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Clinical Study

Retrospective Analysis of Efficacy and Safety of Tocilizumab Treatment in Patients with Severe Systemic-Onset Juvenile Idiopathic Arthritis Followed for 12 Months

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The results of the retrospective study evaluating efficacy and safety of tocilizumab treatment in 75 patients with severe systemic-onset juvenile idiopathic arthritis refractory to standard immunosuppressive therapy are presented in the paper. Inactive disease was documented in 64% of patients after 6 months of treatment and in 73% of patients after 12 months. Adverse events manifested as mild and moderate infections as well as laboratory abnormalities: leukopenia, neutropenia, and elevated aminotransferase levels.

1. Introduction

Systemic-onset juvenile idiopathic arthritis (sJIA) is characterized by the chronic course of arthritis, persisting systemic manifestations (fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis), and by significant elevation of laboratory inflammatory markers (leukocyte count, platelet count, ESR, CRP, and ferritin) [1]. sJIA is the severest type of juvenile idiopathic arthritis (JIA): chronic polyarthritis (with or without systemic manifestations) relapses in half of the patients, bone and cartilage destruction of the joints progresses, and severe functional impairment develop with consistently increasing disability [2, 3].

Treatment of sJIA is a complex problem of pediatric rheumatology due to low efficacy of methotrexate [4] at this type of disease as well as due to development of severe adverse events caused by glucocorticoid therapy.

Many clinical and laboratory manifestations of the disease in sJIA are caused by high level of IL6 both in blood serum and in synovial fluid [5–11]. Hyperproduction of IL6 is associated with development of such extra-articular manifestations as fever and thrombocytosis. IL6 stimulates production of acute-phase inflammatory proteins (C-reactive protein and amyloid A, haptoglobin, and fibrinogen) by hepatocytes and also competitively inhibits synthesis of albumin and transferrin. IL6 stimulates secretion of hepcidin by hepatocytes which reduces absorption of iron in the intestine, and it inhibits its release from macrophages causing iron deficiency in erythropoiesis and development of anemia. IL6 in increased concentrations blocks production of adrenocorticotropic hormone, cortisol, and growth hormone which results in fatigue, sleepiness, depression, cognitive impairments, and growth retardation in children with sJIA. Amyloidosis, a severe complication of this disease, is also associated with activity of this cytokine. Tumor necrosis factor α inhibitors (TNF-α), as a rule, are ineffective in sJIA [12, 13]. Inhibition of IL6 at this type of the disease is more promising.

Tocilizumab is a humanized anti-IL6 receptor monoclonal antibody blocking both soluble and membrane receptors. Positive results from a number of clinical studies on efficacy and safety of tocilizumab therapy in children with

sJIA constituted a ground for approving the drug for treatment of sJIA [14–24].

Taking into consideration international multicenter studies and the need to implement a new biologic for the treatment of sJIA into the practice of Russian pediatric rheumatologists, efficacy and safety of tocilizumab treatment in children with severe refractory sJIA were retrospectively analyzed at the Rheumatology Department of the Scientific Center for Children's Health of the Russian Academy of Medical Sciences.

2. Patients and Methods

Efficacy of tocilizumab was retrospectively assessed in patients with sJIA treated with tocilizumab from June 2009 to January 2013. Prior to approvement (November 2012) of the drug in the Russian Federation for sJIA indications, the use of tocilizumab was approved by the Local Ethics Committee of the Scientific Center for Children's Health of the Russian Academy of Medical Sciences. Prior to the treatment initiation, the parents and the children aged 14 years and older provided the written informed consent.

Treatment results were analyzed in 75 children (35 girls and 40 boys) aged 8.8 (6; 12) years (median (25; 75)) (Table 1). Mean duration of the disease prior to tocilizumab was 3.2 (1.9; 5.2) years. sJIA was diagnosed based on International League of Associations for Rheumatology (ILAR) criteria [1].

All patients receiving tocilizumab underwent the routine clinicolaboratory examination. Assessments of hemoglobin level, erythrocyte count, platelet count, white blood cell count with differential leukocyte count, ESR, serum urea, serum creatinine, serum uric acid, serum bilirubin, serum transaminases, and clinical urinalysis were performed once every 2 weeks. Measurement of blood pressure, body temperature and assessment of rash were conducted daily.

Swollen and tender joint count, joint with limitation of motion count, the number of systemic manifestations of the disease and serum CRP concentration were assessed in a month and then every three months.

Efficacy of conducted therapy was evaluated in accordance with the American College of Rheumatology pediatric criteria for improvement (ACR Pedi 30, 50, 70, and 90) in 1, 3, 6, 9, and 12 months of treatment. These criteria include the following parameters: patient's (parent's) assessment of patient's general condition, physician's assessment of the disease activity using visual analogue scale (VAS), assessment of the functional ability in accordance with the the Childhood Health Assessment Questionnaire (CHAQ), count of joints with active arthritis, count of joints with limitation of motions, and ESR.

The rate of achieving the inactive stage and drug-induced remission of the disease were considered as target efficacy parameters of conducted therapy. Inactive disease status was registered in case of inactive synovitis, the absence of systemic manifestations of the disease, normal ESR and serum CRP concentrations, the absence of disease activity according to physician's global assessment (using VAS), and duration of morning stiffness less than 15 minutes. Remission was registered in case if the disease was inactive during the conducted therapy during 6 consecutive months [25].

Table 1: Demographic and clinical characteristics of patients with sJIA included in the study.

Parameter	Value median (25; 75) ($n = 75$)
Girls/boys	35/40
Age, years	8.8 (6; 12)
Disease duration, years	3.2 (1.9; 5.2)
The number of joints with active arthritis	8 (4; 17)
The number of joints with limitation of motion	9 (3; 17)
CHAQ index of functional disability	1.25 (0.75; 2.0)
The number of systemic manifestations per one patient	3.2 (2.5; 4)
ESR, mm/h	52 (22; 62)
Platelets, $\times 10^9$/L	650 (495; 800)
Hemoglobin, g/L	89 (80; 98)
CRP, mg/L	78 (40; 98)

At the moment of therapy initiation, the majority of children had polyarthritis with significant functional impairment, as suggested by high CHAQ index of functional disability (Table 1). Extra-articular manifestations were observed in all patients: febrile fever in 90% (68), carditis in 2% (2), lymphadenopathy in 86% (65), maculopapular rash in 40% (30), and hepato- and/or splenomegaly in 75% (56) of patients. The number of systemic manifestations per one patient was 3.2 (2.5; 4) (see Table 1). High degree of the disease's clinical activity was accompanied by systemic inflammatory reaction. Hypochromic anemia was observed in 90% (67) of patients, thrombocytosis in 85% (63) of children. The median ESR was 5 times higher, and the serum CRP concentration was 15 times higher the normal values (see Table 1).

Thus, at the moment of therapy initiation, all patients with systemic-onset JIA had active arthritis, severe systemic manifestations, high laboratory parameters of disease activity, and progressive disability.

2.1. Previous Therapy. All patients had various antirheumatic therapies prior to tocilizumab treatment.

Due to severe systemic manifestations at the onset of the disease, oral prednisolone was prescribed in 57% (44) of children at their place of residence in the territorial medical institution at a dose of 9.5 (6.5; 12) mg/day; all children were conducted the pulse therapy with methylprednisolone at a dose of 10–30 mg/kg per administration; 33% (25) were prescribed TNF blockers, and 29% (22) underwent anti-B-cell therapy with rituximab. Also, all children received nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 2).

2.2. Background Treatment. Tocilizumab infusions were accompanied by the intake of immunosuppressors (Table 3).

2.3. Tocilizumab Regimen. Tocilizumab was administered intravenously at a dose of 12 mg/kg per infusion to children

Table 2: Characteristics of previous therapy in patients with sJIA at the moment of enrollment in the study.

Drug	Dose (median (25; 75))	Number of children
Methotrexate, mg/m^2/week	19 (15; 24)	25
Methotrexate, mg/m^2/week +	17 (15; 23)	
Cyclosporine, mg/kg/day	4 (4; 4)	47
Methotrexate, mg/m^2/week +	12	
Mycophenolate mofetil, mg/day	1000	1
Methotrexate, mg/m^2/week +	15	
Leflunomide	20	2
Prednisolone, mg/day	9.5 (6.5; 12)	44
NSAIDs	—	75
Rituximab	—	22
Infliximab	—	17
Adalimumab	—	6
Etanercept	—	2
Number of biologics		
3 products	—	5
2 products	—	10
1 product	—	14

Table 3: Characteristics of background therapy in patients with sJIA at the moment of enrollment in the study.

Drug	Dose (median (25; 75))	Number of children
Methotrexate, mg/m^2/week	19 (15; 24)	17
Prednisolone, mg/day +	8.7 (6.3; 12)	
Methotrexate, mg/m^2/week	19 (15;23)	11
Methotrexate, mg/m^2/week +	17 (15; 23)	
Cyclosporine, mg/kg/day	4 (4; 4)	14
Prednisolone, mg/day +	9.5 (6.5; 12)	
Methotrexate, mg/m^2/week +	17 (15; 23)	
Cyclosporine, mg/kg/day	4 (4; 4)	33
NSAIDs	—	75

weighing less than 30 kg and at a dose of 8 mg/kg to children weighing 30 kg and more. All children were receiving the drug once every 2 weeks for 1-2 months; then, the interval between administrations was increased to 4 weeks as there were no relapses of systemic manifestations of the disease. Treatment regimen once every 2 weeks was restarted in four patients due to recurrence of extra-articular disease manifestations. Infusions were conducted for 1 hour.

Treatment efficacy was analyzed in 1 month in 73 children, in 3 months in 72 children, in 6 months in 67 children, in 9 months in 64 children, and in 12 months in 61 patients. Tocilizumab was discontinued in the rest of the patients at different treatment stages for various reasons (Table 4).

Statistical data processing was performed using STATISTICA 6.0 software (StatSoft Inc., USA). Quantitative signs

Table 4: Causes and schedule of tocilizumab withdrawal.

Causes of withdrawal	Schedule of withdrawal (months)	Patients, n
Insufficient efficacy	3–6	3
Relapses	4–12	7
Anaphylactic reaction	1	1
Disease remission	11	1
Crohn's disease	6	1
Refusal of parents	1	1

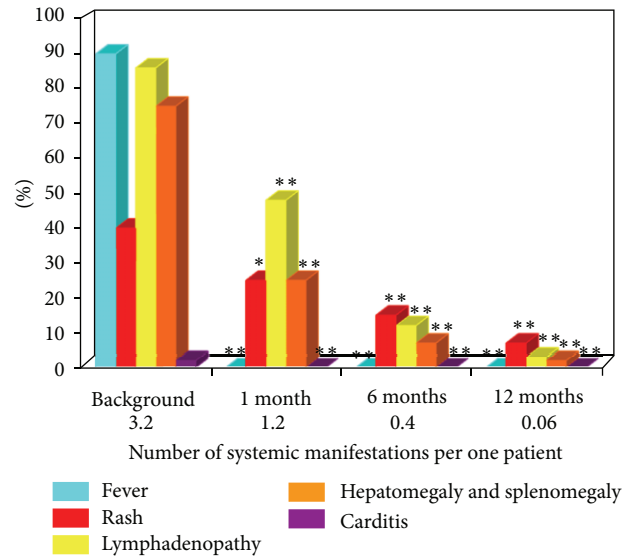

Figure 1: Systemic manifestations over time in patients with sJIA treated with tocilizumab ($n = 75$). Here and after: $^*P < 0.01$, $^{**}P < 0.001$.

are presented as the median (25; 75 percentiles). Changes in quantitative parameters during the treatment were assessed using the Wilcoxon matched-pairs test. The differences were considered significant at $P < 0.05$.

3. Study Results

Analysis of study results demonstrated that tocilizumab treatment provided statistically significant and substantial positive changes in the systemic manifestations, clinical, and laboratory signs of disease activity.

Already after the first tocilizumab infusion, no fever was observed in 100% of patients (Figure 1). In 4 weeks, significant decrease in the number of JIA systemic manifestations was observed (Figure 1). Such life-threatening extra-articular manifestation as carditis was cured in all patients. Skin rash was significantly reduced in 37 (40%) and 18 (25%) children prior to the treatment and after 4 weeks, respectively. The dimensions of liver and spleen returned to the normal range in 38 out of 56 (67%) patients.

In one year, lymphadenopathy persisted in 3 out of 61 children (4%), rash in 4 out of 61 (7%) children, hepato/splenomegaly in 1 out of 61 (2%) patients. The number

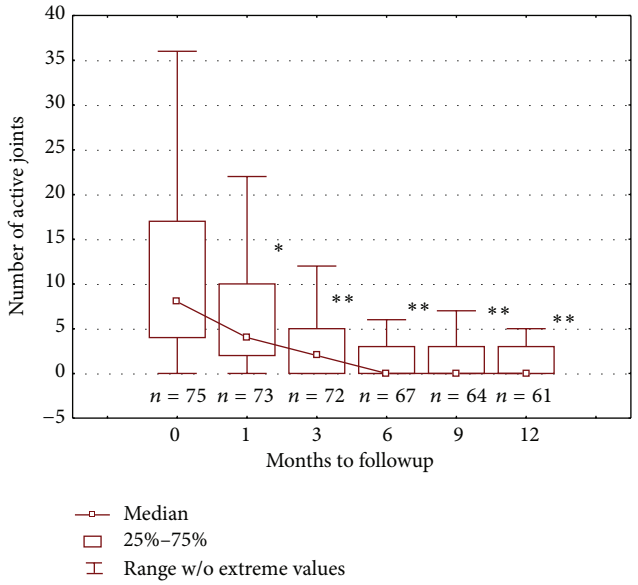

Figure 2: Joint score with active arthritis over time in patients with sJIA treated with tocilizumab.

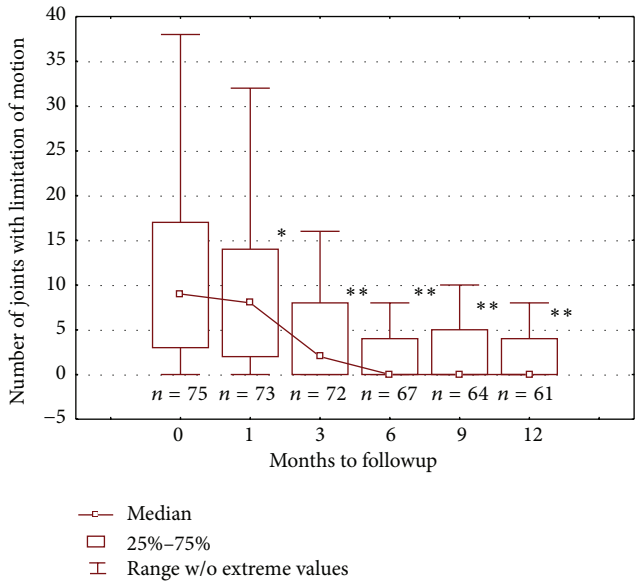

Figure 3: The number of joints with limitation of motion over time in patients with sJIA treated with tocilizumab.

of systemic manifestations per one patient was 0.06 after 12 months of followup (see Figure 1).

Analysis of changes in joint counts over time revealed a significant decrease in the number of joints with active arthritis (8 (4; 17) and 4 (2; 10) prior to and after 4 weeks of treatment, resp.; $P < 0.01$) by week 4 of treatment. By 12 months, this parameter was 0 ((0; 3), $P < 0.001$) (Figure 2). The similar tendency was observed for joints with limitation of motion; their number also significantly decreased in 4 weeks from 9 (3; 17) to 7 (2; 14) ($P < 0.01$) (Figure 3). By 12 months of followup, the median number of joints with limitation of motion was 9-times less ($P < 0.001$).

Along with the decreased number of joints with active arthritis as well as of joints with limitation of motion, a significant improvement of functional ability in the affected joints was observed in patients enrolled in the study (Figure 4). Just in 4 weeks of tocilizumab therapy, CHAQ index of functional disability significantly decreased (1.25 (0.75; 2.0) and 0.75 (0.4; 1.2) prior to and after 4 weeks of treatment, resp.; $P < 0.001$). By month 12, of followup, functional disability index was equal to 0.25 (0; 0.5) ($P < 0.001$), which indicated no functional impairment in the majority of patients.

Tocilizumab treatment also affected the laboratory signs of disease activity. In 12 months of followup, the level of hemoglobin significantly increased from 89 (80; 98) to 125 (120; 130) g/L ($P < 0.001$), the number of platelets decreased from 650 (495; 800) to 300 (250; 320) $\times 10^9$/L ($P < 0.001$), ESR decreased from 52 (22; 62) to 2 (2; 10) mm/hour ($P < 0.001$), and serum CRP concentration reduced from 78 (40; 98) to 0 (0; 1.25) mg/L ($P < 0.001$). In 93% of patients, these parameters returned to normal values already by the third month of therapy.

When tocilizumab efficacy was evaluated using ACR_{pedi} 30/50/70 criteria in 4 weeks, improvement was achieved in

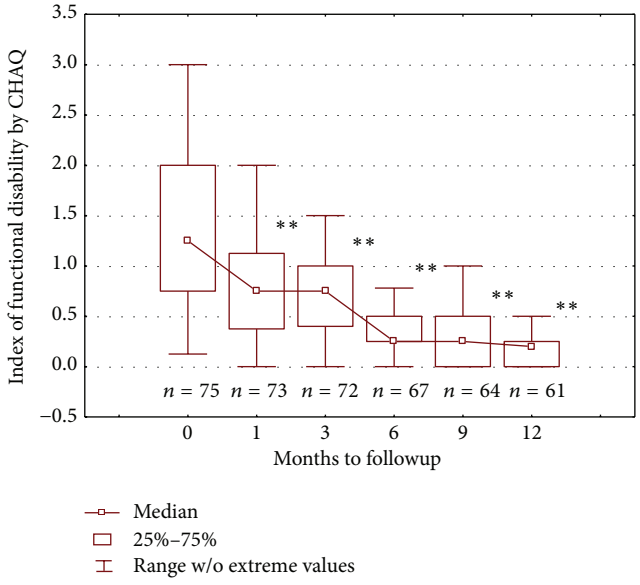

Figure 4: Index of functional disability over time in patients with sJIA treated with tocilizumab.

90%, 55%, and 35% of patients, respectively. ACR30 improvement was maintained in all children who continued therapy, and ACR70 was registered in 80% of children after 6 months of therapy. After 12 months of followup, 50% and 70% improvement was observed in 100% and 95% of patients, respectively (Figure 5).

Overall, analysis of tocilizumab efficacy demonstrated that inactive disease was documented in 64% (43 out of 67) patients after 6 months and in 73% (44 out of 61) patients after

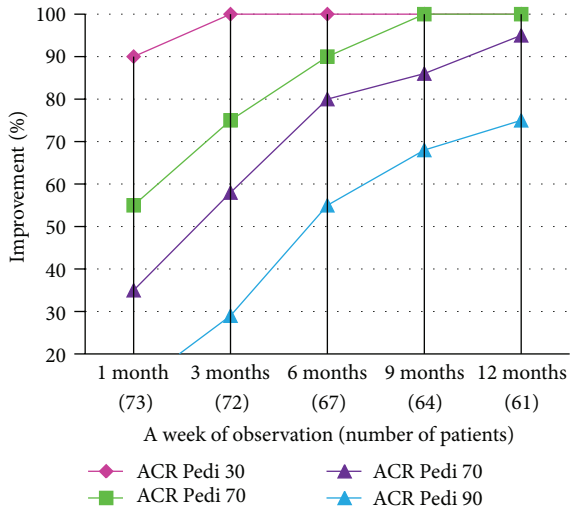

Figure 5: Efficacy of tocilizumab therapy according to ACR pediatric criteria in patients with sJIA.

Table 5: Adverse events in patients treated with tocilizumab.

Adverse events	Patients, *n* (%)
Laboratory abnormalities:	
Neutropenia	30 (40%)
Thrombocytopenia	2 (2%)
Elevation of alkaline phosphatase	1 (1%)
Elevation of aminotransferases	15 (20%)
Infections:	
Gastroenteritis	11 (14%)
Nasopharyngitis	72 (96%)
Upper respiratory tract infections	56 (74%)
Cellulitis	3 (4%)
Herpes outbreak	6 (8%)
Acute focal pneumonia	3 (4%)
Number of infectious AEs per patient-year	2.2
Macrophage activation syndrome	1 (1%)

12 months, and disease remission was achieved in 12 months in 72% (43 out of 61) of patients.

It should be noted that the dose of oral glucocorticoids was reduced in all patients (44) ((0.5 (0.4; 0.7); 0.1 (0.04; 0.2) mg/kg prior to and after a year of treatment, resp. ($P < 0.001$)).

Safety of tocilizumab treatment was assessed according to registered adverse events (AEs), laboratory parameters based on the results of physical examination (blood pressure, heart rate), and ECG data.

Adverse events were assessed in all patients enrolled in the study who received at least one infusion of the drug.

In general, tocilizumab treatment was well tolerated, and the majority of adverse events were mild or moderate, reversible, and not treatment limiting. Infusion-related reactions (i.e., reactions occurring during and within 24 hours after the drug administration) were observed in one patient after the first drug infusion, which was a rationale for treatment discontinuation.

Registered adverse events can be subdivided into two groups: infectious and laboratory adverse events (Table 5).

Most infectious adverse events were mild. They included gastroenteritis, nasopharyngitis, and infections of the upper respiratory tract.

Other infectious adverse events included cellulitis, herpes outbreak, and acute focal pneumonia (Table 5). Cellulitis and acute focal pneumonia were considered as serious adverse events. These children also underwent concomitant methotrexate treatment at a dose of 15 mg/m^2 of body surface area and cyclosporine treatment at a dose of 4 mg/kg of body weight. Antibacterial therapy was prescribed for cellulitis and pneumonia and provided a complete recovery without complications. It should be noted that pneumonia in two patients was not accompanied by elevated CRP concentration and by increased leukocyte count.

Herpes virus outbreak was considered as a nonserious adverse event.

The most common laboratory adverse event was neutropenia (in 30 (40%) patients), which developed within the first days after tocilizumab administration. Absolute neutrophil count decreased less than 1000/μL in 17 (23%) patients, and it equaled to 500/μL in 3 (4%) patients.

In case of neutropenia, neutrophil count was monitored daily and returned to its normal value within a week after infusion. In case of neutrophil count decrease less than 1.0×10^9/L, the patients were administered colony-stimulating factor (filgrastim) at a dose of 5 μg/kg with positive effect.

All cases of neutropenia were associated with tocilizumab infusion. None of the cases were associated with infectious complications and led to treatment discontinuation.

Thrombocytopenia was observed in two patients. In one child, after 11 months of therapy, in 2 weeks after the regular drug administration, the number of platelets reduced to 156×10^9/L. Patient's concomitant therapy included glucocorticoids, cyclosporine, methotrexate, and nonsteroidal anti-inflammatory drugs. Thrombocytopenia was considered as a nonserious adverse event and was unlikely related to tocilizumab treatment. Platelet count returned to its normal value in a week, without dose reduction or treatment interruption. The number of platelets in another patient reduced to 140×10^9/L after 6 months of therapy in a week after a regular tocilizumab infusion. Patient's concomitant therapy included methotrexate. Thrombocytopenia was considered as a nonserious adverse event. Platelet count returned to its normal value in a week, without dose reduction or treatment interruption.

A single increase of alkaline phosphatase activity up to 6200 IU/L was registered in one patient after the first administration of tocilizumab. This parameter returned to its normal value in 8 days without changing the regimen of tocilizumab treatment. Concomitant therapy in this patient included methotrexate and methylprednisolone. Adverse event was considered as nonserious and unlikely related to tocilizumab.

Macrophage activation syndrome was reported in one patient after 2 months of tocilizumab therapy. Patient's concomitant therapy included glucocorticoids, cyclosporine, and methotrexate. The condition was stopped after pulse therapy with methylprednisolone. It should be noted that high CRP and ferritin concentrations were not observed.

Aminotransferase levels were more than 3 times higher than the normal value in 15 patients. All patients were also treated with methotrexate. Within two weeks, laboratory parameters returned to normal values, and no dose reduction or tocilizumab discontinuation was required.

Throughout the followup, no clinically significant changes of the vital signs (diastolic and systolic blood pressure, heart rate) as well as of ECG parameters were observed.

Tocilizumab was discontinued in 14 (10.5%) out of 75 patients (Table 4).

4. Discussion

Persisting extra-articular manifestations of systemic-onset JIA are a complex therapeutic problem. Immunosuppressors and TNFα inhibitors are not effective enough [4, 12, 13]. Long-term use of glucocorticoids results in development of severe adverse events, and reduction of prednisolone dose causes another exacerbation of the disease. Sufficient amount of evidence in favor of IL6s leading role in pathogenesis of sJIA made it possible to develop and create a drug tocilizumab for treatment of this type of JIA [5–11]. Results of two international randomized placebo-controlled studies demonstrated high efficacy of the drug for treatment of arthritis and systemic manifestations of the disease, as well as a good drug safety profile [16, 19].

All patients with sJIA receiving tocilizumab at our site, who were followed up for 12 months, were enrolled in this study. Majority of the patients had late-onset arthritis, their disease lasted for more than 2 years, and also they previously received various combinations of immunosuppressors including biological agents. Therefore, patients with monocyclic or polycyclic course and a highly probable rapid or spontaneous remission were not enrolled in this study. These were the patients with severe long-term persisting sJIA refractory to immunosuppressors, TNFα inhibitors, and rituximab, with active systemic manifestations and a great number of active joints.

The study was designed as retrospective, observational study with no control group. Data from the patients who discontinued the drug for any reasons were excluded from analysis, which possibly explains higher efficacy parameters as compared to randomized studies.

High efficacy of tocilizumab according to ACR pediatric criteria was demonstrated in our study. In a year of therapy, inactive disease was documented in 73% (44) of patients who continued treatment; meanwhile, it was only documented in 30% of patients from the TENDER study during an open-label phase, which can possibly be explained by the study design, as well as by the more severe disease (median count of joints with active arthritis was 21) [19].

Efficacy of therapy is also confirmed by the fact that it was possible to significantly reduce the dose of oral glucocorticoids; anticipating the disease relapse, prednisolone was not completely discontinued but rather tapered maximally to 0.625 mg/day for a long time.

Most infectious adverse events were mild. It should be noted that 3 cases of cellulitis were registered, which is described in tocilizumab studies in adult patients with rheumatoid arthritis [26]. Many patients during infectious adverse events did not experience fever, and CRP elevation was insignificant or absent because of IL6 inhibition and suppression of inflammatory response. No cases of drug discontinuation due to development of infectious adverse events were reported. In total, 2.2 cases of infectious AEs per patient-year were registered as compared to 3.0 in the TENDER study [19].

Elevation of aminotransferase levels was observed within the first 6 months of therapy which may be explained by a unique pathophysiological process in patients with systemic-onset JIA, by concomitant therapy with methotrexate, or by a biological effect of IL6 on the liver [20].

Cases of neutropenia were registered in patients: in some patients, they resolved spontaneously after cell count restoration, and in some patients—after filgrastim injections; no relation with infectious diseases was detected.

Macrophage activation syndrome is one of the most dangerous and life-threatening complications of sJIA. It may be caused by progressive course of the disease, long-term persisting disease activity, drugs, and infectious agents [27]. Therefore, the syndrome can develop during tocilizumab therapy. According to the results of TENDER study, 3 cases of macrophage activation syndrome were registered; in one case, it was caused by type 6 herpesvirus, and in two other cases—by discontinuation and insufficient dose of the drug [19]. There were no trigger infectious agents or therapy interruption in our case prior to development of macrophage activation syndrome. It should be noted that high CRP and ferritin titers were not registered when other symptoms of this syndrome were present.

Therefore, tocilizumab safety profile in our study, in general, did not differ from the safety profile earlier described in patients with sJIA according to the data from randomized studies, and it is expected in the population of patients receiving immunosuppressive drugs. Adverse events manifested as mild and moderate infections as well as laboratory abnormalities. No lethal outcomes were registered during tocilizumab treatment.

5. Conclusion

Therefore, the results of 1-year retrospective observational study demonstrated the high efficacy of tocilizumab in patients with the severest systemic-onset juvenile arthritis refractory to glucocorticoids, methotrexate, cyclosporine, combined immunosuppressive therapy, anti-TNF, and anti-B-cell therapy. The drug induced a remission of the arthritis, extra-articular manifestations, and normalized laboratory parameters of disease activity in 73% of patients without prescribing or increasing the dose of oral prednisolone, thus avoiding severe irreversible complications of glucocorticoid therapy.

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