Immunol Genet J, Vol. 7, No. 2, June 2024, pp.66-71 DOI: https://doi.org/10.18502/igj.v7i2.17852

Original Article

Evaluation of Effectiveness and Outcome of Interleukin-6 Inhibitor Treatment in Patients with Systemic Juvenile Idiopathic Arthritis

Reza Shiari[1], Navid Roshanzamir[2], Mahsa Erfanian-Salim[3*]

[1] Department of Pediatric Rheumatology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Internal Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Pediatrics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 18 March 2024; Accepted: 03 May 2024

Abstract

Background: Systemic juvenile idiopathic arthritis (sJIA) is determined by prominent multisystemic involvements with onset before the age of 16 years, of which IL-6 has a significant role in the inflammatory process. Tocilizumab (TCZ) is a human anti-IL-6 receptor monoclonal antibody, which modulates IL-6 activity by blocking its binding to the soluble and membrane-bound IL-6 receptor. No comprehensive study has been done regarding the use of IL-6 inhibitors in the treatment of sJIA patients in Iran. This study was conducted with the aim of investigating the effectiveness and outcome of IL-6 inhibitor treatment in Iranian children with sJIA.

Methods and Materials: This is a case-control study including twenty patients diagnosed with sJIA divided equally into two groups of case and control who received TCZ and corticosteroids, respectively. Subsequently, various clinical and laboratory features were compared among these two groups.

Results: A significant difference before and after TCZ has been seen in terms of height increase, weight gain, decrease in leukocytosis, thrombocytosis and ESR, CRP negativity, and arthritis improvement.

Conclusion: Considering the favorable effects of TCZ in the control of sJIA, by producing this drug in the country and making it available to patients at a lower cost, it is possible to better control the disease and reduce the harmful effects caused by the disease and reduce the long-term use of corticosteroids.

Keywords: Interleukine-6 (IL-6); Systemic Juvenile Idiopathic Arthritis (sJIA); Treatment; Tocilizumab

***Corresponding Author:** Mahsa Erfanian-Salim, MD
Department of Pediatrics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: mahsa_er2009@yahoo.com

How to cite this article
Shiari R, Roshanzamir N, Erfanian-Salim M. Evaluation of Effectiveness and Outcome of Interleukin-6 Inhibitor Treatment in Patients with Systemic Juvenile Idiopathic Arthritis. Immunology and Genetics Journal, 2024; 7(2): 66-71. DOI: https://doi.org/10.18502/igj.v7i2.17852

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is a severe subtype of JIA patients with no gender predominance (1). sJIA is determined by prominent systemic characteristics such as rash, fever, serositis, lymphadenopathy, hepatomegaly or splenomegaly, and onset before the age of 16 years (2, 3). sJIA is also associated with developmental de-

lay, erosive arthritis, cardiovascular and pulmonary complications, as well as amyloidosis (4, 5).

This disease, in addition to long-term treatment, requires high doses of corticosteroids, which itself leads to an increase in the risk of disability(6). Non-steroidal anti-inflammatory medications alone cannot improve the symptoms of sJIA. For example, methotrexate is one of the disease-modifying antirheumatic drugs (DMARDs) with the lowest level of toxicity, which is available as an adjuvant treatment, but it takes about 6-12 weeks to see the effects of it. Failure of treatment with methotrexate alone indicates the need to add a biological drug (7, 8). Several cytokines play a role in the pathogenesis of rheumatoid arthritis, including tumor necrosis factor-alpha (TNF-α), Interleukin-1 (IL-1), and Interleukin-6 (IL-6) (9), and many clinical studies have reported the pivotal role of IL-6 in the inflammatory process of sJIA (10). IL-6 is a pro-inflammatory cytokine that is elevated in peripheral and synovial fluid and signals through the inflammatory biomarker C reactive protein (CRP) (11). IL-6 has an effect on the immune system, including the stimulation of fibroblasts, osteoclasts, macrophages, T-helper cells, differentiation, and activation of B cells. Moreover, it plays a vital role in the adhesion of neutrophils to fibroblasts and, as a result, causes inflammation and the process of creating pannus in the synovium (12). Of note, IL-6 has an inhibitory effect on growth hormone, which leads to short stature in these patients. Therefore, the necessity of using IL-6 blockers in these patients seems quite logical (13).

In patients with sJIA, IL-6 expression has been correlated with the extent and severity of joint involvement, with fever and platelet counts (11, 14). Tocilizumab (TCZ) is a human anti-IL-6 receptor monoclonal antibody (10), which modulates IL-6 activity by blocking its binding to the soluble and membrane-bound IL-6 receptor, thereby reducing CRP levels (15, 16). The results of several clinical trials have shown that TCZ has improved symptoms such as fever, skin rash, and inflammatory parameters in patients with sJIA (16, 17). TCZ is used in many countries for moderate to severe types of rheumatoid arthritis that do not respond well to DMARDs, and it is effective in rapidly reducing disease activity and the use of high doses of corticosteroids in these patients. Considering that in our country, no comprehensive study has been done regarding the use of IL-6 inhibitors in the treatment of sJIA patients. Therefore, the current study was conducted with the aim of investigating the effectiveness and outcome of IL-6 inhibitor treatment in sJIA patients.

Method and materials

This case-control study was conducted on patients with sJIA based on the International League of Associations for Rheumatology (ILAR) classification criteria (18), referred to the rheumatology clinic of Mofid Children's Hospital, Tehran, Iran, between 2021-2022. According to the ILAR criteria, sJIA patients are defined as having arthritis in one or more joints with or following fever for at least a two-week period, which is constant for at least three days or daily, and accompanied by one or more of one of the following symptoms: 1- Erythematous rash that fades 2- Diffuse enlargement of lymph nodes 3- Hepatomegaly or splenomegaly or both 4- Serositis. Patients who did not have an indication to receive the biological medication and were unable to continue the treatment for any reason were excluded from the study. Our case group included 10 children under 16 years old with systemic type of JIA who were treated with IL-6 inhibitor tocilizumab (TCZ) at the rate of 8-10 mg/kg intravenously every two weeks, then one month and 2 months. The control group included 10 other systemic JIA patients who were treated with one to two pulse doses of methylprednisolone (30 mg/kg) and did not receive any biological therapy. In the meantime, all the patients in both groups underwent treatment with prednisolone 1mg/kg/day as the maintenance therapy. A questionnaire was designed to collect patients' demographic, clinical, and laboratory data. Two groups were compared in terms of weight, height, fever, arthritis, serositis, rash, leukocytosis, thrombocytosis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Lactate dehydrogenase (LDH), Aspartate transaminase (AST), Alanine transaminase (ALT) and triglyceride (TG). The clinical response rate under TCZ at week 8 measured the effectiveness of TCZ and was determined as follows: no symptoms and normal inflammation parameters at that time. Written informed consent was obtained from all patients, their parents, or legal

guardians. This study was approved by the ethical committee of the Shahid Beheshti University of Medical Sciences.

Statistical analysis

Data were analyzed using SPSS software version 16. Descriptive statistics were presented as mean ± standard deviation (SD) for quantity values and frequency (percentage) for qualitative values. Kolmogorov–Smirnov test was applied to test for the data normality. Differences were compared by using the paired sample t-test or Mann-Whitney U test. The McNemar test was used to compare qualitative variables between two groups. A P-value less than 0.05 was considered significant.

Results

The patients in the two studied groups matched each other in terms of age and sex. There are 10 patients in each group, including 5 girls and 5 boys with an average age of 5.3 years old. According to the results outlined in **Table 1**, it is revealed that intervening with tocilizumab provides a statistical difference in increasing height (*P*-value=0.005) and weight (*P*-value= 0.020). Additionally, in this group, a significant reduction in clinical findings such as fever (*P*-value=0.002) and arthritis (*P*-value =0.006) is visible, as well as lab variables such as WBC counts (*P*-value=0.005), ESR (*P*-value=0.008), platelet count (*P*-value=0.020), and CRP (*P*-value=0). Whilst in the control group, obvious alterations are demonstrated in weight gain (*P*-value=0.030) and ECR decline (*P*-value=0.015) before and after the intervention by methylprednisolone. Furthermore, some clinical variables (rash and serositis) and paraclinical ones (LDH, AST, ALT, TG) had no confounder effect before and after interventions in both case and control groups. Regarding serositis in this study, only one of the patients in the control group had pericarditis before receiving methylprednisolone, which disappeared following the intervention. In contrast, none of the subjects in the case group had serositis either before or after the intervention.

In the TCZ group, 40% of patients do not need a maintenance dose of corticosteroids (*P*-value=0.2). In the methylprednisolone group, 10% of patients stopped maintenance treatment (*P*-value=0.125), illustrated in **Figure 1**.

Table 1. Differences in clinical findings between the two groups of patient

Variables	Methylprednisolone group (N=10)			Tocilizumab group (N=10)		
	Before	After	p-value [a]	before	After	p-value [b]
Height (Centimeter)	103.22 ± 2.6	108.22 ± 2.2	0.18	95.14 ± 6.8	107.10 ± 5.5	0.005
Weight (kilogram)	14.6 ± 4.0	17.9 ± 0.3	0.03	16.5 ± 1.9	20.8 ±3.7	0.021
WBC (mm3)	14.7 ± 31.0	11.5 ±11.58	0.44	18.8 ± 29.0	7.4 ± 65.72	0.005
ESR (mm/hr)	68.32 ± 8.4	39.31 ± 6.8	0.015	47.22 ± 5.3	10.5 ±3.1	0.008
Platelet	450000 ± 11	410000 ±2	0.314	430000±11	330000±8	0.021
LDH (IU/L)	547.268 ± 6.7	588.237 ± 7.2	0.249	433.192 ± 3.0	401.171 ± 1.7	0.285
Aspartate transaminase	36.31 ± 8.6	29.4 ± 2.8	0.310	38.20 ± 7.5	26.5 ± 6.8	0.681
Alanine transaminase	33.54 ± 1.0	13.6 ± 7.4	0.236	25.28 ± 5.6	16.7 ± 9.0	0.858
Triglycerides	227.175 ± 9.0	222.89 ± 3.2	1.000	175.89 ± 5.8	179.84 ± 5.1	1.000
Fever	8 (80%)	3 (30%)	0.125	7 (70%)	0 (0%)	0.002
Rash	5 (50%)	0 (0%)	0.250	1 (10%)	0 (0%)	1.000
Arthritis	10 (100%)	5 (50%)	0.250	10 (100%)	2 (2%)	0.006
Serositis	1 (10%)	0 (0%)	1.000	0 (0%)	0 (0%)	1.000
CRP (mg/L)	10 (100%)	5 (50%)	0.250	10 (100%)	0 (0%)	0.000

P-value [a]: Mean comparison before and after the intervention in the Methylprednisolone group, *P*-value [b]: Mean comparison before and after the intervention in the Tocilizumab group.

Discussion

sJIA is a severe multiorgan disease of unknown etiology. Classification and diagnostic criteria are currently under debate because sJIA is not a classic autoimmune disease like other JIA subtypes (19, 20). IL-6 is involved in the pathogenesis of sJIA and its comorbidities(14). TCZ is used in many countries for moderate to severe types of sJIA that do not respond well to DMARDs or cannot tolerate other drugs well. Therefore, this study assessed the effectiveness of interleukin-6 inhibitor treatment in sJIA.

In the study of Yokota et al. in Japan, the effects of TCZ were investigated on 417 patients with

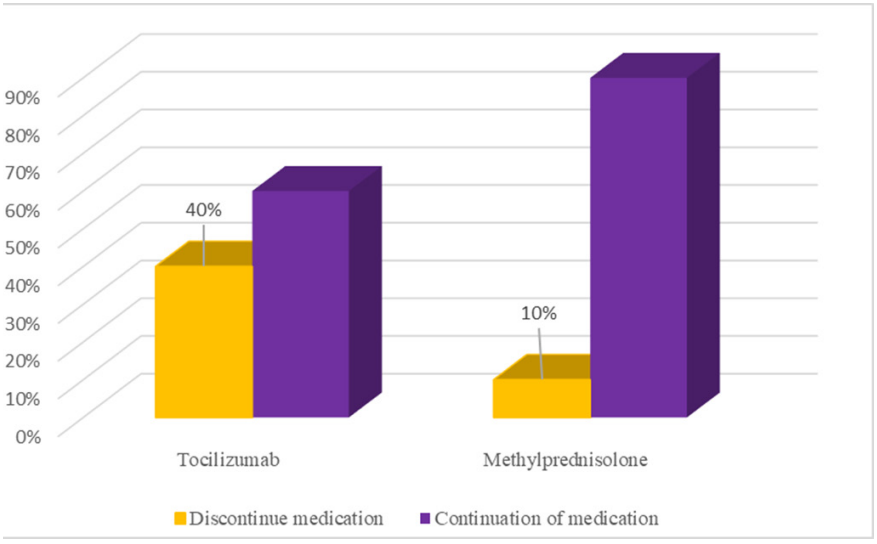

Figure 1. Comparison of corticosteroid discontinuation in two groups of patients

sJIA. The medication was given to the patients at a dose of 8 mg/kg every two weeks, and the patients were followed up for 52 weeks. Based on the results, an improvement in CRP was observed, reaching a normal level in 99% of patients within 52 weeks. In addition, the corticosteroid dose in the fourth week was reduced from 0.9 mg/kg/day to 0.2 mg/kg/day in the 52nd week. The main symptoms of the disease, such as fever, decreased from 54.6% to 5.6% and rash from 43% to 5.6% within 52 weeks (2). In our study, before and after taking TCZ, improvement in CRP (*P*-value=0) and fever (*P*-value=0.002) was observed, similar to the results of Yokota's study, although no significant alterations in the presentation of rash were noticed in both groups, as a result of small sample size.

In the study by Aoki et al., 40 patients with sJIA who received TCZ intravenously at a dose of 8 mg/kg every two weeks, clinical symptoms, and radiographic changes of the hand and large joints were evaluated before and during treatment. After 4.5 years of therapy, the clinical symptoms had clearly improved, and on average, one out of three radiographic criteria had improved (21). The clinical findings of this study are in line with the results of the current study.

In the study of Alekseeva et al., 212 patients were treated with TCZ, and 75 of these 212 patients were followed up for two years. The study's results showed that with the increase in the duration of treatment, the rate of improvement of disease symptoms increased according to ACR criteria. Our study aimed to investigate the drug's implications regardless of the duration of treatment. In addition, Alekseeva et al. reduced the oral corticosteroid dose from 9.5 mg/day at the beginning of the study to 0.5-1 mg/day in week 52. In 5 patients, corticosteroid treatment was completely stopped in the 104th week (21). In comparison, 40% of our case individuals ended up in cessation of maintenance treatment after one year (*P*-value=0.2). Furthermore, Alekseeva et al. assessed complications caused by TCZ use, including pharyngitis, upper respiratory tract infections, and gastroenteritis, and there were no reports of opportunistic infection, malignancy, or death (21). In contrast, we did not evaluate such complications.

Another study was conducted by Yokota et al. in 2008 with the aim of investigating the effectiveness of TCZ in 43 patients aged 2 to 19 years, of which 23 patients were in the TCZ-receiving group, and 20 patients were in the placebo-receiving group. In the group receiving placebo, 4 patients (17%) had CRP decreased to less than 5 mg/dl, while in the group receiving TCZ, 16 patients (80%) had a decrease in CRP. The results of their study showed that TCZ is very effective in treating patients who hardly respond to treatment (22). Our study revealed a significant decline in CRP (*P*-value=0) as well. Similar to our study, in another study, it was reported that in sJIA patients with high fever, the fever subsided, and inflam-

matory markers returned to normal levels (23). In our study, only one of the patients in the Methylprednisolone group had serositis before receiving Corticosteroid, which disappeared after receiving the pulse therapy, and none of the patients in the TCZ group had serositis either before or after receiving the medication. Therefore, it is impossible to judge the effect of either drug on reducing the amount of serositis in these patients.

Conclusion

This study shows a significant difference before and after TCZ in height increase, weight gain, decrease in leukocytosis, thrombocytosis and ESR, CRP negativity, and arthritis improvement. Considering the favorable effects of TCZ in the control of sJIA, by producing this drug in the country and making it available to patients at a lower cost, it is possible to control the disease better, reduce the harmful effects caused by the disease, and reduce the long-term use of corticosteroids. One of the limitations of the study is the small sample size. It is suggested that further multi-center studies with larger sample sizes and longer follow-up periods should be conducted in order to evaluate the effectiveness of TCZ treatment and investigate the possible side effects of its utilization.

Conflict of interest

The authors have no conflicts of interest.

References

1. Lin Y-T, Wang C-T, Gershwin ME, Chiang B-L. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. Autoimmunity reviews. 2011;10(8):482-9.
2. Yokota S, Itoh Y, Morio T, Origasa H, Sumitomo N, Tomobe M, et al. Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan. Ann Rheum Dis. 2016;75(9):1654-60.
3. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Clin Immunol. 2020;211:108322.
4. Woerner A, von Scheven-Gête A, Cimaz R, Hofer M. Complications of systemic juvenile idiopathic arthritis: risk factors and management recommendations. Expert Review of Clinical Immunology. 2015;11(5):575-88.
5. Hinze CH, Foell D, Kessel C. Treatment of systemic juvenile idiopathic arthritis. Nature Reviews Rheumatology. 2023;19(12):778-89.
6. Stoustrup P, Kristensen KD, Verna C, Küseler A, Pedersen TK, Herlin T, editors. Intra-articular steroid injection for temporomandibular joint arthritis in juvenile idiopathic arthritis: a systematic review on efficacy and safety. Seminars in arthritis and rheumatism; 2013: Elsevier.
7. Schulert GS, Minoia F, Bohnsack J, Cron RQ, Hashad S, KonÉ‐Paut I, et al. Effect of biologic therapy on clinical and laboratory features of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. Arthritis care & research. 2018;70(3):409-19.
8. Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. Clinical rheumatology. 2008;27(1):67-76.
9. Pardeo M, Bracaglia C, De Benedetti F. Systemic juvenile idiopathic arthritis: new insights into pathogenesis and cytokine directed therapies. Best practice & research Clinical rheumatology. 2017;31(4):505-16.
10. Yokota S, Imagawa T, Mori M, Miyamae T, Takei S, Iwata N, et al. Longterm safety and effectiveness of the anti-interleukin 6 receptor monoclonal antibody tocilizumab in patients with systemic juvenile idiopathic arthritis in Japan. The Journal of rheumatology. 2014;41(4):759-67.
11. Gabay C. Interleukin-6 and chronic inflammation. Arthritis research & therapy. 2006;8(2):1-6.
12. Kan JH. Juvenile idiopathic arthritis and enthesitis-related arthropathies. Pediatric radiology. 2013;43(1):172-80.
13. Bielak M, Husmann E, Weyandt N, Haas J-P, Hügle B, Horneff G, et al. IL-6 blockade in systemic juvenile idiopathic arthritis–achievement of inactive disease and remission (data from the German AID-registry). Pediatric Rheumatology. 2018;16(1):1-8.
14. Jarlborg M, Gabay C. Systemic effects of IL-6 blockade in rheumatoid arthritis beyond the joints. Cytokine. 2022;149:155742.
15. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti–interleukin‐6 receptor antibody in children with systemic‐onset juvenile idiopathic arthritis. Arthritis & Rheumatism. 2005;52(3):818-25.
16. Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JM, Cohen N, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of

randomized trials. Rheumatology. 2016;55(4):669-79.
17. Yokota S, Tanaka T, Kishimoto T. Efficacy, safety and tolerability of tocilizumab in patients with systemic juvenile idiopathic arthritis. Therapeutic advances in musculoskeletal disease. 2012;4(6):387-97.
18. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-2.
19. Dewitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new□onset systemic juvenile idiopathic arthritis. Arthritis care & research. 2012;64(7):1001-10.
20. Kumar S, Kunhiraman DS, Rajam L. Application of the Yamaguchi criteria for classification of "suspected" systemic juvenile idiopathic arthritis (sJIA). Pediatric Rheumatology. 2012;10(1):1-10.
21. Aoki C, Inaba Y, Choe H, Kaneko U, Hara R, Miyamae T, et al. Discrepancy between clinical and radiological responses to tocilizumab treatment in patients with systemic-onset juvenile idiopathic arthritis. The Journal of rheumatology. 2014;41(6):1171-7.
22. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. The Lancet. 2008;371(9617):998-1006.
23. Yokota S, Kishimoto T. Tocilizumab: molecular intervention therapy in children with systemic juvenile idiopathic arthritis. Expert Review of Clinical Immunology. 2010;6(5):735-43.