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Efficacy and Safety of Thalidomide as Adjunct Therapy in Refractory Systemic Juvenile Idiopathic Arthritis Patients

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Abstract

About 50% of systemic onset juvenile idiopathic arthritis (sJIA) patients run a recalcitrant disease course and resistant to the conventional disease modifying anti inflammatoy drugs (DMARDs), ultimately resulting in permanent disability from joint destructions. Thalidomide has been reported as an effective and safe drug in the management of systemic JIA due to its immunomodulatory properties. This was an interventional study, aimed to evaluate the efficacy of thalidomide in refractory JIA patients. Twenty five systemic JIA patients who were refractory to conventional DMARDs were included in this study. These patients were prescribed thalidomide at a dose of 2-3mg/kg/day for 12 months. Efficacy of thalidomide was assessed by using Wallace criteria at 6th month and 12th month of thalidomide treatment. Active arthritis was improved in 55% and 73% of the patients at 6th and 12th month of thalidomide treatment respectively. Fever and rash subsided in 72.8% and 81.2% of patients respectively at 12th month of follow up. Hepatosplenomegaly and lymphadenopathy regressed in 100% of patients at 12th month follow up. ESR was also improved in 50% and 68.2% cases at 6th and 12th months respectively. Few minor side effects were observed like transient elevation of liver enzyme and somnolence in this study. It may be concluded that thalidomide is safe and effective in refractory JIA patients.

Keywords: Juvenile idiopathic arthritis, Thalidomide, Refractory, Safety, Efficacy

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of children and is a very important cause of short and long term morbidity and disability.[1] It is characterized by idiopathic peripheral arthritis with an immunoinflammatory pathogenesis possibly activated by contact with external antigens.[2]

It is classified into seven subgroups according to International league of associations for rheumatology (ILAR) 2001 classification.[3] Systemic onset JIA (sJIA) is one of the seven subtypes, incidence of which was found in 10- 20% cases.[4] Recently, a study done in Bangladesh found that 14% of patients had sJIA in their study.5 Besides, an Indian and a Canadian study found 7.7 and 4.4 % of sJIA patients respectively in their series.[6,7] Systemic JIA has 2-4% overall mortality rate and accounts for two third of all deaths among children with arthritis. About 50% of these patients run a recalcitrant disease course and resistant to the conventional disease modifying anti rheumatic drugs (DMARDs), ultimately resulting in permanent disability from joint destructions and local growth deformities.[8]

Thalidomide is a unique anti-inflammatory agent that suppresses angiogenesis, cellular adhesion molecule expression and production of tumor necrosis factor- α and interleukin-6. It also inhibits leucocyte chemotaxis and decrease the CD4/CD8 ratio.[9] Thalidomide, once discarded as a potent teratogen, has been reported effective in the management of sJIA due to its immune modulatory properties.[10] Sedation, somnolence, myalgia, constipation, neutropenia and anaphy-laxis were found as common side effects of thalidomide therapy in different studies.[10,6] Till date, so far no study has been done on efficacy of thalidomide therapy in refractory sJIA patients in Bangladesh. The aim of this study was to evaluate the efficacy of thalidomide in refractory sJIA patients.

Materials and Methods

This was an interventional study carried out in the Paediatric Rheumatology follow-up clinic run by the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2013 to December 2014. There were 72 sJIA patients, who were registered in the paediatric rheumatology follow up clinic during study period. Amongst them, 25 were identified as refractory sJIA patients, and were enrolled in the current study.Three patients did not complete their regular follow-up visit, and were subsequently excluded from the study.

After obtaining informed consent from patients/parents, data were collected in a questionnaire. The data included demographic information, detailed history, physical examination and laboratory findings including CBC with ESR, serum aminotransferase and serum creatinine.

The study subjects were administered methotrexate (MTX) by sub cutaenous route at a dose 15 mg/m^2 body surface area/week for at least 6 months along with steroid (starting at 0.5 to 1 mg/kg/day and gradually tappering dose). As no satisfactory improvement occured, hydroxychloroquine at a dose of 5 to 6 mg/kg/day was added for another 3 months.

Working definition of Refractory sJIA patients who were treated with two conventional DMARDs in appropriate dose along with other adjuvant therapy for at least 6 months and failed to achive a remission according to Wallace criteria[11] were considered as refractory sJIA patient. Subsequently these patients were prescribed thalidomide at a dose of 2-3mg/kg/day for 12 months. Methotrexate and hydroxychloroquine were also continued during this period. Efficacy of thalidomide was assessed by using Wallace criteria[11] at 6^{th} month and 12^{th} month of thalidomide treatment. At the same time adverse events of thalidomide if any were also looked for. For statistical analysis, Chi-square and paired t-test were done for qualitative and quantitative data respectively.

Results

A total of 22 patients completed the study. Amongst them, 82% were male and 18% were female, M: F ratio was 5.25:1. Age range of the patients was 5.5 year to 15 year and most of the patients were in the age group of 6-10 year. Disease duration at presentation was more than 12 months in the majority (68%) of cases. The mean dose of steroid was 0.635±0.123 mg/kg at the beginning of the study (table I).

Table I: Baseline demography of cases (n= 25)

Demographic characteristics	Frequency	Percentage (%)
Age		
0-5 yrs	5	20.0
6-10 yrs	13	52.0
11-15 yrs	7	28.0
Total	25	100.0
Sex		
Male	21	84.0
Female	4	16.0
Age at disease onset (years) (mean±SD)	5.50±2.37	
Age at diagnosis (years) (mean±SD)	6.54±2.58	
Disease duration (years)		
1-3 yrs	17	68.0
4-6 yrs	7	28.0
7-9 yrs	1	4.0
Treatment history		
MTX	25	100%
Hydroxychloroquine	25	100%
Prednisolone dose (mean±SD)	0.635±0.123	

All patients presented with fever. Other systemic features like rash were found in 92% of patients, lymphadenopathy and hepatomegaly were found in 84% and 92% of patients respectively (table II).

Table II: Baseline Disease Activity (n=25)

Baseline	Frequency	Percentage (%)
Presence of systemic features		
Fever	25	100.0%
Rash	23	92.0%
Lymphadenopathy	21	84.0%
Hepatomegaly	23	92.0%
Splenomegaly	20	80.0%
Serositis	3	12.0%

At presentation, active arthritis was present in 100% of patients. ESR was high in 84% patients and mean physician assessment of global disease activity was 7.99±0.71 (table III).

Table III: Baseline Lab Parameters (n=25)

Lab parameters:	Range	Mean±SD
Hb (%)	5.7 – 11.4	9.04±1.38
ESR	4.0 – 180.0	76.74±42.15
Platelet	180.0 – 850.0	553.70±173.09
Total count	5.0 – 35.0	15.20±7.00
Neutrophil	52.0 – 84.0	70.48±7.82
ALT	16.0 – 176.0	47.96±46.55
Serum Creatinine	0.30 – 0.90	0.57±0.14

At 6 month of follow-up, active arthritis was improved in 55% of the patients (p <0.001) and ESR was improved in 50% cases (p <0.006). While considering systemic features like fever and rash, 59.1% and 68.2% patients became fever and rash free respectively and lymphadenopathy disappeared in 100% of patients. Hepatomegaly and splenomegaly disappeared in 72.73% and 68.2% patients respectively in this series (p <0.05).

Table IV: Improvement According to Wallace Criteria from Baseline to Follow up (n=25)

Variables	Baseline (n=25)	At 6 months (n=22)	At 12 months (n=22)	p value	
				Baseline Vs. 6 m	Baseline Vs. 12 m
Number of patients with active arthritis	25(100.0 %)	10(45.4 5%)	6 (27%)	<0.001	<0.001
Presence of systemic Features:					
Fever	25(100 .0%)	9(40. 9%)	6(27.2 7%)	<0.001	<0.001
Rash	23(92 %)	7(31. 8%)	4(18.1 8%)	<0.001	<0.001
Lymphadenop athy	21(84 %)	0	0	<0.001	<0.001
Hepatomegal y	23(92 %)	6(27. 27%)	0	<0.001	<0.001
Splenomegaly	20(80 %)	7(31. 8%)	0	0.004	<0.001
Serositis	3(12.0 %)	0	0	0.233	0.233
ESR* > 20 (mm in 1sthr)	21(84 %)	11(50 .0%)	7(31.8 %)	0.006	<0.001
Physician's Visual Analogue Scale Mean±SD$^{\#}$	7.99±0 .71	4.35± 1.92	1.30±1. 56	<0.001	<0.001
Number of patients with active disease	25(100 .0%)	14(63 .6%)	9(40.9 %)	0.004	<0.001
Prednisolone (mg/kg) (mean+SD)$^{\#}$	0.625± 0.125	0.485 ±0.14 2	0.412± 0.119	0.07	<0.001

At 12 month follow-up, 73% improvement was found in active arthritis, 68.2% improvement in ESR and 59.1% in disease activity. While considering systemic features, 72.8%, and 81.2% patients became fever and rash free respectively. Hepatosplenomegaly were regressed in all the patients at 12th month of treatment (p <0.001). It was possible to taper the dose of steroid during follow up at 6 month and 12 month but significant reduction was possible at 12 month (table IV).

Discussion

Systemic arthritis has a variable disease course. Among about the half of the patients, the disease is characterized by monocyclic or intermittent course with relapses followed by remission. Remaining half of the patients, the disease follows an unremitting course.[11] Persistently active systemic JIA represents a major challenge to paediatric rheumatologists. Traditional disease-modifying anti-rheumatic drugs have limited benefit in this type of JIA.[12] In a study, thalidomide was shown efficacious for treating refractory sJIA.[10] The present study have also shown the efficacy of thalidomide therapy in 22 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. Boys and girls ratio was 5.25: 1 which was different from other established study[9] where boys and girls ratio was nearly 1: 1. This may be due to the fact that boys get more preference and attention by the male dominating society in Bangladesh and are taken to health service facilities early. Another study from Bangladesh also showed similar findings where M:F ratio among JIA patients were 2:1.[13]

The number of patients with active arthritis were significantly improved at 6th month (54.55%) and 12th month (73%) of follow-up when compared with time of enrollment (p <0.001). Systemic features like fever, rash, lymphadenopathy, hepatosplenomegaly were also significantly improved in this study. Normalisation of acute phase reactant (ESR) was found in 68.2% cases. These findings were almost similar with Lehman et al's results.[10] García-Carrasco et al reported three cases of recalcitrant sJIA that improved dramatically after treatment with thalidomide.[14] An Indian study with three children with refractory sJIA also reported improvement after treatment with thalidomide.[6]

Dose of steroid was reduced significantly in this study and two of our patients were able to discontinue prednisolone, whereas 6 (out of 13) patients were able to discontinue prednisolone in Lehman et al study.[10] The difference may be explained by the facts that, perhaps severity of the disease at presentation might have been different

in this study. Delay in diagnosis and treatment before seeking medical services might have also influenced the outcome.

Thalidomide is a well-known teratogen which was withdrawn from market in 196[15] but this risk is not a problem in this study population. Tolerability of thalidomide is generally found to be better with single night time administration. Thalidomide is a cheap and available drug in comparison to other biological agents.[6]

Common side effects in this study included transient elevation of aminotransferase in two cases and somnolence in three cases. Short lived paresthesia (tingling, numbness) were found during initial period of therapy in another study.[10] No neurotoxicity amongst the cases of this study was to be found though in literature neurotoxicity/ paraesthesia is commonly found.[1]

Conclusion

Beneficial effects of thalidomide in sJIA patients as adjunct therapy were found in this study amongst the patients, who were non responsive to traditional DMARDs. So, it may be concluded from this study that thalidomide may be used in children with sJIA who have failed to conventional therapy. Though the adverse effects of this drug were minimal, use of this drug in children should be carefully supervised.

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