Leflunomide in Systemic Onset Juvenile Idiopathic Arthritis

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Methotrexate, the mainstay of treatment in Juvenile idiopathic arthritis, might not be effective in a few patients of polyarticular and systemic onset juvenile idiopathic arthritis. Use of biologicals like TNF-α blockers, the next line of preferred drugs is constrained by the high cost. We successfully used leflunomide in four patients.

Key words: *Systemic onset juvenile idiopathic arthritis, leflunomide.*

Leflunomide, an Isoxazole derivative, is a disease-modifying anti-rheumatic drug (DMARD). Its active metabolite A-77 I726 inhibits pyrimidine synthesis, thereby reducing the proliferation of T-lymphocytes, down-regulating autoimmune response [1]. Although, it has been found to be as effective as methotrexate in patients with polyarticular JIA [2,3], it has been infrequently used in children. We used leflunomide in 4 patients of systemic onset juvenile idiopathic arthritis (SOJIA) who did not respond to MTX and could not afford TNF-α blockers.

CASE REPORT

***Case* 1:** A five-year-old girl presented with history of moderate grade fever two spikes per day and swelling, pain and morning stiffness of multiple joints for two months. There was no history of loose stool, dysuria, rash or eye pain. On examination, she had multiple significant lymphadenopathy and hepatomegaly with no subcutaneous nodules, enthesitis or uveitis. Her bilateral ankles, knee, wrist, metacarpophallangeal (MCP) and proximal interphalangeal (PIP) joints were swollen and tender (active joints 26). Investigations revealed hemoglobin, total leukocyte count, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) of 8.6 g/dL, 8750/mm^3, 12 mm first hour and 2.4 mg/dL, respectively. Rheumatoid factor (RF) and antinuclear antibody (ANA) were negative. Liver function tests (LFT), kidney function tests (KFT), and serum immunoglobulin levels were normal. She was diagnosed as a case of SOJIA and was given injection methotraxate (MTX) 10 mg/m^2/ week, S.C. and oral prednisolone 2 mg/kg/day in 4 divided doses. After 2 weeks, patient responded and prednisolone was tapered over next two weeks. She had eight relapses over next five years, first occurring after six months of initial therapy. Each flare-up was associated with fever, lymphadenopathy, hepatosplenomegaly, active joints ranging from six to eighteen, and raised acute phase reactants. Each time prednisolone was added in the dose of 2 mg/kg/day for 2-3 weeks and then tapered over next 2-3 weeks. In the third relapse MTX was increased to 15 mg/m^2/week subcutaneous and hydroxychloroquine (HCQS) at 5mg/kg/day was added. The last of these flares occurred at ten-and-a-half years of age when thalidomide 100 mg once daily (OD) was added to MTX, HCQS and prednisolone. She responded and prednisolone was tapered to 2.5 mg/day over next two weeks. While on MTX, prednisolone (2.5 mg OD), HCQS and thalidomide, she developed another relapse within 4 weeks with six active joints. She also developed side-effects of steroid in the form of cushingoid features; hirsutism and growth failure (height gain of 3 cm in 1 year). At the age of 13, leflunomide was added to these drugs and after eight weeks patient had no active joint disease. All other drugs were withdrawn over next four months. She has been in remission for last 21 months with normal clinical and biochemical parameters.

***Case* 2:** A nine-year-old boy was diagnosed as SOJIA at six year of age on the basis of two months history of fever, pain and swelling of multiple joint and examination showing 18 active joints (bilateral knees, ankles, wrists, elbows and all PIPs), without enthesitis or uveitis. Investigations revealed ESR of 50 mm, CRP of 12 mg/dL, positive RF, negative ANA and normal LFT and KFT. After three weeks of MTX (15 mg/m^2 /week, subcutaneous) and prednisolone (2 mg/kg /day), there was partial response (active joints, 8) and prednisolone was tapered over next three weeks to 2.5 mg OD. Over next one year, he had four flare-ups requiring prednisolone to be increased in each flare. He also developed growth failure, hirsutism and cushingoid features. He was given a trial of thalidomide and HCQS for three months but showed no response. The active joint count persistently remained four. Thalidomide and HCQS were stopped and leflunomide was added to MTX and low dose prednisolone. After three months of

TABLE 1 CHARACTERISTICS OF SOJIA PATIENTS BEFORE AND ON LEFLUNOMIDE THERAPY

Case	*Age (y)/ Sex*	*Total duration of disease (y)*	*Before starting leflunomide*						*After starting leflunomide*				
			No. of flares	*Active joint count*	*ESR*	*VAS*	*PhyGA*	*PGE*	*Response time (mo)*	*Remission period (mo)*	*No. of flares*	*ESR*	*Side effects*
1	13/F	8	9	4	42	7	5	6	2	21	0	8	2 LRTI
2	9/M	3	4	4	120	5	6	8	3	18	0	10	3 LRTI
3	3/M	2	0	12	54	8	6	7	3	13	0	14	Nil
4	3/M	1.5	5	6	34	6	5	7	2	6	0	2	Diarrhea

Leflunomide dose: For case 1 and 2 100 mg OD for 2 days then 10 mg OD. For case 3 &4 100mg OD for 1 day then 10 mg alternate day. Visual analogue scale (VAS), Physicians Global Assessment (Phy GA), and Parents General Assessment (PGA), are in scale of 0 to 10 (higher the score worse is the pain or disease activity, Active joint count, VAS, Phy GA and PGE were zero in patients on leflunomide. LRTI: Lower respiratory tract infection.

leflunomide therapy, there was no active joint disease and acute phase reactants were normal. MTX and prednisolone were withdrawn over next three months. He has been in remission for last 18 months on leflunomide alone.

***Case* 3:** A three-year-old boy was diagnosed at one year of age as a case of SOJIA on the basis of fever, hepatosplenomegaly, lymphadenopathy, morning stiffness, and pain and swelling of multiple joints without enthesitis. He had 28 active joints (bilateral knees, ankles, wrists, elbows, all MCPs, PIPs).His ESR was 34 mm while RF and ANA were negative. Injection MTX and prednisolone in the doses as in case 2 were started. He responded partially over 3 weeks and prednisolone was tapered to 2.5mg/day over next 3 weeks. After six months he had 12 active joints, raised ESR (28 mm) and Leflunomide was started. After three months, all his joints were normal. Over next three months MTX and prednisolone were withdrawn. At present, he is in remission for past thirteen months.

***Case* 4:** A three-year-old boy was diagnosed at one-and half-years of age as SOJIA on the basis of 3 months history of fever, pain, swelling and morning stiffness of ankles and knees, cervical lymphadenopathy and hepatosplenomegaly. His ESR was 80 mm, and CRP 2.5 mg/dL. RF and ANA were negative. He was started on injection MTX and prednisolone in the same dose as case 2. Over next three weeks, swelling and tenderness decreased and steroids were tapered. He took four months to respond completely (all joints, ESR and CRP were normal). Over the next one year, he relapsed five times, requiring high dose prednisolone each time. In the second relapse, HCQS and in the third relapse, thalidomide was added. He also developed cushingoid features, hirsutism, and gained only 2 cm of height in a year. At fifth relapse, leflunomide was added. He started responding and all his joints were normal over next six weeks. HCQS, thalidomide, prednisolone and MTX were withdrawn gradually over the next six months. He continues to be in remission for last six months.

The scores of Visual analogue scale for pain (VAS), Physician global assessment (Phy GA) and Parents general evaluation (PGE) before and after starting leflunomide in these 4 patients are depicted in the **Table I.**

DISCUSSION

Methotrexate has been the mainstay of treatment in most patients of JIA. In a few of the polyarticular and SOJIA patients there might be insufficient response or repeated disease flares, adversely affecting the functional activity, growth and development. Treatment of such patients poses a medical challenge in a resource limited country where biologicals are non-affordable.

Leflunomide has been widely used in adults but not in children. In adults it has been found to be equally efficacious as sulphasalazine and methotrexate, and delays radiological progression [4]. In the three studies conducted in children so far, it has been found to be as effective as methotrexate in polyarticular JIA patients [2,3,5]. Commonly reported side-effects of leflunomide were diarrhea, abdominal pain, anorexia, gastritis, rashe, headache, and raised transaminases [4,5]. In our four patients of SOJIA, the clinical response to leflunomide was found to be good and we were able to withdraw other DMARDs and prednisolone. The response time ranged from two to three months. The side-effects encountered were mild such as lower respiratory tract infections and diarrhea. Leflunomide may serve as an option in poor patients not responding to other drugs. However, well planned randomized controlled trials are required in

various subsets of JIA to define the rightful place of leflunomide.

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Recurrent Neonatal Organophoshorus Poisoning

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Organophosphorus poisoning in neonates is extremely rare and needs high index of suspicion to diagnose it. The clinical presentation is often confused with the features of sepsis like apnea, copious oral secretions, diarrhea, letharginess, seizures. There may be recurrence of manifestations due to chronic exposure. We report a classic case admitted in the intensive care unit of our hospital.

Key words: *Apnea, Seizures, Sepsis.*

Organophosphorus poisoning is rare in neonates.Transplacental route is the most common mode of transmission,others being inhalation and ingestion; either accidental or homicidal. The clinical manifestation often simulates that of sepsis and leads to diagnostic dilemma.Careful clinical examination and early intervention is needed to treat the patient.

CASE REPORT

A 17-days-old Egyptian girl, a product of non-consanguineous parents delivered by full term normal vaginal delivery with no antenatal and perinatal complications was admitted to our hospital with the history of poor feeding and poor activity of one day duration. There was no history of fever or seizures. On examination, child was found to be hypothermic, lethargic, and pale, with mottled skin. She had recurrent apnea associated with bradycardia. She had profuse salivation and frothy secretions from mouth. CNS examination revealed pin-point pupils but other cranial nerves were normal. Child was hypotonic but neonatal reflexes were fairly elicitable. Her hemogram and electrolytes were normal and blood gas analysis showed mild metabolic acidosis. The baby was put on nasal CPAP along with other supportive therapy. Careful interrogation of parents revealed the history of pesticide (Diazinon) spray at home, two days prior to the development of symptoms in the baby. With this history and physical examination findings, strong possibility of organophosphorus toxicity was considered and child was treated with multiple doses of Atropine and two doses of pralidoxime. The patient's activity improved after atropine and pralidoxime doses. There were no further episodes of apnea, bradycardia or miosis. The patient was weaned off from CPAP. Her septic and metabolic screen came negative. Serum cholinesterase level was very low 137U/L (Normal 5000-12000U/L).The patient was discharged without sequale after two days. The patient remained asymptomatic at home and was feeding (breast milk) well. She was admitted again with similar clinical presentation within 48 hours and was treated with atropine and pralidoxime till recovery. She had a very low serum cholinesterase level at this admission (150 U/L). In view of repeated poisoning in the child, breast milk was stopped temporarily as it was suspected as one of the source of repeated exposure and the mother's serum cholinesterase level was also sent, which turned out to be low too (1600 U/L). Child had complete recovery after treatment.