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Reasons for inactive disease and flare in systemic onset juvenile idiopathic arthritis patients during tocilizumab treatment

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Abstract

Objective

The aim of our study was to evaluate disease courses and outcomes of sJIA children undergoing tocilizumab (TCZ) treatment, and to establish the predictors which distinguish inactive disease and disease flares.

Methods

Our retrospective study included 48 active sJIA children who were refractory to different anti-rheumatic drugs and who were then started on TCZ. The effectiveness of TCZ was assessed by the changes of sJIA attributed signs and symptoms and the remission was judged according to the Wallace (2004) criteria.

Results

*The main demographic parameters (Me; IQR) were shown; mean age: 9.9 (5–12.7) years and mean duration of TCZ administration: 27.0 (5.9–89.7) months. During the TCZ treatment 40 cases (83.3%) achieved remission in 138.5 (56.0; 255.0) days. Patients who achieved remission had milder disease course, and presented less frequent hepatosplenomegaly, lung, heart involvement and MAS. They had higher Hb and lower WBC, granulocytes, ESR, CRP, LDH, ferritin. The main predictors of achievement of inactive disease, calculated with Cox-regression models, were CRP≤82.0 mg/l (OR=7.9, HR=1.17), ESR≤32 mm/h (OR=17.0, HR=0.85), ferritin ≤273 ng/ml (OR=56.5, HR=2.6), Hb>113 g/l (OR=17.0, HR=1.33), LDH≤676 U/l (OR=113.6, HR=3.2), PLT>335*10^9/l (OR=5.0, HR=2.5), and intensive depression of WBC in 2 weeks after the 1st TCZ infusion>11% (OR=13.0, HR=6.0) and granulocytes>12% (OR=14.0, HR=4.7).*

Conclusion

sJIA children with milder disease course have more posssibilty of achieving disease remission during TCZ treatment. Male sex, signs of high disease activity, previous CS treatment, the long time needed to achieve inactive disease and treatment protocol deviations increased the risk of sJIA flare.

Key words

systemic juvenile idiopathic arthritis, interleukin-6, tocilizumab, remission

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Introduction

Systemic juvenile idiopathic arthritis (sJIA) is one of the most striking forms of juvenile arthritis, which often requires biologic administration when it is refractory to corticosteroids (CS) and disease-modifying anti-rheumatic drugs (DMARDs) (1). The pathophysiological bases of sJIA are on the uncontrolled overproduction of pro-inflammatory cytokines, especially IL-1β and IL-6 (2, 3). According to the ACR-2013 recommendations, the blockade of cytokine is required as the first or second line therapy depending on disease features (4).

Currently there are two main strategies in the treatment of sJIA; IL-1 and IL-6 biologic blockade (5-7). Despite similar profile of safety and effectiveness in the latest ACR recommendations, blockade of IL-6 is recognised as the second-line treatment following the IL-1 blocker, anakinra, but in some countries Il-1 blockers are still unavailable and IL-6 blockers are the main biologic treatment for sJIA. The effectiveness of anakinra was shown in relatively small studies and could be estimated as the B-code rank accordingly Oxford scale (4). Although the effectiveness of tocilizumab (TCZ), an anti-IL-6 receptor monoclonal antibody, was more representatively shown in the randomised, controlled multicentre trials and was ranked as the Oxford code "A", it was recommended as the second-line biologics. The question arises as to which will be the first line biologic treatment for children with sJIA, anakinra or TCZ (4). The aim of our study was to evaluate disease courses and outcomes of sJIA children under the tocilizumab (TCZ) treatment, and to establish the predictors which distinguish inactive disease from disease flares.

Patients and methods

Written consent was obtained according to the declaration of Helsinki. Approval of the protocol of this trial was approved by local Ethics Committee of St. Petersburg State Paediatric Medical University.

This retrospective study included 48 active sJIA children who were refractory to corticosteroids (CS), methotrexate (MTX), cyclosporine A (CsA) and their combinations. TCZ was initiated every two weeks in these children at an intravenous dosage of 12 mg/kg when the body weight was <30 kg, and 8 mg/kg when the body weight ≥30 kg. The clinical symptoms and signs and laboratorial findings before 1st TCZ infusion were evaluated; fever, hepatosplenomegaly, serositis, rash, lymphadenopathy, number of active joints, macrophage activation syndrome (MAS), levels of haemoglobin, white blood cells, granulocytes, platelets, and LDH. MAS was diagnosed according to both sets of diagnostic criteria: i) developed by Ravelli and co-workers and ii) developed by our group (8, 9). We checked the granulocytes levels through 1 and 2 weeks after 1st TCZ infusion. The efficacy of TCZ was measured through changes of sJIA attributed signs and symptoms, decreased the concomitant treatment, the time and achievement the remission according to the Wallace (2004) criteria (10). Oligoarticular sJIA course was mentioned if the patient had less than 5 active joints, and polyarticular in the cases in which more than 5 joints were affected before the start of TCZ. The systemic feature score was based on the number of systemic manifestations present from eight parameters of sJIA: rash; fever; cervical, axial or inguinal lymphadenopathy; hepatomegaly; splenomegaly; and serositis.

Statistics

Descriptive statistics were reported in terms of medians and interquartile ranges (IQRs) for continuous variables and in terms of absolute frequencies and percentages for categorical variables. We utilised Mann-Whitney U-test for comparison of quantitative variables in two groups and chi-square test for comparison of qualitative data, or the Fisher's exact test in the case of expected frequencies <5. The ability of each variable to discriminate the groups was evaluated with sensitivity and specificity analysis, AUC-ROC (area under receiver operating characteristic curve) with 95% confidence interval (CI), calculating odds ratio (OR) to detect the best cut-offs of continuous variables. For laboratory tests we used AUC-ROC

analysis with 95% CI. Survival analysis with achievement inactive disease (ID) status and flare as the events of interest was conducted by means of the Kaplan-Meier method. Survival curves were compared by the log-rank test. Factors significantly associated with time to achievement ID-status and flares were tested in a Cox proportional hazards regression model. $p<0.05$ was considered as statistically significant. The software Statistica (release 9.0, StatSoft Corporation, Tulsa, OK, USA), Biostat and MedCalc were used for data analyses. p-values <0.05 were considered to indicate a significant difference.

Results

The demographic characteristics and main outcomes are presented in Table I are relative to the time of the start of TCZ, so some characteristics changed due to disease course, previous and concomitant treatment. During TCZ treatment, 83.3% of patients achieved the initial status of ID in approximately 4 months and the main changes in concomitant treatment resulted in CS, methotrexate and cyclosporine A discontinuation. Corticosteroids were rapidly ceased over 3–4 months. Flares were detected in 31.8% of the studied population and were determined as any more than 30% worsening of diseases course in terms of ACR Pedi measurements. During the treatment course TCZ was discontinued in 8 patients (16.7%) due to remission and in 7 patients due to the development of serious side effects, mainly infusion reaction and uncontrolled course of MAS, led to stopping TCZ treatment. Usually discontinuation of TCZ was possible if the patient was at least 1 year in remission without corticosteroids. We prolonged the interval between infusions at average plus 1 week after each 3 infusions and after 3 infusions with 12 weeks interval discontinued TCZ. Fortunately, no flares have so far been observed in these 8 cases. Interestingly, all infusion reactions occurred only at the beginning of the 2nd infusion and was only in the patients with signs of MAS. During the trials, 2 deaths occurred: 1 patient had a fatal course of MAS, accompanied by systemic fungal infection and another patient had amyloidosis. The first patient had MAS before the beginning of TCZ, and TCZ well-controlled her sJIA attributed symptoms, but did not control the MAS. The second patient with severe long-standing poorly-controlled sJIA developed renal amyloidosys before the start of TCZ and proteinuria decreased during the TCZ. Unfortunately, she refused the treatment and died approximately one year later.

The next step of the analysis was to compare the initial clinical features of sJIA patients (before 1st TCZ infusion) to identify the predictors of achievement the status of ID. Patients who achieved ID status had less frequent MAS and organ involvement, such as splenomegaly, lung, heart and CNS involvement. The ID patients less frequently needed systemic corticosteroids and cyclosporine A. The patients who reached ID status were less active: higher haemoglobin levels and lower levels of WBC, CRP, ESR, granulocytes count, LDH and ferritin (Table II). The main predictors of achievement of ID status were assessed with ROC analysis to determine cut-off points, and then by calculating odds ratios and Cox regression models (data in Table III).

Moreover, during the trial it was taken into account the fact of different response by WBC and granulocytes to TCZ by patients who further reached the status of ID. The patients who experienced a more impressive decrease in granulocytes and WBC after the 1st TCZ infusion were more likely to achieve ID status (Fig. 1).

During the TCZ trial, 31.8 patients experienced at least 1 flare episode. To evaluate the flare predictors we compared the initial status before 1st TCZ infusion between patients depend on patient experienced flare or not. Pa-

Table I. Demographics and main outcomes of patients, included in the study.

Characteristics	Me (25-75%), n=48
sJIA onset age, years	4.5 (2.9; 7.8)
Age of the start TCZ, years	9.9 (5.5; 12.7)
Disease duration at the beginning of TCZ, years	2.2 (0.5; 7.5)
Systemic features score, n (%)	
0	6 (12.5)
1	6 (12.5)
2	11 (22.9)
≥3	25 (52.1)
CRP, mg/l	30.5 (10.8; 102.4)
ESR, mm/h	42.0 (21.0; 52.0)
Number of active joints on the start of TCZ	5.0 (2.0; 21.0)
Treatment before TCZ administration:	
- Corticosteroids, n (%)	38 (79.2%)
- Methotrexate, n (%)	40 (83.3%)
- Cyclosporine A, n (%)	18 (37.5%)
MAS before TCZ administration, n (%)	14 (29.2%)
Outcomes	
Corticosteroids discontinuation#, n (%)/days	25/48 (65.8%)/101.0 (63.0; 419.0)
Methotrexate discontinuation#, n (%)/days	12/40 (30.0%)/345.0 (120.0; 780.0)
Cyclosporine A discontinuation#, n (%)/days	8/18 (44.4%)/59.0 (30.0;90.0)
TCZ treatment duration, days, Me (25%-75%)	806.0 (467.0; 1095.0)
Inactive disease, n (%)/days before	40/48 (83.3%)/138.5 (56.0; 255.0)
TCZ, discontinuation, n (%)	15/47 (31.9%)
- remission	8/15 (53.3%)
- adverse events (MAS, infusion reaction)	7/15 (46.7%)
MAS, n (%)/rates*100PY	
- patients	4/48 (8.3) / 3.9
- events	5/48 (10.4) / 4.8
Serious infusion-related reactions, n (%)/rates*100PY	4/48 (8.3) / 3.9
Remission duration after TCZ discontinuation, days**	639.0 (182.0-1111.0)
Deaths, n (%)	2/48 (4.2%)
sJIA flares, n (%)/days before first flare	14/44 (31.8%)/288.0 (169.0; 533.0)

#due to remission of sJIA; sJIA: Systemic juvenile idiopathic arthritis; TCZ: tocilizumab; MAS: Macrophage activation syndrome; LDH: lactate dehydrohenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells; CNS: central nervous system; **Me: min-max.

Table II. The comparison of initial parameters before the 1st TCZ infusion depends on the ability to achieve inactive disease status.

sJIA features	Inactive disease (n=40)	Active disease (n=8)	*p*-value
Symptoms, attributed to sJIA, n (%)			
- fever	29/40 (72.5)	7/8 (87.5)	0.66*
- rash	25/39 (64.1)	7/8 (87.5)	0.41*
- hepatomegaly	18/40 (45.0)	7/8 (87.5)	0.05*
- lymphadenopathy	13/40 (32.5)	5/8 (62.5)	0.13*
- spleenomegaly	7/40 (17.5)	5/8 (62.5)	0.017*
- lung involvement	2/40 (5.0)	4/8 (50.0)	0.005*
- heart involvement	6/40 (15.0)	4/8 (50.0)	0.047*
- CNS involvement	1/40 (2.5)	5/8 (62.5)	0.0002*
- coagulopathy with haemorrhage	1/40 (2.5)	5/8 (62.5)	0.0002*
Active joints before start of TCZ	5.0 (2.0; 22.0)	4.5 (2.0; 11.0)	0.57
MAS preceding TCZ, n (%)	9/40 (22.5)	5/8 (62.5)	0.037*
Haemoglobin, g/dl	11.4 (10.6; 12.6)	10.0 (8.9; 11.1)	0.019
WBC x 10^9/l	11.4 (7.9; 15.4)	18.2 (11.1; 21.3)	0.048
Granulocytes, cells/μl	7587 (4887; 11912)	13465 (9380; 17723)	0.015
CRP, g/l	18.7 (8.5; 89.1)	102.3 (51.4; 152.0)	0.05
ESR, mm/h	34 (13.5; 50.0)	47.5 (43.5; 62.0)	0.034
Ferritin, ng/ml	137.0 (55.0; 224.0)	2949.0 (841.0; 6150.0)	0.0007
LDH, U/l	464.0 (423.0; 571.0)	821.0 (743.0; 1550.0)	0.0003

*Fisher's exact test; sJIA: Systemic juvenile idiopathic arthritis; TCZ: tocilizumab; MAS: Macrophage activation syndrome; LDH: lactate dehydrohenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells; CNS: central nervous system.

Table III. The main predictors of inactive disease in sJIA (Cox regression models).

sJIA features	OR (95% CI)	*p*	HR	*p*
CRP ≤82.0 mg/l**	7.9 (1.4-45.3)	0.016*	1.17	0.66
ESR ≤32 mm/h**	17.0 (0.9-314.3)	0.014*	0.85	0.62
Ferritin ≤273 ng/ml**	56.5 (2.8-1124.9)	0.0001*	2.6	0.02
Haemoglobin >11.3 g/dl**	17.0 (0.9-314.3)	0.014*	1.33	0.38
LDH ≤676 U/l**	113.6 (5.3-2451.8)	0.000014*	3.18	0.029
Platelets >335 x10^9/l**	5.0 (0.9-28.9)	0.11*	2.54	0.007
Age of 1st TCZ infusion ≤11 years**	2.6 (0.6-12.4)	0.24*	1.44	0.3
Decreasing of WBC in 2 weeks >11%**	13.0 (1.4-124.3)	0.03*	6.03	0.019
Decreasing of granulocytes in 2 weeks >12%**	14.0 (1.1-185.5)	0.05*	4.7	0.13
MAS preceding TCZ	0.17 (0.04-0.87)	0.037*	0.7	0.34

*Fisher's exact test; **AUC – area under the curve; sJIA: Systemic juvenile idiopathic arthritis; TCZ: tocilizumab; MAS: Macrophage activation syndrome; LDH: lactate dehydrohenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells.

tients with flare were predominantly males (more frequently), had a lower level of total protein and a smaller degree of decrement of the WBC and granulocytes after the 1st TCZ infusion (data in Table IV).

The main predictors of flares were assessed by ROC analysis to determinant the best cut-off points, and also by calculating odds ratios and Cox regression models (data in Table V). Ii is interesting that the discontinuation of corticosteroids, methotrexate and cyclosporine as well as MAS prior to starting TCZ did not influence the sJIA flare risk. The main flare risk was high disease activity and treatment protocol deviations.

Discussion

sJIA is a challenging disease which requires fast and strong disease control. According to the data of the largest real-world clinical setting trial IL-6 blockade with tocilizumab is a good and safe tool for targeting the remission in sJIA children (11). Unfortunately, the place of TCZ in the treatment of sJIA is not clearly determined yet in treatment plans and strategies. In the ACR-2013 recommendation, TCZ is at least the second-line biologic agent, but today there are no comparative studies and analysis about the benefits of IL-1 and IL-6 blockers. Also, there is no clarity about what kind of sJIA patient requires TCZ: only those who fail standard treatment with MTX and CS or we can use TCZ as a first-line biologic despite the presence of systemic features. The data on the safety and efficacy we can obtain from randomised controlled trials, postmarketing studies and from real clinical life. The data of postmarketing studies (PMS) usually differ from randomised controlled trials due to differences in patient population, baseline characteristics (corticosteroid dosage, combination of non-biologic DMARDs, sJIA features, outcomes, SAE and AE frequency) (12). In comparison with the biggest PMS study of TCZ in sJIA, our patients more frequently had fever (75.0% *vs*. 35.7%), lymphadenopathy (68.1% *vs*. 28.5%), hepatomegaly (52.1% *vs*. 7.9%), splenomegaly (25.0% *vs*. 6.5%), lung and cardiac involvement, and MAS incidence. In addition, there are differences in the systemic features score: **0** - 12.5% *vs*. 61.2%, **1** - 12.5% *vs*. 8.4, **2** - 22.9% *vs*. 12.7%, **≥3** - 52.1% *vs*. 17.5% (11). The patients from RCTs had fewer systemic features compare to our data (5, 13). Despite the high percentage of systemic features, our patients were able to reach inactive disease status and discontinued TCZ due to long remission. However, the patients who were less active were more able to obtain ID status. Also, patients who had fewer WBC and granulocytes after starting TCZ had a higher chance of obtaining remission. Because neutrophilia is an IL-6 dependent condition in sJIA patients, the degree of decreasing WBC and neutrophils can be mentioned as a marker of biologic susceptibility of sJIA patients to IL-6 blockade. The ability to achieve ID in our study was greater, compared to previous trials and was 83.3% in 138.5 (56.0; 255.0) days and 16.7% of the entire studied population discontinued TCZ due to prolonged remission.

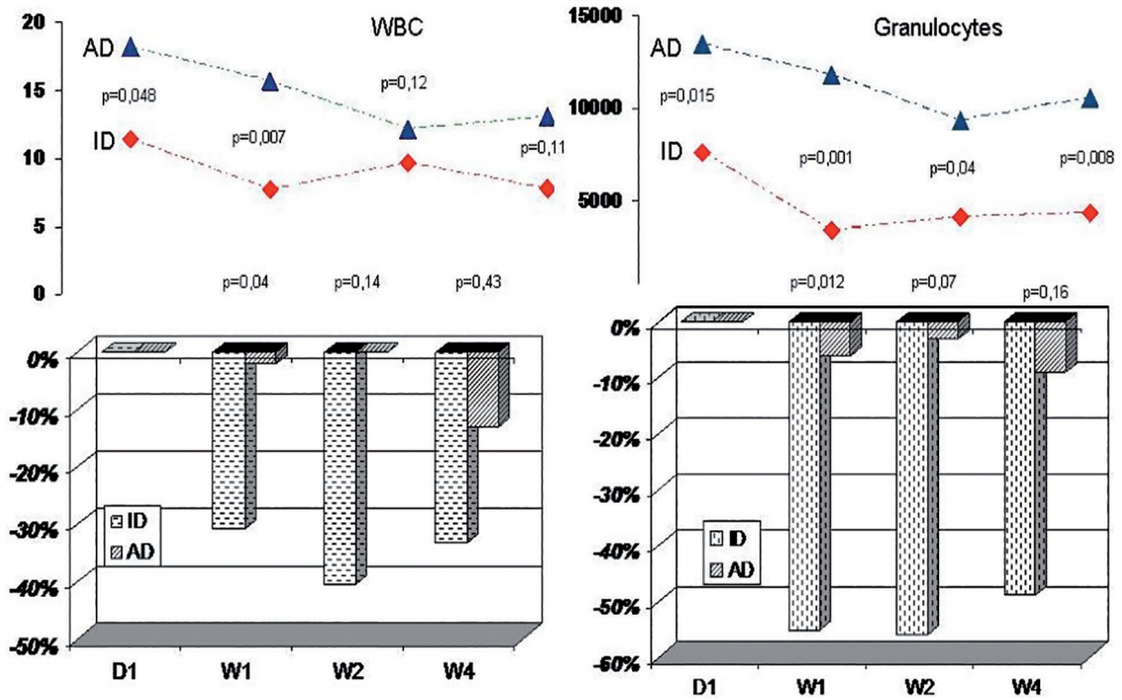

Fig. 1. Change in WBC and granulocytes in patients depends on ability to achieve inactive disease.
ID: inactive disease, AD: active disese, D1: day 1 (1st TCZ infusion), W: weeks, WBC: white blood cells. Differences in absolute numbers of WBC/granulocytes between the two groups (upper part); Differences in the percentage of decrease in WBC/granulocites between the two groups (in the lower part).

Table IV. Differences between the groups of the sJIA patients who experienced the flare and those who did not#.

sJIA features	Flare, yes (n=14)	Flare, no (n=30)	*p*
Sex, females n (%)	5/14 (35.7)	18/26 (69.2)	0.04
Total protein, g/l	67.9 (66.9; 68.2)	72.5 (68.0; 78.0)	0.016
WBC in 1 week after the start of TCZ x 10^9/l	10.9 (9.1; 16.1)	5.5 (4.1; 7.7)	0.001
Granulocytes in 1 week after start of TCZ, cells/µl	7486.5 (5208.5; 9059.0)	2160.0 (1665.0; 3773.0)	0.0015
Decreasing of granulocytes in 1 week after start of TCZ, %	28.4% (1.2; 51.0)	60.4 (37.6; 79.9)	0.017

#event of interest: the 1st flare after the start of TCZ; sJIA: Systemic juvenile idiopathic arthritis; TCZ: tocilizumab; WBC: white blood cells.

Another 14.6% of patients discontinued TCZ due to side effects (serious infusion-related reactions (IRRs), new cases of MAS (n=1; 0,97/100PY) and 1 death due to severe MAS, which started before the 1st TCZ infusion accompanied by systemic fungal infection). The frequency of IRR reaction was 4/48 (8.3%, 3.9/100PY), and 3 of them developed in patients who had active sJIA with MAS. All IRRs developed between the 2nd and 4th infusions, similar to the data of Yokota *et al*. (2015) and led to the discontinuation of TCZ. We have not tested patients with IRRs on the presence of anti-TCZ antibody, but in previous studies the association between IRRS and anti-TCZ antibodies was shown (13, 14). The frequency of IRRs was different from author to author and especially distinguished in JIA categories. In several trials in poly-JIA the frequency of IRRS ranged from 0% (15) to 0.5% (16), but in sJIA it was higher and ranged from 0.9 % (13) to 1.9% (11.3/100PY) (11) and 3.5% (5). In our cohort the frequency was higher, possibly due to the high percentage of patients with MAS, who are usually excluded from randomised trials, but the rate of IRRs was lower (3.9/100PY) when it was reported previously. It is also not clear why in systemic patients the prevalence of anti-TCZ antibodies is higher, despite the fact that this JIA category has autoinflammatory pathogenesis, and poly-JIA with predominant autoimmune disregulations has a lower frequency of anti-TCZ antibodies and IRRs.

During the observation period we saw only one new MAS event (2.1%, 0.97/100PY) in a 2-year-old girl, one year after starting TCZ, which is less than in the previous trials (11). In total during the trial there were 5 MAS events in 5 patients (10.4%, 4.8/100PY), 4 of whom had a history of MAS before TCZ. The MAS incidence in sJIA children who did not receive biologic treatment is 6.8–13.0% in previous studies, in children treated with TCZ approximately 3.0–4.4% (14, 17, 18). Data on new cases of MAS during IL-1 blocking treatment depends on the kind of medication and ranges from (2.3%, 2.8/100PY) on canakinumab, 7.7/100PY on placebo to 20.0% in anakinra (19, 20). Data on new cases of MAS on TCZ is restricted to several

Table V. The main predictors of flares in sJIA during TCZ treatment (Cox regression models)[#].

sJIA features	OR (95% CI)	*p*	HR	*p*
Sex, males	4.1 (1.0-16.0)	0.04	3.16	0.02**
sJIA onset age ≥5 years	3.6 (0.9-14.2)	0.06	2.72	0.06
Preceded corticosteroid treatment	2.7 (0.5-14.8)	0.45[£]	2.32	0.2**
Fever preceded the start of TCZ	3.2 (0.6-17.4)	0.27[£]	2.9	0.17
Absence of inactive disease after 10 TCZ infusions (138 days)*	3.4 (0.8-13.8)	0.08	2.6	0.02**
LDH >340 U/l*	9.4 (0.5-188.2)	0.05	118.8	0.01
Platelets >339 x 10^9/l*	2.7 (0.6-12.0)	0.19	2.16	0.19
WBC >11,5 x 10^9/l*	4.7 (1.1-19.4)	0.026	3.7	0.01
Granulocytes >5530 cells/μl*	5.1 (1.0-27.7)	0.04	3.7	0.04
CRP >19.2 mg/l*	2.9 (0.7-11.1)	0.12	2.1	0.08
Decreasing of WBC in 1 week after start of TCZ ≤20.0%*	7.5 (1.4-40.2)	0.014	3.09	0.05
Decrease in granulocytes in 1 week after start of TCZ ≤ 55.0%*	10.8 (1.8-65.6)	0.005	6.6	0.01
Deviations in infusion schedule	2.9 (0.1-65.6)	0.54[£]	29.4	0.52
Concomitant methotrexate therapy	0.5 (0.1-2.8)	0.65[£]	0.52	0.32
Corticosteroid discontinuation	1.0 (0.1-7.1)	1.0[£]	1.06	0.91
Methotrexate discontinuation	1.3 (0.3-5.9)	1.0[£]	1.29	0.67
Cyclosporine A discontinuation	0.6 (0.1-6.8)	1.0[£]	0.73	0.74
MAS preceded the start of TCZ	0.9 (0.2-4.4)	1.0[£]	0.79	0.72

[#]event of interest: the 1st flare after the start of TCZ); [£]Fisher's exact test; *AUC: area under the curve; **Log-Rank test; sJIA: Systemic juvenile idiopathic arthritis; TCZ: tocilizumab; MAS: Macrophage activation syndrome; LDH: lactate dehydrohenase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells.

reports and ranges from 1.24/100 PY to 6.4/100 PY (11, 23). It seems that the IL-6 blockade is more effective in preventing new cases of MAS compared to non-biologic DMARDS.

Flares affected 31.8% of the studied population. The patients with higher sJIA disease activity and patients with treatment protocol deviations (predominantly missing the infusions) had a higher flare risk. Interestingly, the discontinuation of corticosteroids, methotrexate and cyclospine A and MAS in past medical history did not increase the flare risk.

Our study shows that patients with lower disease activity had a better response to TCZ. Accordingly, we can use it either in severe patients or in mild patients with real benefits, there it shows much better outcomes. It is interesting that previous corticosteroid treatment increased the risk of flare, but discontinuation of MTX, cyclosporine A and corticosteroid as well as concomitant MTX treatment did not involve the risk of flare. There were no differences in the percentage of patients who experienced the flare and time before flares in patients with and without concomitant treatment. In a previous trial there was no evidence of MTX efficacy in sJIA, which can be explained by autoinflammatory mechanisms in the sJIA pathogenesis (21). MTX shows good efficacy in cases where autoimmune mechanisms have a predominant role (22). Possibly, early intervention with TCZ before all other kinds of medication in patients with sJIA without signs of MAS can provide fast and sustained remission.

This study has limitations related to the absence of a control group, necessary comparison analysis with other types of biologics used for the treatment of sJIA and further investigations are required. This was an observational study with real-world clinical settings in patients with sJIA and different from randomised trials with a specific protocol and specially chosen studied population with more severe patients compared to RCT and PMS.

In conclusion, the factors which increased the risk of JIA flares were male sex, signs of high disease activity, previous corticosteroid treatment, late achievement of inactive disease and treatment protocol deviations. The degree of decreasing WBC and neutrophils can be mentioned as a marker of susceptibility to TCZ, possibility to reach inactive disease or to develop flare. We have to recognised the place of TCZ in the treatment plan and we should use it earlier than recommended. Further controlled trials on the comparative effectiveness of the two main treatment strategies (anti-IL-1 and anti-IL-6) are required.

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