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ORIGINAL ARTICLE

Outcomes of Tocilizumab on the Disease Activity in Children with Juvenile Idiopathic Arthritis

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ABSTRACT

Background: Juvenile idiopathic arthritis (JIA) comprises a spectrum of chronic inflammatory joint disorders characterized by joint pain, swelling, stiffnessand restricted mobility in affected children. The interleukin-6 (IL-6) inhibitors, tocilizumab (TCZ), have been researched and authorized for the treatment of rheumatoid arthritis.This study aimed to evaluate the efficacy of tocilizumab in reducing the severity of clinical manifestations in children with Juvenile Idiopathic Arthritis (JIA), specifically those who were resistant to methotrexate and as a first-line treatment for Systemic Juvenile Idiopathic Arthritis (SJIA) patients. **Methods:** This prospective cohort study was carried out in Rheumatology and Clinical immunology unit, department of pediatrics, Zagazig University hospitals, during the period from March 2023 to October 2023. This study included 22 patients with JIA (13 Systemic JIA, 7 Polyarticular JIA and 2 Extended Oligoarticular JIA). Their ages ranged from 3to 15 years. They met the American College of Rheumatology (ACR) classification criteria for active disease despite conventional therapy; that indicated treatment by TCZ. Disease activity scores were assessed using the Juvenile Arthritis Disease Activity Score (JADAS 10) and CBC, ESR, CRP, with ferritin. **Results:** Before treatment (TCZ), all patients had high disease activity. Four months after introduction of TCZ, all patients with non-systemic JIA and 69.2% of patients with systemic JIA scored low disease activity. **Conclusions:** TCZ is the drug of choice as first-line biologic disease-modifying antirheumatic drugs (bDMARDs) in sJIA, and considered highly effective in Extended Oligoarticular JIA and Polyarticular JIA who do not respond to 3monthes course of methotrexate.

Keywords: Tocilizumab, Juvenile idiopathic arthritis, Interleukin-6, Disease Activity.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most prevalent form of chronic arthritis in children. Joint involvement typically begins with synovitis and effusion; it mostly affects children younger than 16 years of age and lasting for six weeks or longer. While the precise etiology of JIA remains unclear, it is

believed to arise from a complex interplay of genetic predisposition and environmental factors **[1]**.JIA encompasses seven distinct subtypes, each is distinguished by particular clinical features, including joint patterns and extra-articular manifestations**[2]**.Notably, systemic juvenile idiopathic arthritis (sJIA) emerges as the most severe subtype, characterized by systemic inflammation marked by fever, lymphadenopathy, arthritis, rash and serositis**[3]**.

Disease-modifying antirheumatic medications (DMARDs) are not effective for many people with polyarticular JIA and extended oligoarticular JIA. Individual responses to these medications can differ significantly and some patients may experience treatment resistance or complications. Therefore, it is important to implement early intervention strategies to manage the disease and reduce the long-term complications associated with JIA**[4]**.Complications in these patients may include persistent arthritis, growth retardation, osteoporosis, vision impairment (especially due to uveitis) and dyslipidemia**[5]**.

There was strong evidence indicating thecrucial role of cytokines (particularly IL-6) in the pathogenesis of JIA.Interleukin-6 (IL-6) has been demonstrated to play a role in various physiological processes, including the activation of T-cells, the induction of immunoglobulin secretion, the commencement of hepatic acute phase protein synthesis and the stimulation of hematopoietic precursor cell proliferation and differentiation. Interleukin-6 (IL-6) is synthesized by synovial and endothelial cells, hence inducing the localized synthesis of IL-6 within inflamed joints. Tocilizumab is the first receptor (IL-6) antagonist**[6]**.

In the year 2011, regulatory authorities in both the United States and Europe provided their clearance for the use of tocilizumab (TCZ). This particular medication is a humanized monoclonal antibody that specifically targets the receptor for interleukin-6 (IL-6). as a therapeutic intervention for children with sJIA. Subsequently, TCZ received approval for treating active polyarticular juvenile idiopathic arthritis (PJIA) in 2013. Importantly, TCZ has also demonstrated efficacy in the management of oligo juvenile idiopathic arthritis (OJIA) **[7]**.This study aimed to assess the efficacy of tocilizumab in reducing the severity of clinical manifestations and inflammatory markers as indicators of disease activity in children with Juvenile Idiopathic Arthritis who exhibited resistance to treatment with methotrexate.

METHODS

After protocol approval by our Local Ethics Committee (IRB # 10480-26-2-2023), this study was carried out at Pediatric Rheumatology and Clinical Immunology unit, department of pediatrics, Zagazig University hospitals, during the period from March 2023 to October 2023. Parental written informed consent was obtained for each patient before enrollment in the study. The study's protocol complied with the Helsinki Declaration, which is the World Medical Association's code of ethics for research on humans.

This prospective cohortstudy included 22 childrentheir ages range from3 to 15 years diagnosed with juvenile idiopathic arthritis according to criteria settled by American College of Rheumatology (ACR).The inclusion criteria were; children aged below 16 years and are diagnosed with Juvenile idiopathic arthritis according to criteria settled by American College of Rheumatology (ACR). Exclusion criteria: Children who hadcertain preexisting diseases as cardiovascular or pulmonary illness, liver function abnormalities andmalignancies. Additionally, patients who have not completed a 3-months course of methotrexate. All participants were subjected to full history taking, assessment of the affected joints and surrounding tissues include; inspection of the joints for any signs of swelling, redness or deformity. Palpation by gently touching and feeling the joints to check for tenderness, warmth or fluid accumulation. Testing the strength of the muscles around the affected joint by asking the child to push or pull against resistance. In addition to functional assessment by evaluating how well the child

is able to perform daily activities such as walking, dressing, and grooming.

Assess the efficacy of treatment: The Juvenile Disease Activity Score (JADAS 10) is an imperative tool for the assessment of changes in disease activity. It is composed of the following four measures: physician's global assessment of disease activity, measured on a 0- 10 visual analogue scale (VAS) where 0 means no activity and 10 means maximum activity; parent global assessment of wellbeing, measured on a 0-10 VAS where 0 means very well and 10 means very poor; ESR, normalized to a 0 to 10 scale as follows: (ESR (mm/h)−20)/10 ; and the number of joints with active disease**[8].**

JADAS 10 =AJC+physician global +parent global (10cmVAS) +ESR(normalized).

The total score of JADAS 10 is calculated by simply summing the scores of its four components (range 0–40). Higher scores indicating more disease activity. Greater than or equal to 10 indicates high disease activity. The SJADAS score is calculated as the straightforward linear sum of its five component scores, yielding a global score between 0 and 50. depending on the version of the score being used. A score of 0-10 indicates inactive disease, while scores above 20 are considered high disease activity. Systemic Manifestation Score (SMS) range from0 to 10 according to systemic manifestations of JIA: fever(4), rash(1), generalized lymphadenopathy(1), hepatomegaly and/or splenomegaly(1), serositis(1), anemia(1) and platelet or ferritin levels(1) **[9]**.

VAS physician score (It is typically measured on a 0-10 visual analog scale (VAS), where 0 represents no disease activity and 10 represents the highest level of disease activity.VAS patient score allows patients to rate their overall well-being or intensity of pain on a scale, typically,on a scale of 0 to 10, with 0 denoting the optimal condition and 10 indicating the least favorable state**[8]**.

Polyarticular Juvenile Idiopathic Arthritis (PolyJIA): Low Disease Activity: JADAS 10 ≤ 2.5. Moderate Disease Activity: JADAS 10 >2.5 to ≤4.5.High Disease Activity: JADAS 10 > 4.5. Oligoarticular Juvenile Idiopathic Arthritis (OligoJIA):Low Disease Activity: JADAS 10 ≤ 1. Moderate Disease Activity: JADAS 10 >1 and ≤ 3.8 High Disease Activity: JADAS 10 > 3.8**[10]**.

Imaging tests X-rays, ultrasound or MRI scans were indicated for some patients to get a more detailed view of the affected joints and surrounding tissues.Laboratory Investigations included Complete blood count (CBC). C reactive protein (CRP), Rheumatoid Factor (RF), Antinuclear Antibody (ANA), the erythrocyte sedimentation rate (ESR) and Ferritin level.

Treatment details: Tocilizumab treatments started after 3 months of methotrexate with no/unsatisfactory clinical and laboratory improvement as following: Systemic JIA (sJIA): Tcz was administered as 60-minute single intravenous drip infusion every 2 weeks, the dose was 12mg per kg (<30kg) and 8mg per kg for patients weighing 30 kg or more.For Polyarticular JIA and oligoarticular JIA, patients weighing 30 kg or more received a monthly dose of 8 mg/kg tocilizumab, while patients weighing less than 30 kg received 10 mg/kg**[11]**. The duration tocilizumab was for 4 months. The assessment of disease severity by checking the clinical response and the inflammatory markers.

Statistical analysis: Descriptive statistics were employed to provide a summary of patient demographics and baseline characteristics. Paired t-tests or Wilcox on signed-rank tests were employed to assess the statistical significance of the differences observed in the measures of inflammatory markers and disease activity levels between baseline and week 16.

RESULTS

For statistical purposes, patients were classified into two groups; systemic JIA and non-systemic (Poly and Extended Oligoarticular JIA) (figure 1). Table 1; showed that non-significant difference between the studied groups regarding gender, age, and disease duration.

Table 2; showed that statistically significant difference between the studied groups regarding number of active joints

(significantly higher in non-systemic group). After treatment by tocilizumab, none of the patients exhibited active joint involvement. There is non-significant difference between the studied groups regarding VAS for patient before or after treatment. Within each group, there is significant decrease in VAS patient score. There was statistically non-significant difference between the studied groups regarding VAS for physician before treatment. Within each group, there is significant decrease in VAS physician score. There was statistically significant difference between the studied groups regarding JADAS score before and after treatment (both are significantly higher among patients with systemic JIA). Within each group, there is significant decrease in JADAS-10 score after treatment. There was statistically significant decrease in SJADAS score among patients with systemic JIA before and after treatment.

Table 3 showed that before treatment, all patients had high disease activity. After treatment, all patients with non-systemic JIA had low disease activity while those with systemic JIA, 69.2% had low disease activity yet with statistically non-significant difference between groups.

Table 4 showed that the differences are statistically Significant in all inflammatory markers. Before TCZ treatment elevated ESR in both groups, and non-significance difference between both groups. There is significant improvement in all laboratory inflammatory markers after treatment. The Systemic JIA group exhibited higher inflammatory markers (ESR, CRP, WBCs, and platelets) and lower Hb, as well as higher ferritin levels compared to the non-systemic JIA group, both before and after treatment with tocilizumab.

In systemic JIA group, table 4there was significant decrease in platelet count while there is non-significant change in non-systemic JIA. There was a significant decrease in ESR, CRP, WBCs, ferritin or platelet count, and significant increase in hemoglobin.

Table (1) Comparison between the studied groups regarding demographic data and disease duration:

	Systemic JIA	Non-systemic JIA	χ^2	p
	N=13 (%)	N=9 (%)		
Demographic data				
Gender: Female Male	 8 (61.5%) 5 (38.5%)	 7 (77.8%) 2 (22.2%)	MC	0.795
	Mean ± SD	Mean ± SD	F	p
Age (year)	7.69 ± 4.66	9.58 ± 4.24	0.508	0.606
	Median (IQR)	Median (IQR)	Z	P
Disease duration:	9(6 – 13.5)	12(9.5 – 18)	-1.526	0.127

F: One way ANOVA test, MC: Monte Carlo test, χ^2: Chi square test . Z: Mann Whitney test, IQR; interquartile range

Table (2) Comparison between the JIA groups before and after treatment (TCZ) regarding elements of Disease Activity Score

	Systemic JIA	Non-systemic JIA	Z	p
	Median (IQR)	Median (IQR)		
Regarding number of affected joints				
No of active joints Before After	 3(1 – 7.5) 0	 8(6 – 8.5) 0	 -2.034 -	 0.042* -
VAS score for patient and physician				
VAS patient Before After	 9(8 – 10) 1(0 – 1)	 9(8 – 9.5) 0(0 – 1)	 -0.036 -1.037	 0.972 0.3
P (Wx)	<0.001**	<0.001**		
VAS physician Before After	 9(8 – 10) 0(0 – 1)	 9(8 – 10) 0(0 – 0)	 -0.106 -2.319	 0.916 0.02*
P (Wx)	<0.001**	<0.001**		
	SJADAS10 (0-50)	JADAS10 (0-40)		
Before After	37(36.25–39.25) 2(1 – 3)	33(28.5 – 35.25) 0(0 – 1)	-2.778 -3.053	0.005* 0.002*
P (Wx)	0.001**	0.008*		
Systemic Manifestation Score (0-10) Before After	 5(3 – 7) 1(0 – 1)	-		
P (wx)	0.003*	-		

Z: Mann Whitney test, IQR: interquartile range, *p<0.05 is statistically significant§ Chi square test, Z: Mann Whitney test, WX: Wilcoxon signed rank test, .p≤0.001 is statistically highly significant,VAS:Visual Analog Scale,JADAS: Juvenile Arthritis Disease Activity Score,SJADAS: Systemic Juvenile Arthritis Disease Activity Score.

Table (3) Comparison between the JIA groups before and after treatment (after 4 months)regarding disease activity score

	Systemic JIA	Non-systemic JIA	χ^2	p
	N=13 (%)	N=9 (%)		
Pretreatment High	13 (100%)	9 (100%)	-	-
Post treatment Low activity Moderate High	9 (69.2%) 4 (30.8%) 0 (0%)	9 (100%) 0 (0%) 0 (0%)	Fisher§	0.115

§ Chi square test Z , pt: paired sample t test, t: Independent sample t test

Table (4) Comparison between the JIA groups regarding laboratory data before and after treatment (4months)

	Systemic JIA	Non-systemic JIA	t	p
	Mean ± SD	Mean ± SD		
ESR Before After	 120 ± 20 14.15 ± 2.67	 94.44 ± 37.37 12.56 ± 3.4	 2.085 1.236	 0.05 0.231
P (pt)	<0.001**	<0.001**		
CRP Before After	 110.23 ± 14.88 4.46 ± 1.2	 58.89 ± 29.87 2.89 ± 0.93	 5.35 3.303	 <0.001** 0.004*
P (pt)	<0.001**	<0.001**		
	Systemic JIA	**Non-systemic JIA**	**t**	**p**
WBCs Before After	 16.12 ± 3.88 8.97 ± 1.07	 12.89 ± 2.48 10.92 ± 1.33	 2.192 2.606	 0.04* 0.017*
P (pt)	<0.001**	<0.001**		
Hemoglobin **Before** **After**	 8.74 ± 1.14 10.95 ± 0.63	 10.73 ± 0.62 11.88 ± 0.48	 -5.29 -3.842	 <0.001** 0.001**
P (pt)	<0.001**	<0.001**		
	Median (IQR)	**Median (IQR)**	**Z**	p
Platelet **Before** **After**	 618(465 – 675) 350(300 – 375)	 320(295 – 350) 300(252.5 – 305)	 -3.111 -2.116	 0.002* 0.034*
P (Wx)	0.001**	0.008*		
Ferritin **Before** **After**	 2500(1096 – 3080) 300(170 – 375)	 210(189 – 1022.5) 100(87.5 – 135)	 -2.813 -2.722	 0.005* 0.006*
P (Wx)	0.001**	0.058		

Pt: paired sample t test, t: Independent sample t test, Z: Mann Whitney test .IQR: interquartile range, WX: Wilcoxon signed rank test, *p<0.05 is statistically significant

**p≤0.001 is statistically highly significant

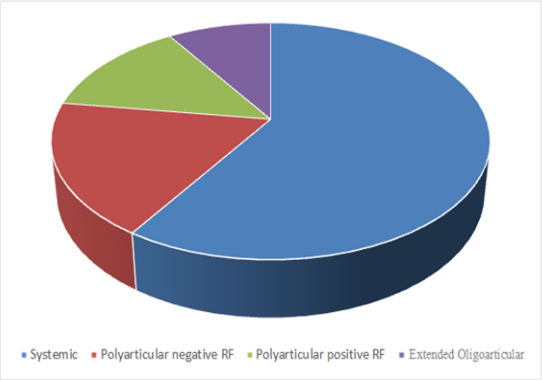

Figure (1) Pie chart showing distribution of studied patients according to JIAsubtypes

DISCUSSION

This study encompassed 22 patients diagnosed with Juvenile Idiopathic Arthritis (JIA). Among the patients, 13 had systemic JIA, 7 had Polyarticular JIA and 2 presented with Extended Oligoarticular JIA. Within the Polyarticular JIA subgroup, 3 patients tested positive for rheumatoid factor (RF), while 4 tested negative. Notably, a predominance of females was observed in both the systemic JIA group (61.5%) and the non-systemic JIA group (77.8%). Importantly, the study revealed no statistically significant differences in gender or age between the groups under investigation. In agreement with our work a study carried by Muzaffer et al[7]their patient population had slight female gender predominance. Also, Marangoni et al[12] found a clear female predominance among the 28 patients studied with Polyarticular JIA .It is well known that females are more commonly affected by JIA than males[3].

This study revealed significant differences among the studied groups concerning the Juvenile Arthritis Disease Activity Score (JADAS 10) before and after 4mths of TCZ treatment. Notably, JADAS scores were significantly higher among patients with systemic JIA than nonsystemic JIA group before treatment, indicating the severity of systemic manifestations[13].However, within each group, there was a significant decrease in the JADAS-10 score after TCZ treatment, indicating a positive response to the intervention.The mean SJADAS 10 & JADAS-10 scores for the systemic JIA group and the non-systemic group before tocilizumab treatment were 37 and 33, respectively. These scores decreased significantly to 2 and 0, respectively, 4 months after the initiation of tocilizumab treatment (P = 0.001, 0.008). These findings suggest that tocilizumab treatment leads to a notable reduction in JADAS-10 scores during the follow-up period, reflecting improved disease activity.These findings were close to the findings of Muzaffer et al[7]in Saudi Arabia, utilized JADAS-10. Prior to starting TCZ, the average number was 22.4 (± 7.9). After three, six, twelve and twenty-four months of taking TCZ, the score went down statistically significantly, with means of 5.7 (± 3.9), 4.4 (± 3.7), 3.5 (± 3.1), and 2.7 (± 2.2) (P = 0.001, 0.001, 0.005, and 0.012, respectively. This shows that the JADAS-10 score went down during the follow-up period. De Benedetti et al[13]. Demonstrated significant improvements in sJIA patients treated with TCZ, with 85% achieving JIA the American College of Rheumatology (ACR) 30 response at 3 months, 80% achieving JIA ACR 70 at 12 months and 59% achieving JIA ACR 90. In addition, 32% had clinically inactive illness and 48% had no arthritis.

In the present work, before treatment, all patients exhibited high disease activity. However, after tocilizumab treatment, all

patients with non-systemic JIA achieved low disease activity status, while among those with systemic JIA, 69.2% achieved low disease activity. Importantly, there was no statistically significant difference in disease activity between these two groups after treatment. These results emphasize the positive impact of tocilizumab treatment in reducing disease activity in JIA patients, particularly in those with non-systemic JIA. However, it's important to note that disease activity can fluctuate over time and may require ongoing monitoring and adjustment of treatment. These results were in accordance with Kasapçopur, & Barut [14], reported improvement in disease activity as a result of treatment in patients with treatment-resistant Polyarticular JIA.

By further analyzing our data, significant changes were observed within each group regarding several clinical parameters before and after tocilizumab (TCZ) treatment over a 4-month period. In the SJIA group, before TCZ treatment, patients exhibited elevated inflammatory markers, with a mean Erythrocyte Sedimentation Rate (ESR) of 120 mm/h and C - reactive protein (CRP) levels of 110 mg/L, indicating significant inflammation compared to ESR (94.4) and CRP(58.8) in nonsystemic JIA group which were lower than those in SJIA group. ESR and CRP increase in response to inflammation which triggers the liver to produce more acute-phase proteins[15].

Elevated ferritin levels are a notable characteristic in children with Juvenile Idiopathic Arthritis (JIA), particularly in those with systemic onset JIA. In this study, ferritin levels in the SJIA group were significantly elevated (mean: 2500 ng/dL) compared to the nonsystemic JIA group (mean: 210 ng /dL), indicating more pronounced inflammation. Research on children with systemic JIA has indicated that a majority, ranging from 60% to 70%, tend to develop hyperferritinemia, especially during active disease phases[16].German consensus-based diagnostic strategies for Systemic Juvenile Idiopathic Arthritis (SJIA) recommend considering the possibility of SJIA in a febrile child with confirmed hyperferritinemia [17].However, following tocilizumab treatment, there was a remarkable improvement in these parameters. Mean ESR and CRP levels substantially decreased to 14.15 mm/h and 4.46 mg/L, respectively, indicating a significant reduction in inflammation. Our findings align with those reported by Nada et al[18].who also demonstrated a significant improvement in serum ferritin levels, ESR and CRP following treatment with tocilizumab (TCZ). This consistency in results reinforces the positive impact of TCZ on disease markers in patients with systemic Juvenile Idiopathic Arthritis (sJIA). Comparatively, the SJIA group exhibited lower mean hemoglobin levels (8.7 g/dL) than the non-SJIA group (10.7 g/dL). Additionally, the SJIA group had higher mean

white blood cell counts (16.12 K/µL) and platelet counts (618 K/µL) in contrast to the non-SJIA group, which had lower mean white blood cell counts (12.8 K/µL) and platelet counts (320 K/µL). Increased production and activation of platelets in response to the systemic inflammation, alsoanemia in JIA is commonly caused by iron deficiency or due to chronic inflammation. Leukocytosis and anemia are laboratory findings that have been associated with systemic juvenile idiopathic arthritis (sJIA) in several studies. Which have reported statistically significant leukocytosis in sJIA patients compared to polyarticular JIA (pJIA) patients. Leukocytosis is a typical finding in patients with active sJIA and may indicate ongoing inflammation[7,13,19].

After 4months of TCZ using, hematological indices normalized, with Hb levels increasing to 11 g/dL and WBC counts decreasing to 8.97× 10^9 cells/L. Ferritin levels reduced to 300 ng/mL, suggesting improved iron metabolism and platelet counts also decreased to 350 × 10^9/L. These findings collectively demonstrate a positive response to tocilizumab treatment, characterized by a reduction in inflammation and improved hematological parameters.

In JIA, elevated levels of proinflammatory cytokines, particularly IL-6, contribute to the disease's pathogenesis and are associated with various clinical manifestations.Additionally, IL-6 can induce leukocytosis, anemia, thrombocytosis, and hyperferritinemia, By blocking the IL-6 receptor, tocilizumab effectively inhibits IL-6 signaling and its downstream effects. This leads to a reduction in disease activity and improvement in clinical symptoms in patients with JIA. Tocilizumab has been shown to be effective in improving the signs and symptoms of JIA, as demonstrated in various clinical trials and real-world studies [20,21].

Limitation: In our study, the duration of tocilizumab therapy was not approved and a longer duration was necessary for a more comprehensive assessment. Second, the present study's results would have been more conclusive if a larger sample size had been included to counter the effect of escaped follow-up and medication withdrawal prior to the inefficacy endpoint. Therefore, larger studies are required to shed further light on this topic and ultimately enhance the care of sJIA patients.

CONCLUSIONS

In conclusion, we demonstrated that TCZ is the drug of choice as first-linebiologic disease-modifying antirheumismdrugs (bDMARDs) in sJIA, and considered highly effective in Extended Oligoarticular JIA and Polyarticular JIA who do not respond to a3months course of methotrexate.

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