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Clinical study of Destructive Articulation Changes in Children with Systemic-Onset Juvenile Idiopathic Arthritis In Samara Region

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Abstract

This article describes the experience in the Samara region, Russia regards the treatment of systemic-onset of juvenile idiopathic arthritis (SoJIA) with destructive articulation changes in children. The aim of our study was to evaluate the clinical responses and outcomes of children with SoJIA using two different types of management with methotrexate only and methotrexate in combination with tocilizumab (TCZ) protocol for severe SoJIA patients, and evaluate the possibility of achieving biologic-free remission. Radiography is the standard modality in the assessment of this condition. We used to modified Sharp method as EULAR's recommended radiographies scoring systems for disease progression assessment.

Keywords: juvenile idiopathic arthritis, tocilizumab, a destruction of joints, the modified Sharp's method, Rheumatology, children, genetically engineered biological drugs, methotrexate, anti-destructive drug, systemic arthritis.

BACKGROUND

Inflammatory joint diseases are often discussed in modern pediatrics. The most frequently reported pathology is juvenile idiopathic arthritis (JIA). [1] Systemic-onset juvenile idiopathic arthritis (SoJIA) is the most striking forms of juvenile idiopathic arthritis. SJIA is characterized by arthritis accompanied by severe joint destruction, inevitable progression and causing significant long-term functional impairment and poor life quality of both children and their parents. [2] Joint pain and swelling are some of the most common symptoms of various diseases. Differential diagnosis of articular syndrome is a basis of right definition of nosological entity. Multidisciplinary approach in the management of SoJIA is becoming more common and requires a consensus built on various expert opinion such as pediatrics, rheumatologists, orthopedic surgeon and infectiologist.

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown cause, with disease duration of more than 6 months, occurring in children under 16 years. [3] It is the most common rheumatic entity in childhood with a prevalence of 2-19 in 1000 children. Children with this disease has extremely limited motion range and possibility of self-care. [4]

The morbidity rate of systemic-onset juvenile idiopathic arthritis in general is approximately 10-20%. In most cases disease starts at age of 18 months till 2 years old and may continue up to an adult. The mortality rate is not farther than 2-4 per cent of all cases of disease, counting up to 67 per cent of all cases of the child's death with arthritis. Severity of disease is versatile [5].

The exact pathology is not fully understood, but is thought to include both immunological aggression and inflammation components. [6,7] Damaged structure of articulation due to this directly affects range of motion and capability of patients. Progressive X-ray changes might occur in patients with stable clinical remission of disease [8]. Deformation of the joints, limited range of motion up to contraction development, myodystrophy might be as a result of proliferative and exudative changes of articulations. [8,9]. In this respect early detection and start of therapy is of a higher importance and may significantly change prognosis and long-term implications of the disease [10].

Radiography is the standard modality in the assessment of this condition. The original Sharp method of X-ray assessment includes 27 joints in each hand and wrist, with each joint being given a separate score for joint space narrowing and erosions. Van der Heijde later added feet to the radiographies analyses, a modification that has also been used by Sharp. Because of their similarities, these radiographic scoring systems will be referred to as "modified Sharp methods" in accordance with EULAR's standardized operating procedures. [10,11,12,13].

Prevention of joint destruction of juvenile idiopathic arthritis is still a challenge for physicians. [14] Understanding the comparative effectiveness of the diverse therapeutic options available for treatment of sJIA can result in better health outcomes. Methotrexate (MTX) is routinely used in the treatment of inflammatory arthritis and in combination with non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstays of treatment for many years. There have been concerns regarding the safety of using them associated with many side effects. Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the interleukin-6 (IL-6) receptor that is approved for the treatment of patients with juvenile idiopathic arthritis. Brunner H.I., Ruperto N, Zuber Z. and others report effectiveness and safety of intravenous infusions of tocilizumab (TCZ) in management of JIA. The recommended dosage of intravenous TCZ for patients at or above 30 kg weight is 8 mg per kg every 4 weeks followed by an assessment of clinical response. For patients less than 30 kg weight the recommended intravenous TCZ dosage is up to 10 mg per kg every 4 weeks of administration. 89% of patients entered Brunner H.I. and others study provided

they had experienced at least a JIA-American College of Rheumatology (ACR) 30 response (JIA-ACR30), defined as 30% or greater improvement in three or more of the six JIA core response variables (JIA-CRVs) without greater than 30% worsening in more than one of the remaining JIA-CRVs compared with baseline, 62% of patients achieved ACR 70, and 26% of patients had an ACR 90. [15].

According to LITHE study if compared with placebo-MTX tocilizumab-MTX significantly inhibited structural joint damage and improved physical function in 83% of patients with RA who previously had an inadequate response to MTX. Clinical remission lasted up to 2 years of the therapy. 93 % of patients reported no progression of articulation destruction between 52 to 104 weeks of administration. Horneff G, Klein A, Klotsche J (2016) come up with conclusion that TCZ may significantly reduce destruction of joints as the basics of juvenile idiopathic arthritis [16].

The aim of our study was to review our use of TCZ at our clinic and evaluate the children's clinical response. We used two treatment protocols, and evaluated outcomes, including the optimal possibility of achieving biologic-free remission.

METHODS

This retrospective research on 240 medical reports of children aged from 3 to 17 with different forms of juvenile idiopathic arthritis was conducted at cardiorheumatologist's department of Samara State Cardiologic dispensary from 2014-2016. Diagnosis of JIA was based on an ILAR definition (ILAR, 2001). Ethical principles of this research meet the World Medical Association Declaration of Helsinki criteria (1964, revised in 2000.) All patients' parents gave their written informed consent.

38 patients of the total group had an active systemic-onset juvenile idiopathic arthritis lasting more than 2 years. Clinical assessment was based on JIA-American College of Rheumatology criteria's (ACR, 2011). Patients were randomized into 2 groups: 22 patients received MTX monotherapy only and 16 patients received MTX in combination with gene-modified synthetic TZC.

The modified Sharp method is detailed and assigns 2 individual ordinal scores, one for erosions (range 0-280 and the maximum for a hand of 160 scores and four foot - 120) and one for joint space narrowing (range 0-168 and the maximum for a hand of 168 scores and four a foot - 120), for various joints of the hands and feets. The total overall maximum score for each patient is 448. In this study efficacy assessments were made in 180, 360 and 720 days from the therapy administration start.

The results were statistically analyzed using computer software «STATISTICA 6.0». All values are presented as the mean (M) and standard deviation (±m). In terms of qualitative characteristics, the Fisher's direct test was used to detect the existence of differences between the compared groups. Normal distribution of variables between groups was performed by using Student's t-test. The level of significance was established at $p < 0.05$, indicating the existence of statistically significant differences or relationships $p<0,001$.

RESULTS AND DISCUSSION.

Main characteristics of both groups and the level of disease activity in respect to patient gender are represented in table 1. Mean age of children of both groups was 7 years and 5 months ± 42 months.

Disease onset was under 3 years old in both groups of patients and counted 21% and 19 % respectfully to 1st and 2nd group. (See figure 1).

Table 1. Level of disease activity in respect of patient's gender.

Parameters	Absolute		Relative	
	Group 1	Group 2	Group 1	Group 2
Gender	girls- 17 boys-5	girls- 10 boys-6	girls- 77% boys-23%	girls- 62,5% boys-37,5%
Activity level	II – 7 II–III – 11 III –4	II – 4 II–III – 10 III –2	II – 32% II–III – 50% III –18%	II – 25% II–III–62,5% III –12,5%

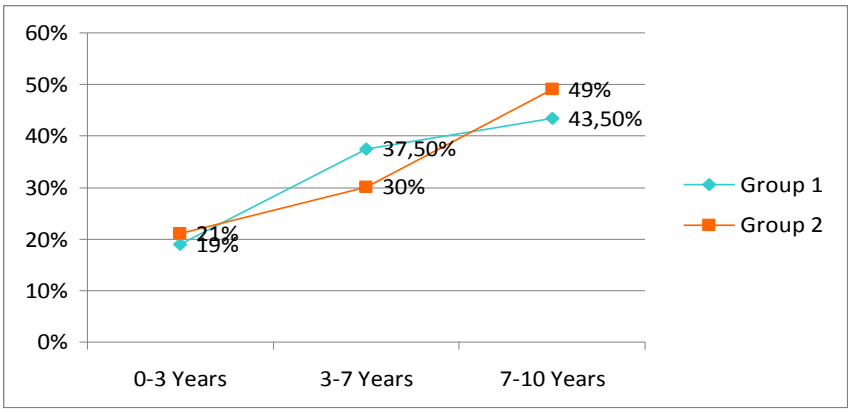

Figure 1. Disease onset age of patients of two groups

Table 2. Modified Sharps method assessment of 1 group after 6 months of treatment

Patients	Max score for hands articulations erosions	Max score for foots articulations erosions	Max score for hands joints spaces	Max score for foots joints spaces	Max total score
1	67	50	48	20	**185**
2	72	53	57	28	**210**
3	54	31	27	18	**130**
4	63	29	33	19	**144**
5	52	29	27	18	**126**
6	38	22	19	9	**88**
7	42	27	22	11	**102**
8	36	21	21	10	**88**
9	71	57	59	8	**195**
10	64	49	28	21	**162**
11	65	53	35	22	**175**
12	75	56	59	28	**218**
13	59	32	28	20	**139**
14	37	47	25	19	**128**
15	40	35	21	17	**113**
16	51	38	43	25	**157**
17	61	37	55	8	**161**
18	27	41	47	19	**134**
19	36	42	38	23	**139**
20	34	28	60	41	**163**
21	51	29	27	10	**117**
22	50	49	34	13	**146**
Mean (M): 146.36 ;Mediana (Me): 141.5 ;Mean quadrate deviation (σ): 35.69 ;Coefficient of variation (Cv): 24.39% Standard deviation of Mean values (m): 7.79					

Table 3. Modified Sharps method assessment of 2 group after 6 months of treatment

Patients	Max score for hands articulations erosions	Max score for foots articulations erosions	Max score for hands joints spaces	Max score for foots joints spaces	Max total score
1	54	21	30	12	**117**
2	23	18	19	6	**66**
3	49	22	23	12	**106**
4	61	29	28	22	**140**
5	31	17	11	8	**67**
6	20	9	5	5	**39**
7	65	31	14	21	**131**
8	47	19	13	10	**89**
9	28	11	7	6	**52**
10	44	15	11	10	**80**
11	39	19	13	10	**81**
12	51	22	31	14	**118**
13	47	21	19	11	**98**
14	43	18	20	13	**94**
15	35	20	12	9	**76**
16	41	18	10	15	**84**
Mean (M): 89.88 ;Mediana (Me): 86.5; Mean quadrate deviation (σ): 27.80; Coefficient of variation (Cv): 30.93%; Standard deviation of Mean values (m): 7.18					

Table 4. Combined vs monotherapy of JIA are important for joint destruction prevention for children with

Parameters	180 days		360 days		720 days	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Mean value ± standard deviation	146,36± 7,79	89,88± 7,18	167,25± 8,23	77,75± 6,59	163,42± 6,47	54,31±4,16
Students t-test value (p<0,05)	5,32		8,49		14,22	

A first group of patients received MTX monotherapy only. Children from second group had an inadequate response to methotrexate15-25 mg/m2 per week intramuscular treatment prior to TZC administration. Patients at or above 30 kg weight TZC intravenous doses were 8 mg per kg every 4 weeks and for patients less than 30 kg weight we gave TZC intravenously 10 mg per kg every 4 weeks with no need to increase this dose.

Effectiveness of JIA treatment is assessed by ability of drug agent to accelerate symptom regression [7] In our study monotherapy of MT with standard doses had no significant influence on the destruction of joints progression according to modified Sharp method assessment score within 2 years of follow-up. Highest score by assessment means X-ray symptom progression. In our study, children from group 1 with monotherapy with MTX had higher scores by assessment compared to group 2 with combined MTX + TZC therapy. Differences between two groups had been significant, according to Students test criteria. See table 4.

CONCLUSION

Type and time to start of the drug administration for the management of JIA are important in terms of joint destruction prevention for children with SoJIA. Early start of therapy significantly reduces the severity of joint destruction. Compared with MTX, tocilizumab-MTX significantly inhibited structural joint damage and improved physical function in patients with SoJIA who previously had an inadequate response to MTX. However, environmental factors also should be taken into account: it is known that food insecticides and pesticides may provoke JIA [17]; some of them may act at very low doses [18].

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