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Comparative Evaluation of the Efficiency and Safety of Treating Children with Polyarticulary Juvenile Idiopathic Arthritis with Methotrexate and with Methotrexate Combined with Tocilizumab

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Substantiation*. Juvenile Idiopathic Arthritis (JIA) is the most frequent rheumatic disease in children and is characterized by primary damage of joints, and also the pathology of other bodies and fabrics with the formation of polyorgan insufficiency of various degree of expressiveness.* ***Research objective****. A comparative assessment of efficiency and safety of tocilizumab in combination with methotrexate in comparison with the therapeutic efficiency of only methotrexate in patients with polyarticulary JIA.* ***Methods****. Clinicallaboratory, biochemical, immunological methods of blood tests were used against the carried-out therapy in dynamics of the disease.* ***Results****. Tocilizumab in combination with methotrexate has an expressed anti-inflammatory effect in children sick with polyarticulary JIA. During treatment with only methotrexate the therapy efficiency was much lower and not always effective.* ***Conclusion.*** *Tocilizumab is a promising drug for treating juvenile arthritis, refractory to standard immunosupressive therapy.*
Key words*: children, juvenile idiopathic arthritis, treatment, tocilizumab, methotrexate.*
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JUSTIFICATION

Juvenile idiopathic arthritis (JIA) is a severe, chronic, and relentlessly progressive disease of unknown etiology with a complex autoaggressive pathogenesis. JIA is one of the most common and most disabling rheumatic diseaseы in children [1]. JIA is characterized mainly by destructive joint damage and pathologies of other organs and tissues with the formation of multiorgan failure of various severity. The disease leads to a drastic restriction of movement ability and self-service, physical, mental and social maladjustment of children [2, 3].

Treatment of juvenile arthritis remains one of the most complex and urgent problems of rheumatology. The therapy uses a wide range of antirheumatic drugs. Pathogenic immunosuppressive therapy significantly improves clinical condition and quality of life for the majority of patients with juvenile arthritis [4]. However, in many patients, the opportunity to achieve sustained remission using antirheumatic drugs on a conventional basis remains unlikely [5-8].

Given the involvement of cytokines in the JIA pathogenesis, use of cytokine blockers in the treatment of this disease was justified. Anticytokine therapy provides quite satisfactory results and can significantly improve the prognosis, even in case of severe forms of JIA, in which conventional therapeutic treatment strategies often do not give positive results.

Of particular interest is the use of monoclonal antibodies, the maximum selectivity of which provides a selective effect on the immune system, allowing to eliminate a necessary link in the pathogenetic chain. The high specificity of antibodies eliminates the possibility of their influence on other physiological mechanisms of the immune system.

In pediatric rheumatology, despite a number of specific problems including *off label*-status of some genetically engineered biological products for children, the importance of these new drugs is increasing. First of all, we got drugs that can effectively treat systemic and polyarticular JIA versions of a severe course.

Genetically engineered biological agents (GEBA) have revolutionized the treatment of rheumatoid arthritis. As a result of their use, the functional activity of patients and their quality of life statistically improve significantly. Many clinical studies have confirmed that the quality of life during treatment with biological agents is associated with increased physical activity, decreased fatigue, and increased emotional background and earning capacity of patients [7-9]. Application of GEBA allows not only to block the symptoms of the disease, but also to suppress the development of the erosive process in joints, to improve functional status and quality of life, and to increase life expectancy to the population level.

Interleukin (IL) 6 and its soluble receptor plays an important role in the pathogenesis of rheumatoid arthritis. In the studies, concentrations of IL 6 increasingly correlate with the disease activity, severity of joint damage, fever, growth retardation and osteoporosis [9-16]. This was the basis for the development of targeted therapy aimed at neutralizing this cytokine. Tocilizumab is a recombinant humanized monoclonal antibody to the human-IL6 from the subclass of immunoglobulin G; it selectively binds to and inhibits both soluble and membrane receptors IL6 (sIL6R and mIL6R) [16, 17].

Comparative studies on the influence of the traditional basic drugs and tocilizumab on a juvenile idiopathic arthritis course are not numerous [17-19].

The aim of our study is to investigate the efficacy and safety of tocilizumab in combination with methotrexate and methotrexate monotherapy in patients with polyarticular JIA.

PATIENTS AND METHODS

Inclusion criteria: patients with polyarticular seronegative JIA version. To set and verify the diagnosis, classification criteria for juvenile idiopathic arthritis of the International League of Associations for Rheumatology (ILAR; Durban, 1997, Edmonton, 2001) were used.

Additional inclusion criteria were normal serum levels of urea, creatinine, bilirubin, alanine aminotransferase and aspartate aminotransferase; the absence of significant pockets of acute and chronic infection. In case of infection, appropriate treatment was provided. All patients, before being prescribed tocilizumab, were subjected to a thorough examination for tuberculosis, including a tuberculin test (Mantoux test) and chest X-rays. In case of TB infection exclusion and phthisiatrician's permission, we began treating the

patient with tocilizumab. Monitoring of clinical and biochemical blood analysis, and urinalysis was conducted every 2 weeks.

The control group included healthy children of the given region of residence and of the same age groups as the sick children.

Exclusion criteria

The study did not include patients treated with glucocorticoids, children with high serum levels of urea, creatinine, bilirubin, and increased activity of transaminase, as well as with the presence of clinically significant pockets of acute and chronic infection. Upon detection of infection, an appropriate antibiotic treatment was provided.

Research results and methods of their registration

The main result was the comparative assessment of the effectiveness and safety of tocilizumab in combination with methotrexate with methotrexate only therapeutic effectiveness in patients with polyarticular JIA.

Evaluation of cellular immunity. Identification of lymphocytes and their subpopulations was conducted by standard immunofluorescence analysis using monoclonal antibodies to their surface antigens (CD). With this method it is possible to implement a one-time determination of two or more surface molecules on each of the test cells. This allows to get information about the subclass of lymphocytes and the stage of their differentiation and activation.

Mononuclear cells were isolated from heparinized blood (25 U/ml) using the centrifugation in ficoll-verografin density gradient (S 1,077 g/cm^3) by standard methods (Frimel, 1987).

To isolate the phenotype, monoclonal antibodies to the CD-antigens of human lymphocytes and labeled FITC Fab-fragments of anti-mouse immunoglobulins of NPF, the "MedBioSpektr" (Russia) facility was used.

The levels of T helpers / inducers (CD4 +), T cytotoxic / suppressor cells (CD8 +), natural killers (CD16 +), mature B-lymphocytes (CD19 +) and lymphocytes expressing specialized receptors of signals to apoptosis induction - Fas-antigen (CD95 +) were determined.

The registration of results was conducted using a fluorescence microscope to determine the percentage of luminous cells out of 200 of counted.

Condition of the humoral immune system

To assess the functional state of the humoral immune system, a quantitative determination of immunoglobulins in blood serum was used. Investigation of major immunoglobulin classes (A, G, M) was carried out by single radial immunodiffusion in agar body by Mancini (Manchini G. et al., 1965) in Fehey modification (Fehey et al., 1965) using monospecific antisera to human immunoglobulin. Cytokines (IL 1 β, IΛ 4, IL 6, IL 8, IL 10, TNF α) in serum were determined by linked immunosorbent assay using commercial test kits for *in vitro* diagnostics ("Protein contour" LLC, St. Petersburg) with accompanying instructions; the results were expressed in pg/ml.

Individual therapy effectiveness in children was evaluated using the pediatric criteria of the American Rheumatologist Board (ACR_{pedi}): reduction (according to the patient's and / or parents' assessment) of health indicators by 30, 50 and 70% on a visual analog scale (VAS); changes (according to the doctor) in indicators of disease activity on VAS, in the index of quality of life on CHAQ, in number of joints with active arthritis, and in number of joints with impairment of function and erythrocyte sedimentation rate. The duration of the

comparative clinical trial was 12 months, as the majority of the investigated drugs start having a basic effect over a period of from 6 weeks to 6 months. In addition, it is only possible to make a reliable estimation of the dynamics of radiological, immunological and functional parameters only for 1 year.

The functional activity of patients with juvenile idiopathic arthritis was assessed by functional class according to the Steinbrocker's criteria:

Tocilizumab was appointed with the approval of the Samara regional clinical cardiological dispensary's ethics committee and with the informed consent of the patient's parents and the children aged older than 6 years.

The effect of tocilizumab treatment was assessed after 4, 8, 12, 24 and 48 weeks of treatment. The main criterion of efficacy was the achievement of at least 50% of improvement according to $ACR_{pedi:}$ at least 50% of improvement compared to the baseline for at least 3 of the 6 indicators presented above, with the possible deterioration by 30% of not more than 1 of 6 indicators. 70% of improvement on the specified criteria was also estimated. The effect was assessed as excellent in case of 70% of improvement, as good – in case of 50% of improvement, as satisfactory - with a 30% improvement. The criteria for remission were the absence of joints with active signs of inflammation; absence of fever and of generalized lymphadenopathy; normal values of erythrocyte sedimentation rate and serum concentration of C-reactive protein; the absence of disease activity by the overall assessment of a doctor (on VAS). The absence of disease activity (inactive phase of the disease) was stated, if the patient corresponded to all of the criteria; clinical remission - if the disease was inactive for 6 consecutive months.

The safety of tocilizumab treatment was assessed by accounting for the adverse events and regular monitoring of clinical-instrumental and laboratory parameters:

- targeted clinical examination of patients for signs of basic drugs side effects;
- clinical hemanalysis, biochemical blood analysis (general protein, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, and potassium), and clinical urine analysis once per month;
- 1 ophthalmologic examination every 3 months;
- 1 chest X-ray every 6 months during taking of the immunosuppressants and cytostatics.

Tocilizumab cancelation was an exclusion criterion.

Ethical review

The research protocol was approved at a meeting of the Local Ethics Committee of Samara Regional Clinical Cardiology Dispensary. We received the following conclusion:

The presented clinical research "Evaluation of the efficacy and safety of treatment with tocilizumab in combination with methotrexate as compared to methotrexate therapy in children with polyarticular form of idiopathic arthritis " can be carried out, as it does not conflict with the Helsinki Declaration of the World Medical Association's "Guidelines for physicians involved in biomedical research with the participation of the people ", the Constitution of the Russian Federation (12.12.1993), the OST branch standard 42-511-99 "Rules of carrying out qualitative clinical trials in the Russian Federation" dated 29.12.1998, and par. 43 of Fundamentals of Legislation on health care in the Russian Federation. Protocol № 14 of 05.14.2014.

Informed consent from parents or legal representatives of the child was obtained Before the research.

Statistical analysis

Statistical processing of the research results was carried out using Statistica 6.0 (StatSoft Inc.). The reliability of differences in quantitative indicators between two independent groups was assessed by the Mann-Whitney criterion, between the two dependent groups - by the Wilcoxon criterion. To identify the dependence between the studied traits, a correlation analysis using the non-parametric Spearman correlation coefficient was applied. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Study participants

The study included 65 patients with polyarticular seronegative form of JIA. The control group consisted of 30 healthy children of the given region of residence and of the same age groups as the patients.

Groups of patients who received only methotrexate or combined drugs as treatment were comparable by age, sex, and duration of disease.

The demographic characteristics of the children included in the study are presented in Table 1. Median age - 4 to 17 years. There were 50 girls and 15 boys. The study included 41 patients with polyarticular JIA (8 boys, 33 girls) treated with methotrexate therapy and 24 patients with polyarticular JIA (7 boys, 17 girls) treated with a combined therapy of methotrexate and GEBA-tocilizumab. Prior to the tocilizumab appointment, patients were treated with methotrexate at a dose of 15-25 mg / m^2 per week by intramuscular injection for 3 months or more without effect. Patients with basal glucocorticoid therapy were excluded. Tocilizumab was prescribed during treatment with methotrexate, doses of which have remained unchanged for at least 4 weeks.

Tocilizumab was prescribed to children weighing less than 30 kg, at a dose of 10 mg / kg of body weight, once every 4 weeks intravenously. To patients weighing more than 30 kg tocilizumab was prescribed at a dose of 8 mg / kg of body weight, 1 time every 4 weeks intravenously. THE DOse of methotrexate remained stable for at least 4 weeks.

Table 1. Demographic characteristics of the patients included in the study (n = 65)

Index	**The control group (n = 41). Methotrexate**	**The main group (n = 24). Metotreksat + tocilizumab**
Age, years	4-17	4-17
Boys / girls	8/33	7/17
Disease duration, years	3.7 (3.7; 5.8)	4.4 (3.8, 5.9)

Key findings

Data from the study shows a rapid positive impact on the activity of the articular syndrome, health and disease activity (VAS score) as well as on the functional capacity (assessed using the CHAQ questionnaire). In all patients with JIA, a pronounced anti-inflammatory effect was observed after the first infusion of tocilizumab (Table 2). In particular, the number of joints with active arthritis reduced by 36% after the third infusion, active articular syndrome maintained in 32% of patients. After 24 weeks of treatment with IL6 blocker there were no joints with active arthritis in children with JIA.

Table 2. ***Dynamics of disease's activity indicators in patients with JIA treating with methotrexate and with methotrexate in combination with tocilizumab***

Index	Drugs	Observation in weeks					
		Before treatment	4th week	8th week	12th week	24th week	48th week
The number of joints with active arthritis, abs.	Methotrexate	5 (4; 9)	4 (3, 8)	3 (3, 7)	3 (3; 6)	2 (2, 5)	2 (2, 5)
	Methotrexate + tocilizumab	7 (6; 12)	2 (0. 2) **	0 (0, 0), **	0 (0, 0), **	0 (0, 0), **	0 (0, 0), **
The number of joints with dysfunction, abs.	Methotrexate	6 (6; 11)	5 (4; 11)	5 (4; 10)	5 (4; 9)	3 (3; 8)	3 (3; 8)
	Methotrexate + tocilizumab	8 (7; 14)	1 (0, 4) **	0 (0, 0), **	0 (0, 0), **	0 (0, 0), **	0 (0, 0), **
The state of health (assessment by the patient or a parent on VAS), mm	Methotrexate	70 (62; 90)	63 (54; 79) *	59 (50; 75) *	58 (51; 71) *	56 (53; 68) *	55 (52; 67) *
	Methotrexate tocilizumab +	76 (64; 85)	38 (22; 68) **	21 (12; 49) **	11 (0; 29) **	0 (0; 11) **	0 (0; 11) **
Activity of the disease (assessment by the physician on VAS), mm	Methotrexate	76 (56; 68)	62 (53; 68)	60 (58; 65)	59 (51; 61) *	55 (52; 59) *	52 (52; 59) *
	Methotrexate + tocilizumab	78 (60; 87)	32 (23:54) *	10 (6; 22) **	11 (0; 21) **	0 (0; 0.9) **	0 (0, 4) **

Note.
* - P <0,01; ** - P, <0,001 - compared with indicators before treatment.

Before the research started, functional failure and the number of joints with dysfunction did not differ in the compared groups of patients. During the combined therapy with tocilizumab and methotrexate the restoration of joint function in patients was significantly faster than in patients treated with methotrexate alone (see table 2). Herewith, the number of joints with dysfunction in the group of children who received tocilizumab decreased after only 4 weeks of treatment and was significantly less than in the comparison group (p <0,05; see table 2). After 48 weeks of combined therapy there was no limitation in the movement of the joints; however, limitation of movement was identified in 50% of patients on methotrexate monotherapy.

The improvement in the functional capacity of the affected joints had a positive impact on the health condition (evaluation using the SHAQ questionnaire). Thus, we noted more rapid positive dynamics in the SHAQ health assessment values in patients who experienced combined therapy, than in patients treated with methotrexate alone (see table 2). After the sixth infusion of tocilizumab (6 months of observation) the median of SHAQ index in all children treated with tocilizumab and methotrexate, has decreased to 0, while in the comparison group of patients - to 0.6 points (p <0.05).

During all the observation period, the disease activity in patients receiving tocilizumab and methotrexate was significantly lower, and the evaluation of health – higher, than in patients treated with methotrexate

alone. In patients experiencing only methotrexate therapy, there were no statistically significant indicators for dynamics of any subjective health assessment by the child or his parents and no disease activity on VAS, registered by a doctor.

The analysis of immunological indices in patients with JIA before the treatment start revealed an increase in the number of T-helper lymphocytes CD4 +, as well as in CD16 + and CD95 + cells, in the concentration of IgG and IgM (Table 3). The content of IL 1β, 4, 6, 8 and 10, TNF α is also considerably higher than the values of healthy children. After 6 months of treatment with methotrexate, the immunological parameters, both cellular and humoral, were significantly lower in patients than they were before the treatment, but significantly higher than in healthy children. After 1 year, no positive dynamics of the values of the studied immunological parameters have been recorded (see table 3).

Table 3. ***Indicators of immune and cytokine status in children and adolescents with JIA after 6 months and 1 year after initiation of treatment with methotrexate and methotrexate in combination with tocilizumab***

Indicators	Reference Group n = 30	Before treatment n = 53	Treatment Methotrexate n = 41		Treatment methotrexate + tocilizumab n = 24	
			After 6 months	After 1 year	After 6 months	After 1 year
Boy / girl	9/21	17/48	8/33	8/33	9/15	9/15
CD4 +%	35,1 ± 1,1	49.4 ± 1,2 *	40.4 ± 1,3 **	39, 6 ± 1,2 **	36.8 ± 1,3 ***	35, 9 ± 1,6 ***
CD8 +%	22.5 ± 0.5	23.6 ± 0.4	22.9 ± 2,1	23.4 ± 2,4	21, 6 ± 0.3	2 1,6 ± 0,4
CD4 + / CD8 +	1.7 ± 0.5	2,3 ± 0.6	1.7 ± 0.4	1.7 ± 0.4	1,4 ± 0.2	1, 3 ± 0.6
CD16 +%	1 4 ± 0.2	14.6 ± 1,1 *	13.5 ± 0.5	13.9 ± 0.4	11, 1 ± 0.3 ***	1 0,6 ± 0,4 ***
CD95 +%	27.5 ± 1.5	49.6 ± 1.6 *	37.6 ± 1.5 **	36.1 ± 1.6 * *	30.4 ± 1.8 ***	28, 1 ± 1,2 ***
IgG g / l	9.8 ± 1,2	13.5 ± 0.2 *	12.5 ± 0.8	12.4 ± 0.9	10,1 ± 1.0 ***	9.7 ± 1,2 **
IgM g / l	0.94 ± 0 7	2,4 ± 0.5 *	1.8 ± 0.7	1,4 ± 0.6	0.91 ± 0.7 ***	0,9 1 ± 0,5 ***
IL-1 β pg / ml	46.8 ± 3.7	106, 5 ± 3,6 *	85.5 ± 2,3 **	71.6 ± 2,6 * *	52.4 ± 2,0 **	49, 6 ± 4,1 ***
IL4 pg / ml	45.5 ± 3,1	52.3 ± 1.5 *	47.8 ± 1.8 **	48.9 ± 1.9 **	44.2 ± 1,3 ***	4 6,6 ± 1,1 ***
IL6 pg / ml	7.5 ± 1,1	12.3 ± 1,3 *	11.6 ± 1,2	11,3 ± 1,3	8,2 ± 1,1 ***	7 6 ± 0.5 ***
TNF-α pg / ml	43.2 ± 1,1	99.6 ± 2.8 *	78.4 ± 2,1 **	73.1 ± 2,6 * *	44.3 ± 1,2 ***	43 9 ± 1,4 ***
IL8 pg / ml	19.8 ± 1,2	42.1 ± 2.8 *	35.4 ± 1,3 **	27.6 ± 1,4 * *	20.6 ± 1,2 ***	19.6 ± 1,4 ***
IL10 pg / ml	9.8 ± 1,2	26.6 ± 2.8 *	20.4 ± 1.5 **	16.6 ± 1.6 * *	10.8 ± 1,3 ***	9 1,7 ± 1,1 ***

Note:

* - $P < 0.05$ compared to the norm;

** - $P < 0.05$ in the treatment of patients with methotrexate compared with patients before treatment;

*** - $P < 0.05$ in the treatment of patients with methotrexate + tocilizumab compared with patients on the methotrexate treatment.

In patients treated with a combination of tocilizumab and methotrexate, serum concentrations of C-reactive protein normalized after 6 months of treatment; levels of TNF α, IL 1ss, 4, 6, 8 and 10 after 6 and 12 months of treatment were nearly 2 times lower than in children on methotrexate monotherapy. Despite the positive dynamics, levels of cytokines in the serum of patients treated with the combined therapy were higher than the same index in healthy children (see Table 3).

The effectiveness evaluation of treatment with methotrexate in combination with tocilizumab by ACR_{pedi} criteria in children with polyarticular JIA is presented on Fig. 2. After 6 months of treatment, satisfactory, good and excellent results were registered in 94, 62 and 36% of patients, respectively; after 1 year - in 100, 73 and 44%, respectively. In patients treated with methotrexate, the level of response by ACR_{pedi} criteria was significantly lower: satisfactory, good and excellent effects after 6 months were achieved in 72, 17 and 11% of the patients; after 1 year - 58, 26 and 16%, respectively (Fig. 1).

Fig.1. The effectiveness of methotrexate in the treatment of juvenile idiopathic arthritis in children.

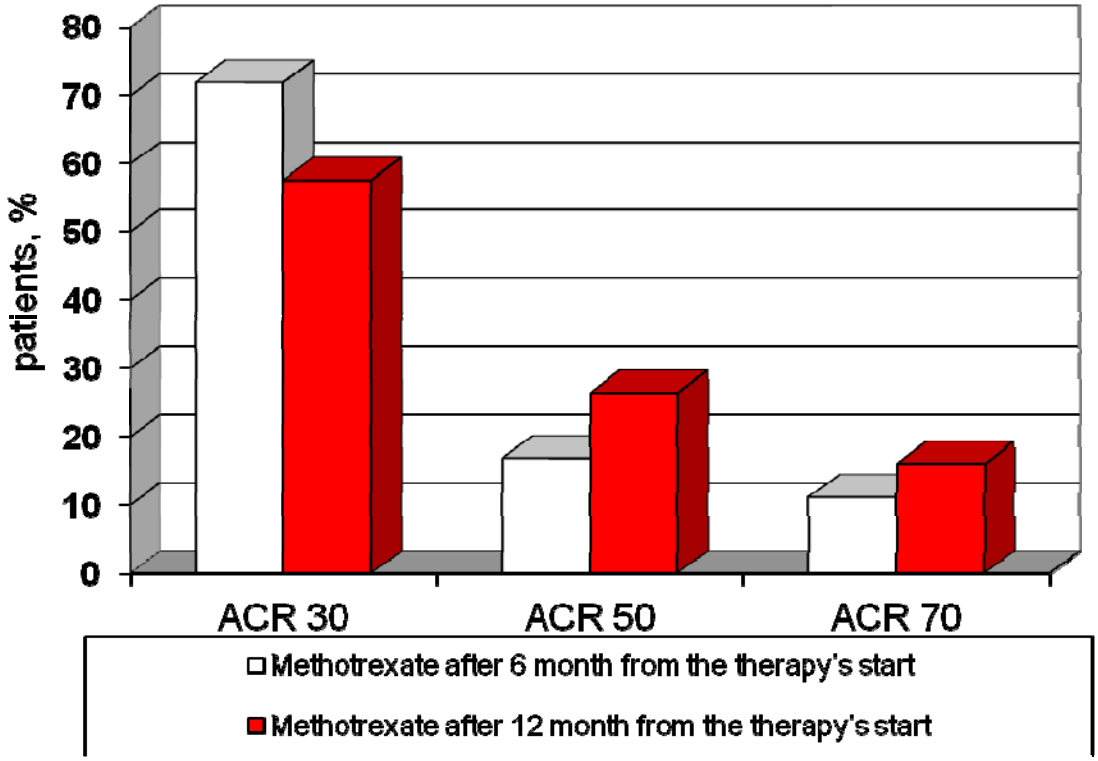
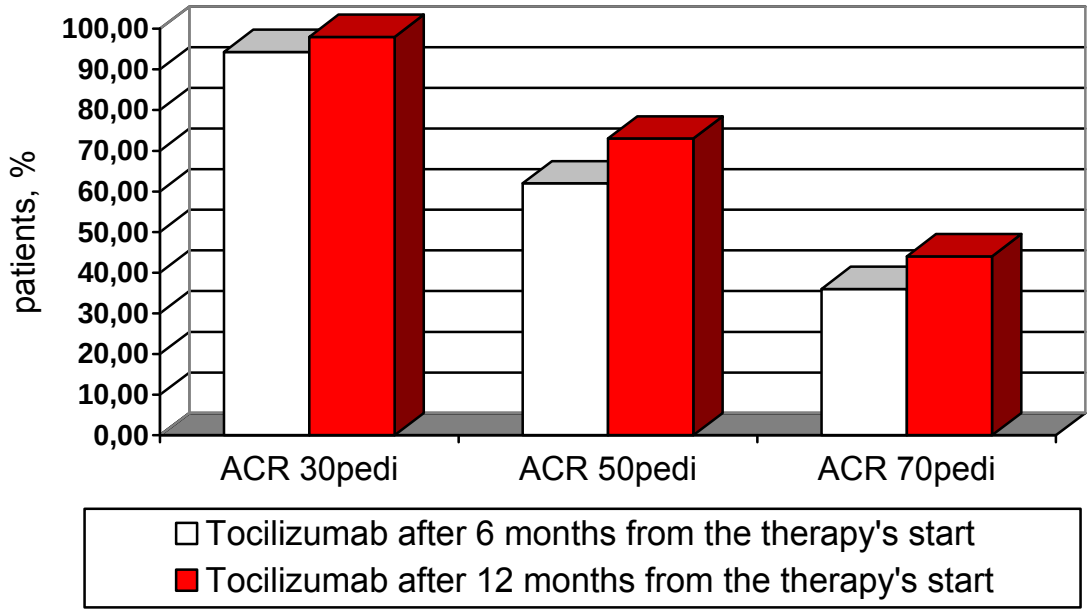


Fig. 2. The effectiveness of tocilizumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis



Additional study results

All the adverse reactions observed during the monitoring of the patients are presented in Table 4 (distributed by use of basic drugs).

Table 4. ***Adverse reactions identified during treatment with methotrexate and tocilizumab in combination with methotrexate in patients with polyarticular JIA***

Side effects	Methotrexate n = 41	Tocilizumab + methotrexate n = 24
Stomachalgia	eleven	
Dyspeptic disorders	16	
Erythematous rash	3	
Leukopenia, agranulocytosis	2	
Microhematuria	1	
Headache	3	
Vertigo	4	
Alopecia	6	
Increased transaminases activity	15	5
Total:	61	5

Based on the obtained data, there were more side effects in the treatment of patients on methotrexate (61 cases) than in the tocilizumab with methotrexate therapy (5 cases). Such a low amount of undesirable effects in combined therapy in JIA patients is probably connected with reducing the methotrexate dose up to its cancelation during treatment with tocilizumab.

Thus, tolerability of tocilizumab in combination with methotrexate was generally satisfactory. There were no severe and serious adverse effects. A rise in the transaminase activity was not accompanied by clinical symptoms, did not lead to serious violations of the liver and was stopped in the ongoing joint use of tocilizumab and hepatoprotector (Geptral).

DISCUSSION

Research has shown that tocilizumab in combination with methotrexate has a pronounced anti-inflammatory effect in children with polyarticular JIA. When treating only with methotrexate, the therapy efficacy was significantly lower and it was not always effective. In the vast majority of patients treated with tocilizumab in combination with methotrexate, a significant decrease in clinical, laboratory and immunological parameters of disease activity was noted after the first infusion, whereas in children on methotrexate monotherapy it was noted only after 24 weeks of treatment. Evaluating the effectiveness of treatment by pediatric criteria of the American Rheumatologist Board in the combined therapy group showed a faster and more pronounced therapeutic effect than in the comparison group. Tocilizumab in combination with methotrexate induced the development of a resistant clinical and laboratory remission (by ACR_{pedi} criteria) in 44% of patients after an average 1 year of treatment, whereas the methotrexate therapy gave the remission after 12 months of therapy in only 16% of children. Along with a high therapeutic efficiency, tocilizumab in combination with methotrexate was well tolerated by patients. There were no severe and serious adverse events recorded. An increase in transaminases activity (at 5) was not accompanied by clinical symptoms, did not lead to serious violations of the liver, and stopped during the continued use of tocilizumab and hepatoprotectors after a short-term reduction of the single tocilizumab dose.

CONCLUSION

Studies have shown that tocilizumab in combination with methotrexate has a pronounced anti-inflammatory effect in children with polyarticular JIA. When treating only with methotrexate, the efficacy of therapy was significantly lower. In the vast majority of patients treated with tocilizumab in combination with methotrexate, a significant decrease in clinical, laboratory and immunological parameters of disease activity was noted within 4 weeks, whereas in children on methotrexate monotherapy it was noted only after 24 weeks of treatment. Evaluating the effectiveness of treatment with tocilizumab in combination with methotrexate using the pediatric criteria of the American Rheumatologist Board showed a faster and more pronounced therapeutic effect than treatment with only methotrexate. Tocilizumab in combination with methotrexate induced the development of a resistant clinical and laboratory remission (by ACR_{pedi} criteria) in 44% of patients on average after 1 year of treatment, whereas the methotrexate therapy - only in 16% of children. Along with a high therapeutic efficiency, tocilizumab in combination with methotrexate was well tolerated by patients.

CONFLICT OF INTEREST

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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