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Thalidomide Is an Adjunct Therapy for the Refractory Systemic Juvenile Idiopathic Arthritis Patients in a Tertiary Hospital Study

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Abstract

Background: Systemic JIA (sJIA) is one of the subtypes of JIA, which is most difficult to treat among all JIA cases. About 50% of sJIA cases did not respond to traditional disease modifying anti-rheumatic drugs (DMARDs)—methotrexate (MTX). Thalidomide is an immunomodulating and anti-inflammatory drug that induces sustained improvement of refractory sJIA cases. **Objectives:** To evaluate the efficacy of thalidomide in refractory sJIA patients. **Methods:** This was a prospective interventional study carried out in the Paediatric Rheumatology and Immunology follow-up clinic run by the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2019 to July 2020. Twenty-five sJIA patients who were refractory to conventional DMARDs were included in this study. These patients were prescribed thalidomide at a dose of 3 - 5 mg/kg/day for six months and efficacy was assessed by using juvenile arthritis disease activity score (JADAS 27) at 12th and 24th weeks of treatment. **Result:** Active joint counts and ESR improvement were observed in 90.69%, 97.67% and 69.84%, 100% of sJIA patients respectively at 12th and 24th weeks of treatment. Improvement of physicians and parent global assessment of VAS were 77.56%, 97.43% and 70.62% and 96.04% respectively at 12th and 24th weeks of treatment. Improvement of the total score of JADAS-27 was 77.51% at 12th week and 97.52% at 24th of week follow-up which was statistically significant. Somnolence, constipation and paresthesia were found as common adverse effect in this study. **Conclusion:** Efficacy of thalidomide was assessed by JADAS 27 criteria showed significant improvement in refractory sJIA patients in this study. It may be concluded that Thalidomide is safe and effective as an adjunct therapy of refractory sJIA patients.

Keywords

Juvenile Idiopathic Arthritis, Thalidomide, Refractory sJIA

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and an important cause of short and long-term disability [1]. JIA is defined by the International League of Associations for Rheumatology (ILAR) as arthritis of unknown etiology beginning before the sixteenth birthday and persisting for at least six weeks with other known conditions excluded [2].

Worldwide incidence of JIA ranges from 0.8 to 22.6 per 100,000 children per year with the prevalence ranges from 7 to 401 per 100,000 children [3]. The exact incidence and prevalence of JIA data is not available in our country. A study conducted in a semi-urban area of Bangladesh showed prevalence of JIA as 60.5 per 100,000 children [4].

JIA is classified into seven subgroups according to International league of association for rheumatology (ILAR) 2001 classification. sJIA is one of the subgroups of JIA [5]. Sjia constitute 5% - 15% of all JIA cases [6]. A study conducted by Islam MI *et al.* at Bangabandhu Sheikh Mujib Medical University over a decade showed sJIA constitutes 17% of total JIA patients [7].

Systemic JIA has 2% - 4% overall mortality rate and accounts for 2/3rd of all death among children with arthritis [8].

Though exact cause is not known, hypothesis exists that abnormalities in innate immunity plays a major role in pathogenesis of sJIA. The cytokines playing important role are IL-1, IL-6, TNF-alpha and IL-18 which are secreted from T lymphocytes, macrophage, and monocyte [9].

Systemic JIA is most difficult to treat among all arthritis. About 50% of children with sJIA do not respond to drug that work for others subtype of JIA [10].

Thalidomide is an immunomodulating agent which reverses many of the cytokine's disturbances. Also it is a remission producing, corticosteroid sparing agents in refractory sJIA patients [11]. It was observed that a quite good number of refractory sJIA patients were attending in the Paediatric Rheumatology and Immunology clinic in Paediatric Department of BSMMU. These patients were not improved to traditional treatment like MTX and other drugs.

So, this study was aimed to evaluate the efficacy of thalidomide in refractory sJIA patients who didn't respond to traditional DMARDS.

2. Methods and Materials

This was a prospective interventional study carried out in the Paediatric Rheumatology and Immunology follow-up clinic run by the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2019 to July 2020. There were 29 refractory sJIA patients, were regis-

tered in this clinic, among them four patients did not complete their regular follow-up and subsequently excluded from the study. Informed written consent was taken from parents, and Institutional Review Board Clearance Certificate (NO. BSMMU/2019/2714) was taken before enrollment of the study. Data were collected in a semi-structured pretested questionnaire which included demographic information, detailed history, physical examination and laboratory findings including CBC with ESR, urine R/M/E, serum aminotransferase and serum creatinine. After confirmation of diagnosis, sJIA patients are treated with MTX by sub cutaneous route at a dose 15 mg/m^2 body surface area for at least 6 months along with steroid and other adjuvant drugs. If patients failed to respond in six months then they were considered as refractory sJIA patient. Subsequently these patients were added thalidomide at a dose of 3 - 5 mg/kg/day along with MTX. Efficacy of thalidomide was assessed by using JADAS 27 criteria at 12th week and 24th week of treatment. At the same time adverse events of thalidomide were also assessed. For statistical analysis, Chi-square and paired t-test were done for qualitative and quantitative data respectively.

3. Results

A total of 25 patients completed the study. Amongst them, 64% were female and 36% were male and M: F ratio was 1.77:1. Age range of the patients was 4 - 14 years. The mean age at disease onset was 5.45 years. Disease duration at presentation was 1 to 3 year in the majority (92%) of cases. The mean dose of steroid was 0.52 ± 0.33 mg/kg/day at the beginning of the study. (Table 1)

All patients presented with arthritis and fever. Along with fever 96% presented with lymphadenopathy, 88% presented with rash. Hepatomegaly and splenomegaly were present in 84% & 80% of cases respectively. (Table 2)

Significant improvement of Hb% and ESR level were observed from baseline to subsequent follow up. The others parameter like total count of WBC, neutrophil count, platelet count were also decreased significantly from baseline to 12th week and 24th week follow up. (Table 3)

All the parameters of JADAS-27 includes physician VAS, parents/patients VAS, active joints count and ESR improved significantly from baseline to 12th week and 24th week follow up. Statistical analysis was done using student paired t test. (Table 4)

Table 5 shows that few adverse effects occurred during 24 weeks of Thalidomide therapy. Somnolence developed in 28% and 24% cases at 12th week and 24th week respectively. Hb was low in 4% of cases at 24th week follow up. Neutropenia was present in 4% case.

The improvement of total score of JADAS-27 was 77.51% at 12th week and 97.52% at 24th week (Figure 1). Improvements were statistically significant (p value < 0.001).

It was possible to taper the dose of steroid during follow up at 12th week but significant reduction was possible at 24th week (Figure 2).

Table 1. Baseline demographic characteristics of cases (n = 25).

Characteristics	Frequency (n)	Percentage (%)
Age		
<5 years	10	40
5 - 10 years	8	32
>10 - 16 years	7	28
Mean age ± SD	7.57 ± 3.01	
Age at disease onset (years), (mean ± SD)	5.45 ± 3.10	
Disease durations (years)		
1 - 3 years	23	92%
>3 years	2	8%
Mean ± SD	2.12 ± 0.87	
Doses of prednisolone at study entry (n = 20) (mg/kg/day), (mean ± SD)	0.52 ± 0.33	

Table 2. Baseline clinical characteristics of cases (n = 25).

Variables	Frequency (n)	Percentage (%)
Arthritis	25	100
Fever	25	100%
Lymphadenopathy	24	96%
Rash	22	88%
Hepatomegaly	21	84%
Splenomegaly	20	80%

Table 3. Changes in the laboratory parameters from baseline to follow up among study participants (n = 25).

Variables	At Baseline	At 12th week	*p value	At 24th week	*p value
Hb (%)	9.77 ± 1.63	10.35 ± 1.26	0.006	11.07 ± 1.45	<0.001
ESR (mm in 1st hr.)	71.40 ± 31.38	32.75 ± 20.24	<0.001	16.30 ± 15.50	<0.001
Total WBC (×10^9/L)	13.91 ± 4.96	9.45 ± 3.11	<0.001	8.26 ± 2.05	<0.001
Neutrophil (%)	71.90 ± 10.66	59.15 ± 12.84	0.002	55.30 ± 8.77	<0.001
Lymphocyte (%)	22.35 ± 9.48	32.95 ± 11.40	0.004	34.75 ± 9.19	<0.001
Platelet (×10^9/L)	533.25 ± 181.01	454.20 ± 146.57	0.005	382.40 ± 89.11	<0.001
S. Alt	14.50 ± 6.53	13.35 ± 6.11	0.479	15.60 ± 13.12	0.747
S. Creatinine	0.44 ± 0.13	0.39 ± 0.11	0.148	0.41 ± 0.13	0.559

Table 4. Changes in the JADAS-27 variable from baseline to follow up among study participant (n = 25).

Variables	At baseline	At 12th week	Improvement (%)	*p value	At 24th week	Improvement (%)	*p value
Physician global assessment 0 - 10-cm VAS	7.80 ± 1.64	1.75 ± 1.97	77.56%	<0.001	0.20 ± 0.52	97.43%	<0.001

Continued

Parent/patient global assessment 0 - 10-cm VAS	8.85 ± 1.22	2.60 ± 2.77	70.62%	<0.001	0.35 ± 0.87	96.04%	<0.001
Active joint count (0 - 27 joints)	6.45 ± 7.19	0.65 ± 0.74	90.69%	<0.001	0.15 ± 0.36	97.67%	<0.001
Acute-phase reactant (0 - 10 mm) Normalized ESR	5.14 ± 3.13	1.55 ± 1.70	69.84%	<0.001	0.00 ± 0.00	100%	<0.001

Table 5. Number of adverse clinical and laboratory events during follows up period.

Events	At 12th week		At 24th week	
	Frequency	Percentage	Frequency	Percentage
Clinical				
Somnolence	7	28%	6	24%
Constipation			2	8%
Short lived paresthesia	1	4%		
Laboratory features				
Anaemia			1	4%
Neutropenia	1	4%		

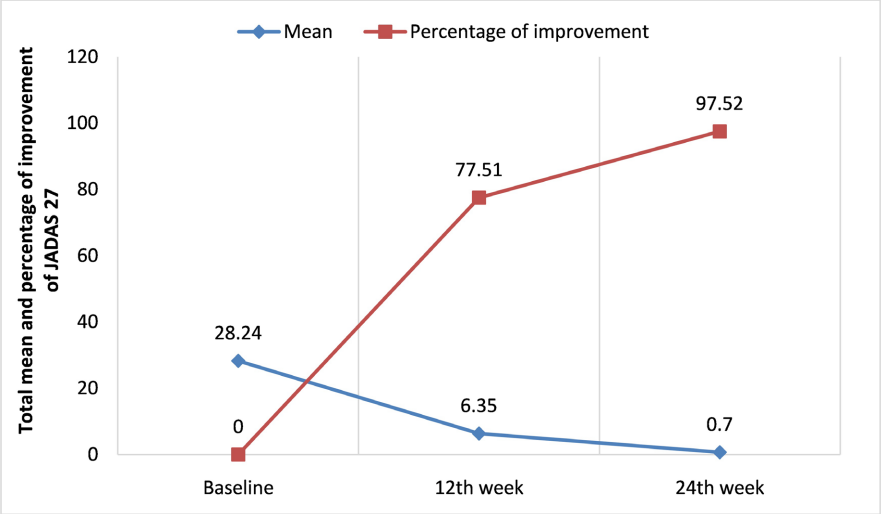

Figure 1. Changes in the total JADAS-27 from baseline to follow up among study participants (n = 25).

4. Discussion

Systemic arthritis has a variable disease course. sJIA is the most difficult to treat among all arthritis. In most severe cases of sJIA up to 2/3rd of children experience chronic arthritis and approximately 50% develop significant joint disabilities despite of available traditional treatment. About 50% of children with sJIA

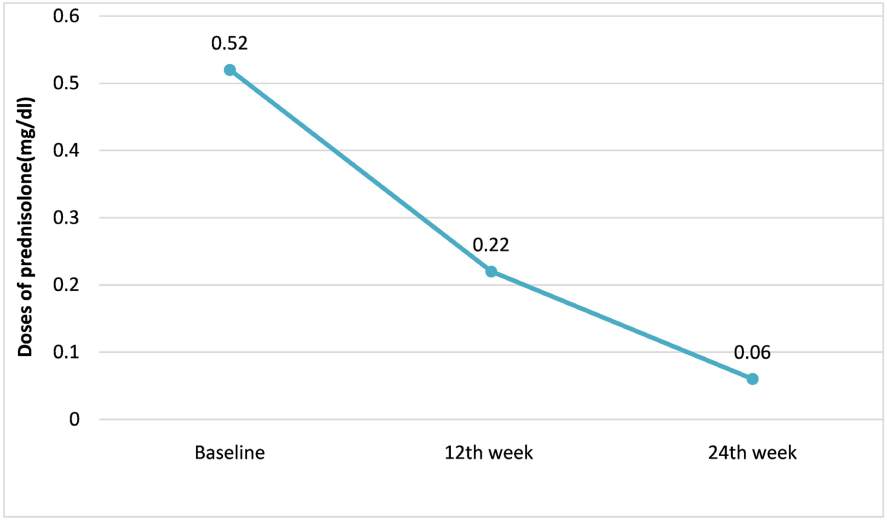

Figure 2. Dose of steroid from baseline to follow up among study participants (n = 20).

do not respond to drugs that work for other subtypes of JIA. In a study by Islam, *et al.* found thalidomide was shown efficacious for treating refractory sJIA.

There was 73% improvement of arthritis from baseline to 12 months follow up [12].

The present study has shown the efficacy of thalidomide therapy in 25 patients who were nonresponsive to traditional DMARDs. Before starting thalidomide they were offered biological therapy, but due to economic constraint they could not afford that. Among the patients 16 were female and 9 were male, the ratio being 1.77:1. This study showed mean physician VAS at baseline was 7.8 cm which was almost similar to the study done by Islam, *et al.* [12]. At 12th week and 24th weeks of treatment, mean physician VAS were improved significantly. At 12th and 24th week of follow up mean joints count reduction were significant (p value < 0.001). Our study showed mean normalized ESR at baseline was 5.14, which was similar to Carrasco *et al.* study. At 12th and 24th weeks, the ESR was significantly reduced compared to baseline in our study. The percentage of improvement of Physician VAS, Parents/patients VAS, active joints count and ESR at 12th and 24th week were significant observed in this study.

García-Carrasco, *et al.* reported three cases of recalcitrant sJIA that improved dramatically after treatment with thalidomide. An Indian study with three children with refractory sJIA also reported improvement after treatment with thalidomide [11]. Steroid sparing effect of Thalidomide was observed in the Lehmanet, *et al.* study where they discontinued prednisolone at 13 patients out of 20 after 24th week of treatment which was also matched with the present study [13].

Tolerability of thalidomide is generally found to be better with single night time administration. Some adverse effects were noted during 24 weeks treatment with Thalidomide. Among the adverse effects somnolence, anemia and neutropenia were found during follow up.

5. Conclusion

Significant improvement in all the variables of JADAS in refractory sJIA patients were found after thalidomide therapy during follow-up. Somnolence, paresthesia, constipation was found as a side effects in a small number of patients.

Limitation of Study

This is single center study with small study population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Data Collection Sheet

Principle Investigator: Dr. Md. Taiyabur Rahman, MD (Phase B Resident).

Place of Study: Paediatric Rheumatology and Immunology Clinic and Inpatient, Department of Paediatrics, BSMMU.

ID No: Date:
Name: Age:
Father's Name: Contact Number:
Address:

Section A:

SL. No	Question	Option	Skip
1	How old are you?	0 - 5 years = 1 6 - 10 years = 2 11 - 16 years = 3	☐
2	Sex	Male = 1 Female = 2	☐
3	What is your father occupation?	Businessman = 1 Service = 2 Others = 3	☐
4	Average monthly income?	<10,000 = 1 10,000 - 20,000 = 2 20,000 - 30,000 = 3 >30,000 = 4	☐
5	How old were you when the disease started?	Years ☐ Month ☐	
6	How long are you suffering from the disease?	<1 years = 1 1 - 2 years = 2 >2 years = 3	☐
7	Type of JIA?	Refractory sJIA	

Section B:

SL. No	Question	Option	Skip
1	Joint Pain	Yes = 1 No = 2	☐
2	Joint swelling	Yes = 1 No = 2	☐
3	Fever	Yes = 1 No = 2	☐
4	Duration of fever		
5	Type of fever	Intermittent = 1 Continued = 2 Remittent = 3	☐

Continued

6	Rash	Yes = 1 No = 2	☐
7	Other complaints		☐
8	Family history	Yes = 1 No = 2	☐

Past Treatment History:

No	Drug	Starting date	Dose	Duration

Present Treatment History:

No	Name of drug	Starting date	Dose

Dose of Prednisolone:

At baseline	At 12th week	At 24th week

Information of Physical Examination:

Sl. No	Physical findings	Result	
1	Temperature		
2	Pulse	Beats/min	
3	Blood pressure	mmHg	
4	Respiratory rate	Breath/min	
5	Pallor	Yes = 1 No = 2	☐
6	Severity of pallor, if present	Mild = 1 Moderate = 2 Severe = 3	☐
7	Jaundice	Yes = 1 No = 2	☐
8	Edema	Present = 1 Absent = 2	☐
9	Rash	Present = 1 Absent = 2	☐

Continued

10	BCG mark	Present = 1 Absent = 2	☐
11	Lymph node	Enlarged = 1 Not enlarged = 2	☐
12	If lymph node enlarged	Cervical = 1 Axillary = 2 Inguinal = 3 Others = 4	☐
13	Hepatomegaly	Present = 1 Absent = 2	☐
14	Splenomegaly	Present = 1 Absent = 2	☐
15	Serositis	Present = 1 Absent = 2	☐
16	Slit lamp examination and findings	Yes = 1 No = 2	☐

Anthropometric Information:

Sl. No	Variable	Result
1	Weight	kg
2	Height	cm
3	BSA	m^2

Locomotors System:

1	Look	Muscle wasting	Present = 1 Absent = 2	☐
		Deformity	Present = 1 Absent = 2	☐
		If deformity, which joint		☐
		Swollen joint count		☐
2	Feel	Tender joint count		☐
		Grade of tenderness	Gr 1/4 = 1 Gr 2/4 = 2 Gr 3/4 = 3 Gr 4/4 = 4	☐
		Enthesitis	Present = 1 Absent = 2	☐
		Gait	Normal = 1 Abnormal = 2	☐

Laboratory Investigations:

Laboratory parameters	At baseline	At 12th week	At 24th week
Hemoglobin			
ESR			
Total WBC count			
Neutrophil			
Lymphocytes			
Platelet count			
Serum ALT			
Serum creatinine			
Urine R/M/E Pus cell: Protein: RBCs: Cast			

Presence of Common Drug Related Adverse Events:

Adverse events	12th week		24th weeks	
Somnolence	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Peripheral Neuropathy	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Constipation	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Anaphylaxis	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Septicemia	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Low Hb%	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Neutropenia	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Thrombocytopenia	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐
Raised ALT	Yes = 1 No = 2	☐	Yes = 1 No = 2	☐

JADAS-27