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Efficacy of Tocilizumab in the Treatment of Systemic Onset Juvenile Idiopathic Arthritis

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Abstract

***Background**: Systemic JIA (sJIA) is the most severe sub type of JIA with limited treatment option and responsible for most of the disability and morbidity in JIA.*

***Objective:** To assess the efficacy of Tocilizumab (TCZ) in refractory sJIA patients according to disease activity score in 28 joint criteria.*

***Methodology:** This interventional study was carried in the department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU). A total number of 22 sJIA patients who were refractory to traditional DMARDs were offered TCZ. Among them 15 patients agreed to take TCZ (cases) and 7 patients did not (controls). All the cases and controls were assessed according to DAS 28 criteria at enrollment, 12 weeks and 24 weeks of TCZ therapy. DAS 28 scores during assessment were compared.*

***Results:** After TCZ therapy systemic features subsided and laboratory features improved in 100% cases. Among cases 93.3% and 92.3% had moderate response at 12 and 24 weeks respectively according to DAS 28 criteria. Among controls 71.5% and 85.7% had moderate response at 12 and 24 weeks respectively (p0.001). Among cases 40% and 60% patients achieved remission at 12 and 24 weeks, where as among controls none achieved remission. Dose of steroid was significantly reduced among cases but was increased significantly among controls. Few side effects like pharyngitis, Varicella, septicemia, anaphylactoid reaction and raised ALT were observed.*

***Conclusion:** Tocilizumab therapy was effective according to DAS 28 criteria refractory sJIA.*

***Key words:** Refractory sJIA, TCZ, DAS 28 criteria.*

Introduction

Systemic JIA (sJIA) is the most difficult to treat among all arthritis cases. About 50% of children with sJIA do not respond to drugs that work for other subtypes of JIA.[1] In most severe cases of sJIA 2/3 of children experience chronic arthritis and approximately 50% develop significant joint disability despite of the available traditional treatment.[2] sJIA has 2-4% overall mortality rate and accounts for 2/3 of all deaths among children with arthritis.[3] Pathogenesis of sJIA remains obscure. However interleukin 6 (IL-6) and soluble IL-6 receptor plays an important role as inflammatory mediators.[4] Elevation of IL-6 was found both in peripheral blood and synovial fluid.

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Its level correlates with disease activity.[5] The clinical use of Tocilizumab (TCZ), an IL-6 receptor antibody showed long lasting effect on both systemic and articular manifestations even in patients with severe disease that was refractory to other therapies.[6] No study so far had been done regarding the effectiveness of TCZ therapy in sJIA patients according to DAS 28 criteria in our country. This study therefore was done with the aim to assess the efficacy of TCZ in refractory sJIA patients according to DAS 28 criteria.

Materials and Methods

This interventional study was carried out from March 2013 to June 2014 in Paediatric Rheumatology Clinic and in patient department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Total JIA patients registered in Paediatric Department of BSMMU up to December 2012 was 450. Among them 46 patients were suffering from sJIA and 22 patient had refractory sJIA who were included in this study. Prior to the commencement, the study research protocol was approved by the institutional review board of BSMMU. Written consent was taken from the parents/guardian of sJIA patients before enrollment of their child in the study. After enrollment, a detailed history, thorough physical examination and baseline investigations were done. Presence of any active infection (including tuberculosis), serum ALT > 2 times of upper limit of normal, raised serum creatinine level, Platelet count < 100000/mm^3 of blood and total leucocyte count <3500/mm^3 were excluded from the study. DAS 28 core set variables[7] (Swollen joint, tender joint, ESR, VAS) were assessed at baseline, 12 weeks and 24 weeks.

A DAS 28 score of higher than 5.1 were indicative of high disease activity, whereas a DAS 28 below 3.2 indicates low disease activity. Cutoff point of improvement is different for different disease activity. Improvement is categorized by European League Against Rheumatism (EULAR) as good response, moderate response and no response.[8]

All the 22 patients were offered TCZ. Among them 15 patients agreed to receive TCZ who were considered as cases. Seven patients did not agree to receive it and they were considered as controls for this study. Cases received TCZ 8mg/kg initially 2 weekly for 12 weeks and then 4 weekly for next 12 weeks along with traditional DMARDs (Methotrexate, Hydroxychloroquine) and oral prednisolone. Control groups were on treatment with traditional DMARDs and oral prednisolone routinely and dose of steroid were increased from time to time when indicated. Both the groups were followed up 2 weekly for initial 12 weeks and subsequently 4 weekly for next 12 weeks to assess disease activity improvement and to identify any adverse clinical and laboratory events. Among the cases all patients (n=15) completed initial 12 weeks follow up and 13 patients completed 24 weeks follow up (2 patients were lost from follow up, 1 from 7^{th} dose and 1 from 6^{th} dose). Efficacy of TCZ was assessed at 12 weeks and 24 weeks follow up according to DAS 28 response criteria. Data were collected in a pre-designed data collection sheet and P value was calculated by Fisher exact and Mann Whitney test at significance level 0.05.

Working definition of refractory sJIA: After confirmation of diagnosis, sJIA patients were treated with MTX by sub cutaneous route at a dose of 15 mg/m^2 body surface area along with other adjuvant drugs. Patients who failed to respond in three months were added with 2nd DMARD (hydroxychloroquine orally at a dose of 5-6 mg/kg). After three months, who failed to achieve ACR Pedi 30 criteria[9] were considered as refractory sJIA patients.

Results

Males were 40% and female were 60% among the study population and 66%, and 34% among control group. Majority of the sJIA patients presented at the age group of 6-10 years (60%). Systemic features (fever, rash) and laboratory parameters (anemia, leukocytosis and thrombocytosis) of both the groups were comparable (p >0.05) [Table-I].

Table-I

Baseline Demographic and Clinical Characteristics of Cases (n= 15) and Controls (n=7)

Characteristics	Cases (n=15) No (%)	Controls (n=7) No (%)	P value
Sex			
Male	6 (40)	5 (66)	0.170
Female	9 (60)	2 (34)	
Age groups (%)			
0-5 years	5 (33)	1 (14)	
6-10 years	9 (60)	6 (86)	
11-15 years	01 (7)	0	
Mean (SD)	8.03±3.90	7.42±1.98	0.705
Age at disease onset(years)	4.1±1.35	5.1±1.85	0.591
Fever	15 (100)	7 (100)	1.00
Rash	13 (86.6)	6 (85.7)	0.952
Anemia	14 (93.3)	6 (85.7)	0.563
Thrombocytosis	11 (73.3)	5 (71.4)	0.926
Leukocytosis (mm^3/blood)	13 (86.6)	6 (85.7)	0.952
Disease duration (years) %	Number (%)	Number (%)	
0-3 years	8 (53)	6 (86)	
4-6 years	2 (7)	1 (14)	
7-9 years	5 (33)	0	
Mean (SD)	4.80±2.81	4.25±2.52	0.620
Weight (kg)	18.11±8.29	22.14±6.35	0.258
Dose of prednisolone at study entry (mg/kg/day)	0.60±0.15	0.62±0.2	0.60

DAS 28 score gradually decreased in both the group but it was significantly decreased among cases at 24 weeks (P< 0.01) and it came down below the remission level after 12 weeks [Fig.-1].

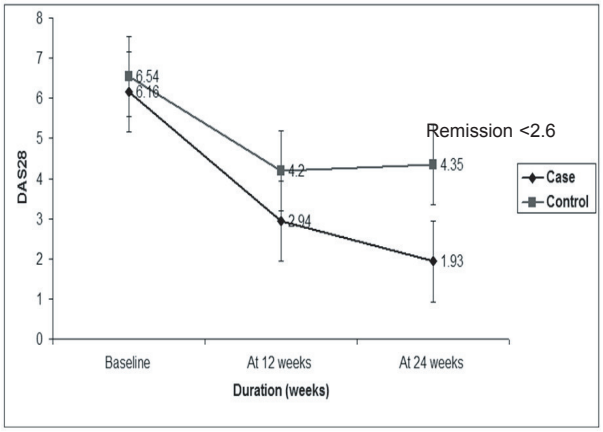

Fig.-1: *Mean Disease Activity Score (DAS) in 28 joints at Baseline and Follow Up among Cases (n=15) and Controls (n=7).*

Among cases 93.3% and 92.3% patients had moderate response at 12 and 24 weeks respectively. Among controls 71.5% and 85.7% had moderate response at 12 and 24 weeks respectively. Among cases 40% and 60% patients achieved remission at 12 and 24 weeks. Among control group no patient achieved remission [Fig.-2].

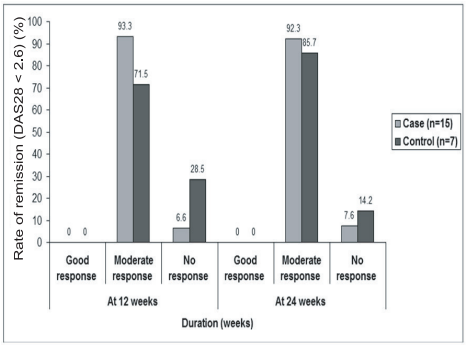

Fig.-2: *Response Over Time Point According to DAS 28 among Cases (n=15) and Controls (n=7)*.

Dose of prednisolone was reduced significantly from baseline to 12 weeks and 24 weeks (p<0.001) among cases and was significantly increased from baseline to 12 weeks and 24 weeks among controls (p<0.001) [Table-II].

Table-II

Dose of Steroid from Baseline to Follow up among Cases (n=15) and Controls (n=07)

	Dose of Prednisolone (mg/kg)					P value (comparison of case and control)	
	Baseline	12 weeks (n=15)	P value	24 weeks (n=13)	P value	12 weeks	24 weeks
Case	0.60±0.15	0.30±0.1	0.001	0.18±0.05	0.001	0.001	0.001
Control	0.62±0.2	0.80±0.23	0.001	0.90±0.3	0.001		

Discussion

Juvenile idiopathic arthritis (JIA) belongs to autoimmune disorder of unknown specific etiology, with some evidence referring to genetic and environmental factors.[4] Persistently active systemic JIA (refractory cases) represents a major challenge. Traditional disease-modifying anti-rheumatic drugs have limited benefit in this group of children. On the other hand the long term use of prednisolone exposes the patients to substantial toxicity with little effect on the real outcome.[10] TCZ 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 sJIA.[11] TCZ is reported to be beneficial for children with systemic onset JIA as TCZ target both membrane bound and soluble IL-6 receptor.[12] TCZ was approved for use in sJIA in USA and Europe in 2011.[13]

Among the 22 patients (cases + controls) in this study, 11 were male and 11 were female, the ratio being 1:1. Sex ratio in this study was similar to the established findings showing no sex predilection in sJIA.[2] Mean age of the patients (8.03 years) were similar to the study done by Yokota et al's where mean age was 8.3 years.[14] Duration of disease (mean) was 4.8 years which was almost similar to Benedetti et al's[15] multicentered study (5.1 year) and Sujata et al's [16] study (6.1 year) from India. Most of the patients were in the age group of 6-10 years (60% of case and 86% of controls) which was also similar to Yokota et al's study[6,14] but the mean age at disease onset was a little bit lower (4.5 years) than the study done in India (8 years) by Sujata et al[16].

Systemic features like fever and rash was present in most of our patients among both the cases (100%, 86.6%) and controls (100%, 85.7%) which was much higher than Benedetti et al study where systemic features were present in 55% & 29% of cases and 65% & 49% of controls.[15] Anemia and thrombocytosis was present in 93.3% and 73.3% among cases and 85.7% and 71.4% among controls respectively. This finding was more or less similar to Benedetti's findings where anemia and thrombocytosis was present in 67% and 69% of cases and 78% and 70% of controls.[15]

Our study found improvement of systemic features (fever, rash) as well as laboratory profile of the disease activity like anemia, leukocyte count and platelet count at 12 weeks of TCZ therapy. These findings were consistent with the study of Yokota et al where they found significant (p<0.05) improvement in laboratory profile and systemic manifestations.[17, 18] Patients with chronic inflammation usually have mild to moderate anemia driven largely by hepcidin, a peptide hormone induced by IL-6.[19] IL-6 receptor inhibition by TCZ treatment in our study possibly resulted in marked improvement in hemoglobin level from 8.5 gm/dl to10.3 gm/dl among cases at 24 weeks treatment.

Mean DAS 28 in this study was 6.16 and 6.35 among cases and controls respectively which gradually decreased over time. But the decrease was significant among cases at 24 weeks (P < 0.01) and mean score was in remission level among cases (1.93) but was higher among controls (4.35). A total of 40% and 60% achieved remission at 12 weeks and 24 weeks respectively among cases. None among controls achieved remission. These findings were consistent with the findings of Imagawa et al's study where it was found that 52% and 82% patients were in remission at 12 week and 48 weeks.[20] As defined by the EULAR response criteria, we did not find any good response. Imagawa et al found 73.7% and 94.1% good

response at 12 weeks and 24 weeks respectively. This can be explained by the fact that at baseline our mean DAS 28 score was much higher (6.16 among cases and 6.54 among controls). For achieving good response, initial score has to be below 3.2.[8] This is important to mention here that very high mean DAS 28 score at presentation indicated the severity of our sJIA patients. Most of the patients in our study had high disease activity (case: 66.6% and control group: 71.4%) according to DAS 28 at presentation. This may be due to long disease duration, inadequate treatment and refractory nature of the disease with traditional DMARDs. Previous studies from our country also reported long duration and very high disability and severity of JIA patients at presentation.[21, 22] Moderate response was found as 93.3% at 12 weeks and 92.3% at 24 weeks among cases and 71.5% and 85.7% among controls at 12 weeks and 24 weeks respectively.

One patient (6.6%) among cases and 2 (28.9%) among controls at 12 weeks showed no improvement. At 24 weeks 7.6% of the cases and 14.2% of controls did not show any improvement at all. It is to be mentioned here that no study so far have found efficacy of TCZ in 100% of resistant systemic JIA cases.[6,17,18] This non response could be due to very high disease activity level or due to development of anti-TCZ IgE antibodies.[17]

The corticosteroid-sparing effect of TCZ is another substantial benefit, and reduction of complica-tions, such as corticosteroid-induced growth retardation and osteoporosis is also anticipated.[5] Steroid sparing effect of TCZ was significant among cases at 12 weeks and 24 weeks ($P<0.001$) with sustained improvement. But in controls steroid dose could not be reduced, rather it was increased significantly ($p< 0.001$), to combat flare, persistent systemic symptoms and disease activity. We were able to stop steroid in 1 patient (6.66%) during TCZ therapy but Yokota et al's[18] in their 2014 study were able to discontinue steroid in 22 patients (33.8%). The number of cases was more in their study (67), duration was much longer (3.4 years) and dose was more frequent (8 mg/kg 2 weekly throughout the study). These factors might be the reasons for this difference.

In this study, some adverse events were noted during 24 weeks treatment with TCZ. This may be explained by the immunosuppressive effect of TCZ itself. Our series found mild adverse events including pharyngitis and transient raise of alanine aminotransferase. Among serious adverse events, anaphylactoid reaction was found in 6%, Varicella infection in 13% and septicemia in 13% cases. The anaphylactoid reaction occurred during 5th dose of that particular patient and was managed accordingly. Subsequently she was continued with TCZ therapy taking all the precautionary measures and no problems were encountered. Neutropenia and thrombocytopenia was found in 2 cases following septicemia. The most common adverse events among 56 patients of Yokota et al's[17] study were nasopharyngitis (59%), upper-respiratory-tract infection (34%) and gastroenteritis (29%), increases in alanine aminotransferase (29%) and aspartame (21%) were also reported. Transaminases usually tend to increase early during TCZ administration and then subside during continuation of treatment.[18] Our study also supported this fact.

Some serious adverse events were also observed in Benedetti et al's study including macrophage activation syndrome, Herpes zoster and Varicella.[15] We did not find any tuberculosis, though tuberculosis is common in our country. This finding is consistent with the results of Benedetti and Yokota's study who also did not find any tuberculosis.[15,18]

The dosing regimen of TCZ therapy was not universal throughout the world. Different study had chosen different dosing protocol. In Japan the study done by Yokota et al used TCZ 2 weekly (8 mg/kg) throughout the period of study (168 weeks) in 67 patients[18] but in TENDER multi centre study by Benedetti et al[15] on 112 patient dose schedule was different (2 weekly for 12 weeks and then 4 weekly). Both the study showed significant and sustained improvement in disease activity. In our study, the dose schedule was similar to Benedetti's study. We had chosen the schedule considering the cost as well as socioeconomic condition of our patients.

In this study, sample size was small, duration of study period was short and all the patients presented with high disease activity score. So outcome of patients with low and moderate disease activity could not be assessed. However, it may be concluded from this study that, overall efficacy of TCZ in children with refractory sJIA according to DAS 28 criteria was very good given the severity of the disease and its complications.

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