according to hypothesis of de Benedetti et al (32), indicates the relationship of IL-1 and IL-6 with the development of anaemia in JIA. Special attention should be paid to the undesirable side effects of taking tocilizumab and anakinra. Despite the studies of Yokota et al (30), de Benedetti et al (32), which described deaths from taking tocilizumab, in this study, no deaths from taking tocilizumab or anakinra were recorded during the entire time of its conduct. In addition, the described cases of side effects of drugs in the form of infections, neutropenia, and macrophage activation syndrome mostly had a mild or moderate severity, which allowed not to cancel the drug in such patients. However, the infectious morbidity of 3.7 and 4.2 patients/year in the treatment with tocilizumab and anakinra, respectively, requires increased care from the doctor who prescribes these drugs to patients with a predisposition to the development of infectious diseases.

2 cases of macrophage activation syndrome were described when taking tocilizumab and 1 case when receiving anakinra. According to the study by de Benedetti et al (32), similar changes may occur as a result of infection or as a result of taking an incomplete dose of the drug. In addition, Strippoli et al (36) found that high levels of IL-6 under the action of an infectious trigger can cause the development of macrophage activation syndrome, however, this requires further investigation. An increase in the level of alanine aminotransferase by more than 2.5 times from the upper limit of the norm occurred in 25 patients taking tocilizumab and in 21 patients in the anakinra group. In 35 % of patients in the tocilizumab group, an increase in cholesterol and/or low-density lipoproteins was observed during the study, while in the anakinra group, similar changes in lipid metabolism were detected in 27 % of patients. The clinical value of changes in lipid metabolism of children with systemic JIA has not been fully studied to date, however, recent studies claim that an increase in low-density lipoprotein levels when taking interleukin inhibitors is associated with an increase in the number of large, not small particles (the latter are considered proatherogenic) (33).

Notably, patients with a disease duration of less than six months were excluded from this study, which could affect the reliability of the results. However, the study included patients with persistent systemic JIA resistant to basic therapy, for whom there was no effective treatment, which was reflected in the long duration of the disease, a large number of active joints, and a high frequency of previous exposure to biological agents at the baseline, therefore, regarding this cohort of patients, it is possible to accurately state the efficacy of tocilizumab and anakinra. Further studies are required to investigate the effect of these drugs on other forms of JIA.

Conclusions

Systemic JIA resistant to basic therapy is a serious therapeutic problem that often leads to irreversible consequences. Conventional methods of treatment, including GEBD – tumour necrosis factor inhibitors, often have a limited clinical effect, and long-term use of GCS or basic therapy exposes patients to danger because of an unfavourable safety profile. However, the use of interleukin inhibitors allows achieving the desired clinical effect and remission in patients with systemic JIA resistant to basic therapy. During the double-blind phase of the study, both the IL-1 inhibitor anakinra and the IL-6 inhibitor demonstrated high clinical efficacy in the treatment of the disease. During the 12 weeks of the double-blind phase of the study, ACR Pedi 30, 50, and 70 in the tocilizumab group were achieved in 82 %, 71 %, and 69 % of patients, and in the anakinra group – in 89 %, 81 %, and 80 %, respectively, which statistically differed from the placebo group ($p < 0.001$).

By the end of the open phase of the study at 48 weeks, ACR Pedi 70 in the tocilizumab group was reached by 85 % of patients, and ACR Pedi 90 – by 55 % of patients, while in the anakinra group these indicators were 89 % and 61 %, respectively. Moreover, the positive dynamics in the clinical status of patients in both groups of patients were accompanied by an improvement in laboratory parameters in the form of a decrease in the levels of C-reactive protein and other pro-inflammatory markers, an increase in erythrocytes and haemoglobin, which may be associated with the influence of IL-1 and IL-6 on the development of anaemia in JIA and requires further investigation. In addition, the low percentage of adverse reactions in the form of infectious diseases, neutropenia, macrophage activation syndrome, and elevated transaminases and cholesterol and low-density lipoprotein concentrations indicate a high safety profile of both anakinra and tocilizumab. However, in patients at risk, the benefit of treatment with these drugs should be weighed against the risk of adverse events. The prospect for further studies is to investigate the effect of tocilizumab and anakinra on the efficacy of therapy in other forms of JIA and/or in other patient populations.

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