Thalidomide for Systemic Onset Juvenile Idiopathic Arthritis

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Systemic onset juvenile idiopathic arthritis (SOJIA) is the most common autoimmune auto inflammatory disease in childhood. A sizeable number of these patients run a recalcitrant disease course, resistant to the conventional line of management, ultimately resulting in permanent disability from joint destruction, local growth deformities or iatrogenic side effects. The new biological agents although very effective, are beyond the affordability of most in our country. Thalidomide, a cheaper option has been shown to be very effective in the disease control of patients with SOJIA. We report three Indian children with a chronic refractory course of SOJIA, all of whom had failed conventional line of treatment but improved with thalidomide.

Keywords: *Thalidomide, Juvenile idiopathic arthritis.*

More than 40% of children with juvenile idiopathic arthritis present with systemic onset juvenile idiopathic arthritis (SOJIA) in India [1], in contrast with 10% in the Western population. The disease is characterized by dominant systemic features associated with or without arthritis and usually runs a polycyclic course with multiple exacerbations and remissions with almost 50% patients eventually recovering completely, while the rest run a progressive downhill course of disabling arthritis [2]. The conventional treatment options can completely control the disease in only about 60% cases [3]. The realization of the role of the proinflammatory cytokines in the pathogenesis of SOJIA has led to introduction of newer biological agents for management. However, their prohibitive cost remains the greatest obstacle in their use in the economically weaker section.

Thalidomide, once discarded as a potent teratogen, has been reported effective in the management of SOJIA on account of its immunomodulatory properties [2,4].We share our experience in managing three patients with refractory course of SOJIA.

CASE REPORT

Details of the children are presented in **Table I**. *Case* 1 improved in the form of mobility and physical well being, weight gain, decrease in mean joint count and normalization of acute phase reactants.At 10 months post thalidomide follow up she was off steroids and there was functional improvement from Steinbroker class 3 to class 1 without any side effects of therapy. *Case* 2 improved with remission of fever, improved physical mobility, decrease in mean joint count and normalization of acute phase reactants. At 4 months post thalidomide follow up the steroids were completely stopped with functional improvement from class 3 to class 1 without any adverse effects of therapy. *Case* 3, over a period of follow up of 25 months after starting thalidomide, showed improved mobility with minimal aids, decrease in the mean joint count and functional improvement from Steinbroker Class 3 to 1 without any adverse effects of therapy.

DISCUSSION

All the three children had failed multiple conventional drugs before being started on Thalidomide. They were all offered biological therapy but refused after being explained the cost of therapy. The background history of thalidomide was explained to them and one adolescent girl refused the drug. It was started after due informed consent at a dose of 2-3 mg/kg/day in a nightly dose to combat its sedative side-effects. They were all steroid-dependent with its attendant short and long term side effects in the form of osteoporosis, infections and growth retardation. They all had significant improvement after beginning thalidomide therapy. There was normalization of the acute phase reactants (hemoglobin, total counts, platelets and ESR), decrease in the mean joint count and improvement in physical wellbeing and growth. There was functional improvement from Steinbroker class III to class I [5] and could be successfully weaned off steroids. Thus they all achieved inactive disease stage as per Wallace criteria [6].

Thalidomide is a unique immunomodulator agent with an anti-angiogenesis effect in addition to inhibition of TNF-

TABLE I THREE CHILDREN WITH SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS (SOJIA) MANAGED WITH THALIDOMIDE

Age (y), sex	*7, F*		*4.5, F*		*9,M*	
Course/joint involvement#	SOJIA, Polycyclic, Polyarticular		SOJIA,Persistent, Predominant systemic features,Macrophage activation syndrome		Persistent, polyarticular	
Co-morbidities	Anemia,Growth retardation, Intercurrent severe varicella, restricted mobility, steroid dependency and toxicity		Anemia,lymphadenopathy, hepatosplenomegaly		Bony deformities ofTM joint & peripheral joints,	
	Pre-thalidomide	*On thalidomide*	*Pre-thalidomide*	*On thalidomide*	*Pre-thalidomide*	*On thalidomide*
Functional Class*	III	I	III	I	III	I
Fever	Quotidian, high grade	absent	Quotidian, high grade	Absent	Quotidian, high grade	absent
Significant lymphadenopathy	Cervical, axillary, inguinal	regressed	axillary	regressed	Not present	Not present
Hepatosplenomegaly	Present	regressed	present	regressed	Not present	Not present
Skin rash	Present	disappeared	present	disappeared	Not present	Not present
Inflamed / swollen joints	Bilateral wrists,knees and cervical joints	none	Bilateral wrists, knees	improved	Cervical, bilateral shoulders, Right hip and right knee	none
Laboratory parameters	*Presentation*	*10 mo later*	*Presentation*	*4 mo later*	*Presentation*	*25 mo later*
ESR	41	28	80	45	84	9
Hb (g/dl)	10	12	6.9	8.4	9	11.9
Platelets ($\times 10^3\mu L$)	8.17	2.75	5.26	5.6	5.23	2.76
WBC ($\times 10^3\mu L$)	13,500	6,300	16,300	11,600	17,700	6300
Thalidomide dose (mg/kg/day)	1.4		2.9		2.5	
Other concurrent/previous medications						
Prednisolone (mg/kg/day)	0.4	0.2	0.4	0.3	0.1	omitted
Methotrexate ($mg/m^2/wk$)	12.5	14.3	20	20	15	11
Cyclosporine (mg/kg/day)	-	-	2	-		
Leflunomide	100mg load, 10mg alt day maintainence	-	-	-	100mg/d ×2d load, 10 mg daily maintainence	-
Methylprednisolone pulses					+	-
Naproxen(mg/kg/day)	15	15	15	15	25	-
Other therapy					Corrective osteotomies	-

*#Course: Persistent: Characterized by continuous symptoms without apparent clinical relief. Polycyclic: Characterized by intermittent periods of quiescence with multiple flares. *Steinbroker class I: Complete functional capacity with ability to carry on all usual duties without handicaps. II: Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints. III: functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care. IV: Largely or wholly incapacitated with patient bedridden or confined to wheel chair, permitting little or no self-care [5].*

α. TNF-α is a potent pro-inflammatory cytokine, over-production of which has been implicated in mouse models of inflammatory arthritis and also in plasma and synovial fluid in patients with active arthritis including children with JIA. Thalidomide is also thought to suppress other proinflamatory cytokines including IL-6 [2,7], to down regulate adhesion molecules as well as to inhibit leukocyte chemotaxis and decrease the CD4/CD8 ratio [2,7]. Evidence concerning the use of thalidomide in SOJIA is limited [4]. In the largest of these studies, Lehman, *et al.* [4] and colleagues have reported the use of thalidomide (2 to 5 mg/kg/day) in 13 children with severe, refractory SOJIA. Six children were able to discontinue chronic steroids, thus highlighting its steroid sparing effect.

Thalidomide being a potent teratogen, birth-control is necessary for both males and females and extreme caution would be necessary when our patients achieve adolescent or child-bearing age. Another major though rare adverse effect is permanent peripheral neuropathy with long term use, for which, regular monitoring including physical (neurological) examination and nerve conduction velocity studies need to be performed [7]. We routinely enquire about the occurrence of tingling, numbness, paraesthesiae and perform a detailed neurological exam in all the three patients on every follow-up visit. So far we have not had reason to suspect peripheral neuropathy in any of our children.

Other side effects include sedation, somnolence, myalgia, constipation, neutropenia and anaphylaxis. The tolerability is generally found to be better with single night time administration. It is also highly economical, (approximate Rs 40/- per tablet of 50 mg the daily dose for a 15-25 kg child), which is in sharp contrast to the other reserve drugs available for this disease.

We advocate careful closely supervised use of thalidomide in consenting refractory cases of SOJIA where biologicals are unaffordable. Larger studies in our country on this 'poor man's biological' are in order.

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Decade Long Unexplained Anemia: Alert to ANCA Associated Vasculitis

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A 13-year old girl presented with a decade long anemia, diffuse alveolar hemorrhage and interstistial lung disease; was eventually diagnosed as ANCA associated vasculitis. High index of suspicion is thus warranted for alternative diagnosis in chronic anemia, despite increased prevalence of infectious diseases and nutritional anemia.

Key words: *Chronic anemia, Diffuse alveolar hemorrhage, Interstitial lung disease, Microscopic polyangitis.*