



Research Article

EFFECTIVENESS AND SAFETY OF TOCILIZUMAB IN SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS: A RETROSPECTIVE STUDY IN A LARGE PEDIATRIC HOSPITAL, TRIPOLI-LIBYA

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Abstract

**Background:** Systemic onset juvenile idiopathic arthritis (SoJIA) is the most severe subtype of juvenile idiopathic arthritis (JIA); treatment options are limited. Interleukin-6 plays an important role in remission. **Aim:** This study aimed to evaluate the effectiveness and safety of Tocilizumab for the treatment of children with SoJIA. **Methods:** A retrospective, consecutive case series study was conducted at Tripoli Children Hospital. The study involved all cases who were diagnosed as SoJIA in the period from May 2015 to June 2020 who has received Tocilizumab therapy for at least 12 weeks. Besides demographic data, data relevant to effectiveness and safety of the therapy were extracted from medical records. **Results:** A total of 15 patients were eligible and included in the analysis. The mean age was 10.9 ±3.6 years old, and males accounted for 53.3% of patients. Significant improvement in several clinical manifestations of active SoJIA was reported after 12 weeks post Tocilizumab therapy. The mean number of joints with active arthritis reduced from 5.3± 4.4 to 0.4±0.7 (p=0.001), and the mean number of joints with limited motion dropped from 3.8±3.10 to 0.8±1.3 (p=0.002). The percentage of patients who had no fever ameliorated to 100% compared to 33.3% only at baseline (p=0.021), and the proportion of patients who had no rash increased from 66.7 to 100% (p=0.032). The median physician's global VAS score diminished from 6 to 1 (p=0.001). Statistically significant reduction in several laboratory markers of active disease was also reported, for instance, the median ESR decreased from 30 to 5 (p=0.001) and the median CRP dropped from 12 to zero (p=0.016). The reported adverse effects post Tocilizumab were limited and occurred at a low rate, this included gastroenteritis (13.3%) and acute focal pneumonia (13.3%). Neutropenia was the only laboratory abnormality, and was found in one case (6.7%). **Conclusion:** The overall risk/benefit profile of Tocilizumab used among SoJIA pediatric patients was acceptable, as indicated by the significant practical improvement in clinical symptoms and laboratory findings. This provides further support to previous research findings on the effectiveness of Tocilizumab to treat patients with SoJIA.

**Keywords:** Efficacy, safety, Tocilizumab use in Systemic Onset Juvenile Idiopathic Arthritis.

INTRODUCTION

Systemic-onset juvenile idiopathic arthritis (SoJIA) is characterized by chronic course of arthritis, persisting systemic manifestations (fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis), and by significant elevation of inflammatory markers (leukocyte count, platelet count, ESR, CRP, and ferritin) (Petty *et al.*, 2004). SoJIA is the most severe type of juvenile idiopathic arthritis (JIA), is associated with severe joint damage, prolonged course, poor outcome with severe functional impairment and disability, and usually refractory to treatment (Lomater *et al.*, 2000; Ravelli and Martini, 2007) Treatment of SoJIA is a challenging situation in pediatric rheumatology practice due to inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs) and non-biological disease modifying anti rheumatic drugs (DMARDs) as methotrexate (Woo *et al.*, 2000) as well as due to development of severe adverse effects caused by glucocorticoid therapy. The clinical and laboratory manifestations of SoJIA are mediated by dysregulation and continuous production of interleukin 6(IL6) both in blood serum and in synovial fluid (De Benedetti and Martini, 1998). IL6 is a proinflammatory cytokine that plays an important role in the articular and extra articular manifestations of the disease.

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. Increased concentrations of IL6 blocks production of adrenocorticotrophic hormone, cortisol, and growth hormone, which results in fatigue, sleepiness, depression, cognitive impairments, and growth retardation in children with SoJIA. Amyloidosis, a severe complication of this disease, is also associated with activity of this cytokine. Tumor necrosis factor inhibitors (TNF) as a rule are in-effective in treatment of SoJIA (Horneff *et al.*, 2009; Prince *et al.*, 2009). Inhibition of IL6 at this type of the disease is more promising. Tocilizumab is a recombinant humanized monoclonal antibody that binds to IL6 receptors and commonly used for treatment of SoJIA either alone or in combination with methotrexate. Tocilizumab is an effective treatment that reduces the signs and symptoms of disease, and improves quality of life and physical functioning in patients with SoJIA. With Positive results from a number of clinical studies on efficacy and safety of tocilizumab therapy in children SoJIA constituted a ground for approving the drug for treatment of SoJIA (Yokota *et al.*, 2009). Although several researches have studied the effectiveness and safety of tocilizumab in systemic onset

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juvenile idiopathic arthritis, this is the first report from the Libyan clinical settings. This study evaluated the effectiveness and safety of the interleukin-6 receptor inhibitor; tocilizumab for the treatment of children with Systemic-onset juvenile idiopathic arthritis (SoJIA) in Tripoli children's hospital.

## METHODS

This is retrospective, consecutive case series study. The study was undertaken in the rheumatology clinic at Tripoli Children Hospital after obtaining the approval from the relevant authorities at the hospital. Tripoli Children hospital is a tertiary and teaching hospital in Tripoli, Libya. It is the only referral center in the west region of Libya, and the only center that includes pediatric rheumatology. All medical records of children on follow-up at rheumatology clinic in the period from May 2015 to June 2020 were screened for SoJIA cases. All identified patients who have received Tocilizumab therapy for duration of at least 12 weeks were included in the study. Exclusion criteria were receiving Tocilizumab for less than 12 weeks and inadequacy of follow-up data on most of the study variables. The included patients had received Tocilizumab in a dose between 8 and 12mg/kg of body weight depending on their disease. Infusions were received every 2 weeks. Data extracted from medical records of the eligible patients included their demographic characteristics like age, sex and nationality, as well as selected clinical profile data. For tocilizumab safety assessment, medical records were screened for selected adverse outcomes that could be developed post treatment with some medications of juvenile idiopathic arthritis like Methotrexate and steroid. We focused on infections, macrophage activation syndrome (MAS), and selected laboratory parameters like neutrophils and platelets counts, as well as alkaline phosphatase and transaminases levels. For the evaluation of the effectiveness of Tocilizumab, we extracted data reported at baseline (before starting Tocilizumab), and 12 weeks post Tocilizumab use that are relevant to disease activity. These included clinical manifestations like the number of joints with active arthritis, the number of joints with limitation of motion, fever, rash and the global physical VAS score. Data on selected laboratory markers of active disease, like electrolyte sedimentation rate (ESR) and C- reactive protein (CRP), were also extracted from medical records. The statistical package for social science (SPSS) version 26 was used for data analysis. Frequency and percentage were used to present the categorical data. Mean and standard deviation, and median along with the interquartile range, were used as appropriate to the type of distribution to summarize the continuous data. Paired t test, Wilcoxon Signed-rank, and Exact McNamara's tests were used, as appropriate to data type and distribution, to examine for any significant differences between baseline and post-tocilizumab treatment assessments. For the continuous variables, when data met the assumptions of normality, Paired t test was used to test for significant mean differences between baseline and post-treatment assessments. However, when variables violated the normality assumptions, Wilcoxon Signed-rank was used to test for any significant median differences before and after the treatment. For the categorical variables, Exact McNamara's test was used to examine for significant changes in proportions before and after treatment. The statistical significance level was set at  $p < 0.05$ . The effect sizes were also reported to show the magnitude of the difference after treatment for the statistically significant results, and thus their practical significance. The effect size

Cohen's d (d) was used with paired t-test, while the effect size r was used with Wilcoxon Signed-rank test.

## RESULTS

A total of 15 SoJIA patients were eligible and included in the analysis. Table 1 summarizes the baseline demographic, clinical and laboratory characteristics of those patients (before starting Tocilizumab treatment). The mean age of patients was 10.9 (SD=3.6) years old, and males constituted 53.3% of them.

**Table 1. Baseline demographic, clinical and laboratory characteristics of patients (n=15)**

Characteristic	f	(%)
<b>Gender</b>		
Male	8	(53.3)
Female	7	(46.7)
Age (yrs) (Mean±SD)	10.9	±3.6
<b>Nationality</b>		
Libyans	13	(86.7)
Non-Libyans	2	(13.3)
<b>Disease activity assessment</b>		
Continued	5	(33.3)
Minimum	1	(6.7)
Moderate	4	(26.7)
High	4	(26.7)
Flare	1	(6.7)
<b>Fever</b>		
Yes	10	66.7
No	5	33.3
<b>Rash</b>		
Yes	5	33.3
No	10	66.7
Physical global VAS score <sup>†</sup>	6.0	(11-5)
<b>Morning stiffness &gt;15 min (n=14)</b>		
Yes	12	(80.0)
No	2	(13.3)
<b>Number of joints with Active arthritis<sup>‡</sup></b>	5.3	±4.4
None	2	13.3
1-2 joints	3	20.0
3 joints	1	6.7
4-5 joints	2	13.3
> 5 joints	7	46.7
<b>Number of joints with limited motion<sup>‡</sup></b>	3.8	±3.1
None	2	13.3
1-2 joints	5	33.3
3 joints	1	6.7
4-5 joints	1	6.7
> 5 joints	6	40.0
<b>ESR (mm/hr)<sup>†</sup></b>	30	(95-15)
High ESR	9	(60.0)
Low ESR	6	(40.0)
<b>CRP (mg/l)<sup>†</sup></b>	12	(24-6)
Positive	12	(80.0)
Negative	3	20.0
<b>Platelets (10<sup>3</sup>/μl)<sup>†</sup></b>	416	(612-360)
High	6	(40.0)
Normal	9	(60.0)
<b>Haemoglobin (g/dl)<sup>‡</sup></b>	11.0	±1.4
Low	7	46.7
Normal	8	53.3
<b>WBC (10<sup>3</sup>/μl)<sup>†</sup></b>	10.8	(15.1-6.4)
High	5	33.3
Normal	10	66.7
<b>Neutrophils (%)<sup>‡</sup></b>	52.7	±20.1
<b>Lymphocytes (%)<sup>‡</sup></b>	38.1	±17.0

<sup>†</sup> Median (IQR), <sup>‡</sup> Mean± SD

Disease activity assessment revealed a continued activity in 33.3% of cases, while the majority of others had either moderate (26.7%) or high activity (26.7%). Fever was reported in 10 (66.7%) cases, and rash in 5 (33.3%). The median physical global VAS score was 6.0. (IQR=6), with 12 (80%) out of 14 patients had morning stiffness. The mean number of

joints with active arthritis among the patients was 5.3 (SD=4.4), with 7(46.7%) them had more than 5 joints with active arthritis. The mean number of joints with limited motion was 3.4 (SD=3.1) joints, with 6 (40%) patients had more than 5 joints with low motion. ESR was high in 60.0% of patients, and CRP was positive in 80.0% of them. Thrombocytosis and anemia were reported in 40.0% and 46.7% of patients respectively. Leukocytosis was found in 33.3% of patients, and the mean neutrophils was 52.7 (SD=20.1) %.

**Table 2** presents the observed adverse outcomes post Tocilizumab treatment, focusing on infections, macrophage activation syndrome (MAS), and selected laboratory parameters. The reported infections among patients were limited, and occurred at low frequencies. These included, gastroenteritis (13.3%) and acute focal pneumonia (13.3%). Neutropenia was the only laboratory abnormality, and was found in one case (6.7%). None of the patients developed MAS.

**Table 2. Frequency of the reported adverse outcomes in post Tocilizumab treatment**

Variable	Yes		No	
	f	(%)	f	(%)
Infections				
Gastroenteritis	2	(13.3)	13	(86.6)
Pneumonia	2	(13.3)	13	(86.6)
Nasopharyngitis	0	(0.0)	15	(100)
URTI	0	(0.0)	15	(100)
Pneumonia	0	(0.0)	15	(100)
Cellulitis	0	(0.0)	15	(100)
Herpes zoster	0	(0.0)	15	(100)
Laboratory abnormality				
Neutropenia	1	(6.7)	14	(93.3)
Thrombocytopenia	0	(0.0)	15	(100)
Elevated alkaline phosphatase	0	(0.0)	15	(100)
Elevated aminotransferases	0	(0.0)	15	(100)
Macrophage activation syndrome	0	(0.0)	15	(100)

**Table 3** shows a comparison of the clinical and laboratory assessments of the patients before and after 12 weeks of Tocilizumab treatment. The mean number of joints with active arthritis was lower (mean=0.4, SD=0.7) in the post treatment, than in the pre-treatment (mean= 5.3, SD=4.4) assessment, and the mean difference was statistically significant ( $t=4.191$ ,  $p=0.001$ ), with a large effect size ( $d=1.10$ ).

Likewise, the mean number of joints with limited motion was lower (mean=0.8, SD=1.3) in the post treatment, than in the pre-treatment (mean= 3.8, SD=3.1) assessments, and the mean difference was statistically significant ( $t=3.756$ ,  $p=0.002$ ), with a large effect size ( $d=0.96$ ). The percentage of patients who had no fever after tocilizumab treatment was higher (100%) than the proportion of those who had no fever before the treatment (33.3%), and the difference was statistically significant ( $p=0.021$ ). Likewise, the proportion of patients who had no rash after tocilizumab treatment was higher (100%) than the proportion of those who had no rash before the treatment (66.7%), and the difference was statistically significant ( $p=0.032$ ). The median physician's global VAS score post tocilizumab was lower (Mdn=1) than its median before the start of treatment (Mdn=6), and the median difference was statistically significant ( $Z=-3.219$ ,  $p=0.001$ ), with a large effect size ( $r=0.58$ ). Statistically significant changes in several laboratory characteristics were also reported after tocilizumab use.

A statistically significant reduction in median ESR was found following the use of tocilizumab ( $Z=-3.409$ ,  $p=0.001$ ), with a large effect size ( $r=0.62$ ). The median ESR decreased from pre-treatment (Mdn=30) to post treatment (Mdn=5). The median post treatment CRP (Mdn=0) was also statistically significantly lower than the median pre-treatment CRP (Mdn=12) ( $Z=-2.414$ ,  $p=0.016$ ), and the effect size ( $r$ ) was 0.44, which indicates a medium magnitude of change. Concerning thrombocytosis, the median platelets count decreased from pretreatment (Mdn=416) to post treatment (Mdn=299), and the median difference was statistically significant ( $Z=-3.237$ ,  $p=0.001$ ), with a large effect size ( $r=0.59$ ). Improvement in haemoglobin level was also reported, whereby the mean haemoglobin level after tocilizumab use was higher (Mean=12.6, SD=0.09) than its mean before the start of treatment (Mean=11.0, SD=1.4), and the mean difference was statistically significant ( $t=-6.472$ ,  $p<0.001$ ), with a large effect size ( $d=1.67$ ). While no statistically significant change in the mean neutrophils or lymphocytes counts were found, the median white blood cells count before treatment (Mn=10.0) was decreased after treatment (Mn=7.7), and the median difference was statistically significant ( $Z=-3.039$ ,  $p=0.002$ ), with a medium effect size ( $r=0.55$ ).

**Table 3. Comparison of clinical and laboratory assessments before and after 12 weeks of Tocilizumab treatment (n=15)**

Characteristic	Baseline		After 12 weeks		Z statistic <sup>b</sup>	P value	Effect size (r) <sup>†</sup>
	Median	IQR	Median	IQR			
Number of joints with active arthritis	5.3	±4.4 <sup>a</sup>	0.4	±0.7 <sup>a</sup>	4.191 <sup>c</sup>	0.001*	1.105 <sup>‡</sup>
Number of joints with LOM <sup>§§</sup>	3.8	±3.1 <sup>a</sup>	0.8	±1.3 <sup>a</sup>	3.756 <sup>c</sup>	0.002*	0.969 <sup>‡</sup>
<b>Fever</b>							
Yes (f, %)	10	66.7	0	0.0	- <sup>d</sup>	0.001* <sup>c</sup>	
No (f, %)	5	33.3	15	100.0			
<b>Rash</b>							
Yes (f, %)	5	33.3	0	0.0	- <sup>d</sup>	0.032* <sup>c</sup>	
No (f, %)	10	66.7	0	100.0			
VAS score <sup>§</sup>	6.0	11-5	1	1-1	-3.219	0.001*	0.588
ESR (mm/hr)	30	95-15	5	6-5	-3.409	0.001*	0.62
CRP (mg/l)	12	24-6	0	0-0	-2.414	0.016*	0.44
Platelets (10 <sup>3</sup> /μl)	416	612-360	299	310-242	-3.237	0.001*	0.59
Hemoglobin (g/dl)	11.0	±1.4 <sup>a</sup>	12.6	±0.9 <sup>a</sup>	-6.472 <sup>c</sup>	0.000*	1.67 <sup>‡</sup>
WBC (10 <sup>3</sup> /μl)	10.8	15.1-6.4	7.7	8.3-5.4	-3.039	0.002*	0.55
Neutrophils (%)	52.7	±20.1 <sup>a</sup>	46.7	±21.2 <sup>a</sup>	0.826 <sup>c</sup>	0.423	0.213 <sup>‡</sup>
Lymphocytes (%)	38.1	±17.0 <sup>a</sup>	40.7	±15.4 <sup>a</sup>	-0.595 <sup>c</sup>	0.562	0.125 <sup>‡</sup>

\* $p<0.05$ , <sup>a</sup> mean± SD, <sup>b</sup> Z statistic (Wilcoxon rank sum test), <sup>c</sup> t statistic (paired t test), <sup>d</sup> Exact McNemar test, <sup>e</sup> Mid p value (Exact sig. 2 tailed- point probability) <sup>†</sup> r size effect, <sup>‡</sup> Cohen d effect size, <sup>§</sup> Physical global Visual Analog Scale score, <sup>§§</sup> Limitation of Motion

## DISCUSSION

Tocilizumab is a humanized monoclonal antibody targeting both the membrane bound and soluble IL-6 receptor. In 2003 the first report was published showing encouraging use of IL-6 blocker in children suffering from SoJIA (Yokota, 2003). Tocilizumab shows both high effectiveness and a satisfactory drug safety profile, which makes it an invaluable treatment option even as monotherapy (Turnier and Brunner, 2016). We describe the tolerability profile of Tocilizumab in fifteen children followed in a pediatric rheumatology department the findings from the present study retrospective consecutive case series showed that intravenous Tocilizumab may be acceptable for treating SoJIA. The percentage of patients with SoJIA-associated symptoms, such as fever, rash and arthritis, significantly decreased after treatment with Tocilizumab, Clinical improvement was observed in all patients, 100 % for fever and rash (P=0.001, p= 0.031 respectively), the median number of joint with active arthritis 0.4(p=0.001), the median number of joint with LOM 0.8 (P=0.002) and the median physicians global VAS score 1(p=0.001) after treatment with Tocilizumab, which is a higher success rate than previously reported (Saini *et al.*, 2016; Yokota *et al.*, 2012; Zhang *et al.*, 2017). Adverse events which reported in our study were low 13.3% gastroenteritis, 13.3% pneumonia, while the frequency for nasopharyngitis, URTI, cellulites, herpes zoster were nil, as previously reported (12) The laboratory changes after 12 weeks Tocilizumab treatment includes significant reduction in ESR (P=0.001) and CRP (P=0.016), Patients with chronic inflammation usually have mild to moderate anemia driven largely by hepcidin, a peptide hormone induced by IL-6. IL-6 receptor inhibition by TCZ treatment in our study possibly resulted in marked improvement in hemoglobin level from 11 gm/dl to 12.6 gm/dl among cases at 12 weeks treatment, with no change in lymphocyte count(p= 0.562), neutropenia was the most common biological adverse event, and increased liver enzymes were not reported as well, but treatment was not modified, which are the study by Yokota *et al.* (2012). No cases of macrophage activation syndrome and no anaphylactic reactions were reported. TCZ was never stopped for a clinical adverse event. Among them 15 patients achieved remission with tocilizumab treatment for 12 weeks. Thus, it can be speculated that anti IL-6 treatment is very beneficial in this specific group of patients. The major limitation of the present case series was its single-center retrospective design. The small number of patients, short follow-up and the absence of a control group limited the evaluation of the effect of treatment in this case series.

## Conclusion

This retrospective small series described patients with systemic onset juvenile idiopathic arthritis that had been response to Tocilizumab therapy with limited adverse effect.

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